

Intra and Intermolecular Modulation of $n \rightarrow \pi^*$ Non-covalent Interaction: Gas-phase Laser Spectroscopy and Quantum Chemistry Calculations

विद्या वाचस्पति की उपाधि की अपेक्षाओं की आंशिक पूर्ति में प्रस्तुत शोध प्रबंध

A Thesis submitted in the partial fulfilment of the requirements of the degree of Doctor of Philosophy

द्वारा / By

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INDIAN INSTITUTE OF SCIENCE EDUCATION AND RESEARCH PUNE
(2023)

Dedicated to My Parents & Indian National Army

(INA)

&

In Loving Memory of My Chachu



INDIAN INSTITUTE OF SCIENCE EDUCATION AND RESEARCH PUNE

भारतीय विज्ञान शिक्षा एवं अनुसंधान संस्थान पुणे

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I declare that this written submission represents my ideas in my own words and where others' ideas have been included; I have adequately cited and referenced the original sources. I declare that I have acknowledged collaborative work and discussions wherever such work has been included. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea/data/fact/source in my submission. I understand that violation of the above will be cause of disciplinary action by the institute and can also evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when needed.

The work reported in this Thesis is the original work done by me under the guidance of Prof. Alope Das.

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Certificate

Certified that the work incorporated in this thesis entitled “Intra and Intermolecular Modulation of $n \rightarrow \pi^*$ Non-covalent Interaction: Gas-phase Laser Spectroscopy and Quantum Chemistry Calculations,” submitted by Mr. Prakash Panwaria was carried out by the candidate, under my supervision. The work presented here or any part of it has not been included in any other thesis submitted previously for the award of any degree or diploma from any other University or Institution.

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Acknowledgments

I am thankful to *The Prabhu Shri Ram* that I got such loving parents, *Shri Kuldeep Panwaria* and *Smt. Anita Panwaria*. They have made many sacrifices to fill my life with joy and comfort. I cannot imagine my life without their support and motivation. They always understood my pain and sorrow, even while on a phone call, just by listening to my voice. They always believed in me and supported me in all of my dreams. My deepest gratitude and love go to my parents, to whom I owe my very existence. I humbly dedicate this thesis to their feet, honouring their love, support, and guidance that have shaped every step of my journey. I also want to thank my dearest brother, *Er. Chirag Panwariya*, for his continuous support and motivation to deal with my problems and for showing me the right path. His guidance and its connection to spirituality has always helped me. I thank my sister-in-law, *Er. Shivani Gupta* for cheering me towards my goal and reminding me to believe in today without caring for the future so I can live happily. I thank my lovely and dearest sister, *Smt. Jyoti Panawariya*, for her support. I thank all my family members for their constant support during my life, especially during my Ph.D. tenure. It would have been impossible for me to achieve my goal without their blessings and continuous support during the hurdles of my life. It is not easy to express my feelings right at the moment by memorizing the love and support I got from all of you. Thank you for everything.

I want to thank my Ph.D. advisor, *Prof. Alope Das*. He is not only my Ph.D. advisor but also a mentor for my M.S. research project performed with him. He has introduced me to the concept/idea of this research, and I am thankful for him to give me the opportunity to work with him and explore the field of non-covalent interactions. I cannot forget the early phase of my Ph.D.; his guidance, motivation, and inspiration have led me to think about various aspects of my research interests. During my Ph.D. tenure, he has also made me self-reliable in every aspect, like designing research projects, solving problems, scientific paper writing, project proposal writing, and presenting my data confidently in front of the scientific community. I have spent a very hard and rough phase of my life during my Ph.D. tenure. My supervisor has led me to develop personal skills, which has immensely helped me sustain myself in every environment without getting tired or feeling like losing everything. These learning from my advisor would help me become an independent researcher and a successful human being.

I would also like to thank my research advisory committee (RAC) members, *Prof. Sayan Bagchi* and *Prof. Partha Hazra*, for their discussions, comments, and suggestions to

improve my results. I always feel encouraged and motivated to discuss my scientific data outside the RAC meeting whenever I need their insightful comments.

I would also like to thank former chair **Prof. Hosahudya N. Gopi** of the chemistry department and Dean of Academics **Prof. Girish S. Ratnaparkhi** for their help and cooperation so that my scientific progress could not be halted because of the unwanted obstacles. I also thank the current chair of the chemistry department, **Prof. Nirmalya Ballav**.

I owe my gratitude to **Prof. Shabana Khan** for having faith in my ability to contribute to their research work. This has led me to learn various aspects of main-group chemistry. I am grateful to her for being there and lending support even amidst the dark days. I especially thank my research collaborators **Prof. Alberto Lesarri**, **Prof. José A. Fernández**, **Marcos Juanes**, **Rizalina Saragi**, **Imanol Usabiaga**, and **Ander Camiruaga** for contributing to one of my research works. I also thank my research collaborators, **Prof. Partha Hazra**, **Prof. Pinaki Talukdar**, **Joy Chatterjee**, and **Debashis Mondal**, for giving me the opportunity to contribute to their research work.

I thank IISER Pune for my fellowship and for providing state-of-the-art research facilities that have shaped my academic journey. I also thank the director of IISER Pune, **Prof. Sunil Bhagwat**, and former directors, **Prof. Jayant Udgaonkar** and **Prof. Krishna N. Ganesh**. I also thank Param Brahma Facility, under the National Supercomputing Mission (NSM), Government of India at IISER Pune, for allowing me to perform the quantum chemistry calculations smoothly. I am also thankful to the Trimurti research grant for funding the procurement of the chemicals. I also acknowledge the Infosys Foundation travel award for attending the SDMC-2022 conference. I would like to acknowledge the invaluable assistance of **Mr. Parveen Nasa** and **Er. Nilesh Dumbre**, technical officer at IISER Pune, whose expertise proved invaluable in diagnosing and resolving technical issues related to instruments. Special thanks to **Er. Hrishikesh Sawant** for his prompt support regarding laser-related challenges. I sincerely thank **Dr. Sandeep Mishra** for his help in analyzing the NMR data. I also thank the non-teaching staff of the chemistry department for their support wherever required.

I thank former group member **Dr. Santosh K. Singh** for introducing me to the laboratory equipment during the initial days of my M.S. programme. I also thank former group members **Dr. Kamal K. Mishra** and **Dr. Satish Kumar** for creating such a friendly and joyful environment in the laboratory. I wish to express my heartfelt gratitude to my labmate, the late **Mr. Kshetrimayum Borish**. His sudden demise was a huge loss, and it felt very personal as a labmate. Losing someone at such a young age was utterly unfortunate. He was a remarkable individual with a great sense of humor and cherished with a photogenic personality. I fondly

remember our sudden outing and cooking plans. He will be dearly missed, and his contributions towards my doctoral journey will always be remembered. I often wish for his presence, especially today when we would have graduated together. Many things would have been different if you were here. I hope that the Almighty has granted you a peaceful abode in heaven.

I thank the *professors of the chemistry department at Dayalbagh Educational Institute, Agra*, who introduced advanced chemistry in such an interesting and lucid manner, which inspired me to think about opting for higher studies. I also thank *Prof. Richa Agarwal* and *Prof. Agam P. Tyagi* from the Department of Mathematics at Dayalbagh Educational Institute, Agra, for their continuous motivation to pursue higher studies.

I feel incredibly fortunate to have my dearest friend, *Moushakhi Ghosh*, by my side throughout this journey. Her support and encouragement have been my driving force, pushing me to excel without dwelling on setbacks. I owe part of my success to her constant companionship and steadfast support, which have been invaluable. It is no exaggeration to say that she has been my rock at IISER Pune. I vividly recall the sheer joy on her face when my first authored paper was published. I wish our friendship remains like this over the years to come. I still recall those memories, such as sudden cooking plans and scientific/political discussions. I learned to cook many new dishes from you. Thanks for everything.

I cherish the delightful memories of my early days at IISER Pune, particularly those shared with *Ateek Shah*. I also thank my friend *Umashankar Rajput* for always being there with me in all the situations and hurdles of my life. He always showed me a different aspect of the situation, leading me to think critically about it.

I am deeply indebted to *Prabhu Shri Ram* for bestowing upon me the priceless treasure of genuine friendships. *Tanvi Jain, Abhishek Mahajan, Sonali Agarwal, Manpreet Kaur Arora, Kalpit Agarwal, Saganpreet Kaur, Monika Thakwani*, and *Priya Maheshwari* hold a special place in my heart for their support and companionship throughout my journey. Their encouragement was invaluable during our college days, notably amidst the preparations for IIT-JAM. Their continuous motivation not only helped me focus but also instilled a sense of determination and served as a guiding light, aiding my dedication to studying effectively. These connections have evolved and flourished over the years, enriching my academic pursuits and contributing immeasurably to my personal growth. I hold their friendship in the highest regard and am immensely grateful for their enduring presence in my life. I also thank my friend *Ravi Sharma*, and I still remember the beautiful time when I was in Agra for my B.Sc. Hons.

Finally, I would like to express my heartfelt gratitude to those whose names, despite their invaluable support, might have been inadvertently missed from this thesis. Their unconditional help has been deeply appreciated.

Prakash Panwaria

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List of Abbreviations

R2PI	Resonant two-photon ionization spectroscopy
UV-UV HB	UV-UV hole-burning spectroscopy
RIDIRS	Resonant ion-dip infrared spectroscopy
IRIGS	Infrared ion-gain spectroscopy
REMPI-TOF-MS	Resonantly enhanced multiphoton ionization time-of-flight mass spectrometry
MCP	Microchannel plate detector
Ar	Argon
He	Helium
Nd: YAG	Neodymium Yttrium Aluminium Garnet
BBO	β -barium borate
KTA	Potassium titanyl arsenate
KTP	Potassium titanyl phosphate
KD*P	Potassium dideuterium phosphate
OPO	Optical parametric oscillator
OPA	Optical parametric amplifier
BS	Beam splitter
7AI	7-azaindole
Py	Pyridine
EDG	Electron-donating group
EWG	Electron-withdrawing group
CSD	Cambridge structural database
PDB	Protein data bank
NMR	Nuclear magnetic resonance
DFT	Density functional theory
MP2	Second-order Moller-Plesset perturbation theory
S ₀	Ground electronic state
S ₁	First excited electronic state
BSSE	Basis set superposition error
ZPE	Zero point energy
E _{rel}	ZPE corrected relative energy
ΔE_0	BSSE and ZPE corrected binding energy

EDA	Energy decomposition analysis
ALMO	Absolutely localized molecular orbital
SAPT	Symmetry adapted perturbation theory
NBO	Natural bond orbital
NSA	Natural steric analysis
WBI	Wiberg bond index
QTAIM	Quantum theory of Atoms-in-Molecules
NCI	Non-covalent interaction index
RDG	Reduced density gradient

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Synopsis

Non-covalent interactions are ubiquitous in small molecules to aggregates, supramolecular assemblies, biomolecules, peptides, proteins, drugs, crystal structures, and materials. These non-covalent interactions are essential in determining the specific structures, functions, and drug designing. The importance of non-covalent interactions can be envisaged by the existence of water in the liquid state by hydrogen bonding. Thus, an in-depth study of the non-covalent interactions is crucial in improving the drugs, molecular recognition, and materials. There are various non-covalent interactions present in the literature, such as hydrogen bonding, halogen bonding, chalcogen bonding, pnictogen bonding, π - π stacking, cation- π interactions, and anion- π interactions. However, this thesis involves understanding weak $n \rightarrow \pi^*$ interaction and tuning its strength intramolecularly and intermolecularly using gas-phase electronic and vibrational spectroscopy combined with quantum chemistry calculations. $n \rightarrow \pi^*$ interaction is analogous to hydrogen bonding ($X-H \cdots Y$) in terms of lone pair electron density delocalization. Hydrogen bonding involves the delocalization of lone pair electron density of electronegative element (Y) into σ^* orbital of the X-H bond. In contrast, $n \rightarrow \pi^*$ interaction involves delocalizing the lone pair electron density of the nitrogen, oxygen, and sulfur atoms into the π^* orbital of the carbonyl group or aromatic ring. In general, $n \rightarrow \pi^*$ interaction is weak in strength compared to hydrogen bonding. Even though it is weak, $n \rightarrow \pi^*$ interaction is omnipresent in biomolecules and materials and can dictate the conformational preferences of the molecules.

$n \rightarrow \pi^*$ interaction was first discovered in 1953 in protopine (an alkaloid) by E. H. Mottus, 40 years after the discovery of the hydrogen bond (1912). The presence of $n \rightarrow \pi^*$ interaction, though named “*nitrogen bond*” then, was confirmed by the ultraviolet-visible (UV-Vis) and infrared (IR) spectroscopy and the chemical reactions. Subsequently, Leonard and co-workers made the cornerstone of the $n \rightarrow \pi^*$ interaction in the next few years by studying $n \rightarrow \pi^*$ interaction using similar approaches. A revolutionary report from Bürgi *et al.* in 1973 on studying the reaction coordinates for nucleophilic attack on the carbonyl group brought the importance of $n \rightarrow \pi^*$ interaction. They observed the short contact between the nitrogen atom (donor) and the carbonyl carbon with an angle of $\sim 107^\circ$ in protopine, cryptopine, and clivorine crystal structures. It put forth the Bürgi-Dunitz trajectory, which became the criterion of having $n \rightarrow \pi^*$ interaction in a molecular system. Raines and co-workers resurfaced this interaction using NMR spectroscopy around the end of the 20th century. They showed the significance of $n \rightarrow \pi^*$ interaction in the stability of biomolecules, especially in the collagen triple helix. $n \rightarrow \pi^*$ interaction has emerged as a promising candidate for non-covalent interactions due to its

diverse applicability in isomerization, transition state stabilization, dynamic covalent chemistry, stabilizing molecular complexes, and folding of flexible side-chain.

The presence of $n \rightarrow \pi^*$ interaction has been detected from the crystal structures, UV-Vis, IR, and nuclear magnetic resonance (NMR) spectroscopic studies. In the solution-phase, intermolecular interactions arising due to solute or solvent might perturb the strength of weak $n \rightarrow \pi^*$ interaction. Also, the crystal packing forces can lead to short contact between the atoms, misleading the presence of $n \rightarrow \pi^*$ interaction or vice-versa. Thus, these additional forces in the molecular system bring ambiguity in the understanding of $n \rightarrow \pi^*$ interaction. However, the isolated gas-phase studies allow the study of the isolated molecule or molecular complex to be free from the perturbation caused by the solute and/or solvent molecule otherwise present in the solution-phase or crystal structures. Thus, it is imperative to have a detailed understanding of $n \rightarrow \pi^*$ interaction by gas-phase spectroscopy. Additionally, microsolvation in the gas-phase allows exploring the $n \rightarrow \pi^*$ interaction in a sequentially solvated environment, mimicking its behavior in a solution-phase. This thesis involves studying $n \rightarrow \pi^*$ interaction using isolated gas-phase electronic and vibrational spectroscopy combined with quantum chemistry calculations. This thesis focuses on understanding and tuning the strength by varying the electron density at the $n \rightarrow \pi^*$ donor/acceptor sites. It also involves determining the strength of $n \rightarrow \pi^*$ interaction by detecting the redshift in carbonyl stretching frequency using experiments parallel with theoretical approaches. This thesis fills the void arising due to the lack of literature reports for the systematic study of tuning the strength of $n \rightarrow \pi^*$ interaction. This thesis covers several goals in understanding $n \rightarrow \pi^*$ interaction and tackles the following questions.

- ⌘ Can $n \rightarrow \pi^*$ interaction govern the conformational preference of molecular systems?
- ⌘ Can $n \rightarrow \pi^*$ interaction and hydrogen bonding coexist in the gas-phase involving the same lone pair electron density donor?
- ⌘ Can $N \cdots C=O$ $n \rightarrow \pi^*$ interaction be probed using the gas-phase vibrational spectroscopy?
- ⌘ Can the strength of $C=O \cdots$ aromatic or $N \cdots C=O$ $n \rightarrow \pi^*$ interaction be tuned by varying the electron density at the $n \rightarrow \pi^*$ donor/acceptor?
- ⌘ Can $n \rightarrow \pi^*$ interaction resemble hydrogen bonding in terms of its applications in folding the flexible side-chain and stabilizing the molecular complexes?
- ⌘ What is the role of $n \rightarrow \pi^*$ interaction in the carbonyl stretching frequency, where the carbonyl group is free from hyperconjugative interaction from nearby heteroatoms such as oxygen and nitrogen atoms in the case of ester and amide, respectively?

This thesis involves the detailed exploration of $\text{C}=\text{O}\cdots\text{aromatic}$ and $\text{N}\cdots\text{C}=\text{O}$ $\text{n}\rightarrow\pi^*$ interaction using electronic and vibrational spectroscopy performed in the isolated gas-phase environment using supersonic jet-cooled expansion and state-of-art quantum chemistry calculations. Thus, experimental and theoretical approaches deal hand-in-hand with detecting the conformers in the experiments and studying $\text{n}\rightarrow\pi^*$ interaction in detail. This thesis is divided into eight chapters, where $\text{n}\rightarrow\pi^*$ interaction and the need to study this interaction have been introduced in detail. The experimental setup, spectroscopic techniques, and theoretical approaches used to complete this thesis have also been discussed. Furthermore, the findings of the results have been discussed in detail, along with the conclusion and future directions.

Chapter 1 starts with introducing $\text{n}\rightarrow\pi^*$ interaction with a brief discussion regarding its discovery and how the foundation for $\text{n}\rightarrow\pi^*$ interaction was laid down in the mid of the 20th century. It also discusses the significance of this interaction in crystal structures, biomolecules, and drugs. It briefly touches upon the various experimental and theoretical approaches used in the literature reports to analyze $\text{n}\rightarrow\pi^*$ interaction. It is not possible to thoroughly understand $\text{n}\rightarrow\pi^*$ interaction in a single Ph.D. thesis; however, we have tried to achieve some of the goals that will help and ease in better understanding of $\text{n}\rightarrow\pi^*$ interaction. Eventually, this chapter ends with introducing the objectives covered in this thesis.

The home-built experimental set-up has been used to perform the experiments, which has been discussed in detail in **Chapter 2**. Various parts of the instruments, such as the pulse valve used to generate the supersonic jet-cooled molecular beam, time-of-flight mass spectrometry, UV/IR laser sources used to perform the spectroscopy, spectroscopic techniques used to record the electronic and IR spectra have also been discussed. This chapter also discusses how the several conformations of a molecular system can be obtained theoretically.

Our group has shown the direct spectroscopic evidence of $\text{n}\rightarrow\pi^*$ interaction in phenyl formate, where the *cis* conformer was found to be more stable and have $\text{n}\rightarrow\pi^*$ interaction from the lone pair orbital of the carbonyl oxygen to the π^* orbital of the aromatic ring. In comparison, the *trans* conformer is less stable and does not have $\text{n}\rightarrow\pi^*$ interaction as the carbonyl group is oriented away from the aromatic ring. **Chapter 3** shows the role of $\text{C}=\text{O}\cdots\text{aromatic}$ $\text{n}\rightarrow\pi^*$ interaction and steric repulsion in governing the conformational preference of phenyl acetate, an ester analogue of phenyl formate. In this chapter, we have shown that the substitution of the formyl hydrogen of phenyl formate with the methyl group increases the strength of $\text{n}\rightarrow\pi^*$ interaction in the *cis* conformer and selectively increases the steric repulsion in the *trans* conformer, resulting in the exclusive observation of the *cis* conformer of phenyl acetate in the experiment.

Subsequently, in **Chapter 4**, we tried to mask the strength of $\text{C}=\text{O}\cdots\text{aromatic } n\rightarrow\pi^*$ interaction by forming the hydrogen bond with the same carbonyl oxygen lone pair involved in $n\rightarrow\pi^*$ interaction. We showed that the $n\rightarrow\pi^*$ interaction cannot be turned off entirely in the presence of a hydrogen bond; instead, it makes a balance between both interactions. 1:1 phenyl formate $\cdots$ water (phenyl formate $\cdots\text{H}_2\text{O}$) complex was synthesized in gas-phase to give the overview of the behavior of $\text{C}=\text{O}\cdots\text{aromatic } n\rightarrow\pi^*$ interaction in the presence of strong hydrogen bond. The structure of phenyl formate $\cdots\text{H}_2\text{O}$ and various non-covalent interactions were investigated using gas-phase electronic, vibrational, and microwave spectroscopy combined with quantum chemistry calculations. It shows that the conformational preference of the monomer is retained in its monohydrated complex. Chapters 3 and 4 show that the strength of $\text{C}=\text{O}\cdots\text{aromatic } n\rightarrow\pi^*$ interaction can be tuned successfully by tuning the electron density at the $n\rightarrow\pi^*$ donor.

Chapter 5 shows the first gas-phase IR spectroscopic evidence of $\text{N}\cdots\text{C}=\text{O } n\rightarrow\pi^*$ interaction in ethyl 2-(2-(dimethylamino) phenyl) acetate ($\text{NMe}_2\text{-Ph-EA}$). Gas-phase experiments of $\text{NMe}_2\text{-Ph-EA}$ were performed in the mass channels of two distinct fragments of $m/z=15$ and 192, showing the presence of the conformer stabilized by $\text{N}\cdots\text{C}=\text{O } n\rightarrow\pi^*$ interaction. In this chapter, we have demonstrated that the $\text{N}\cdots\text{C}=\text{O } n\rightarrow\pi^*$ interaction stabilizes all six low-energy conformers of the $\text{NMe}_2\text{-Ph-EA}$. First-time variable temperature (VT) ^{13}C NMR spectroscopy has been performed to delineate the presence of $\text{N}\cdots\text{C}=\text{O } n\rightarrow\pi^*$ interaction by measuring the ^{13}C chemical shift of the carbonyl carbon.

Chapter 6 involves the theoretical study of the intramolecular modulation of $\text{N}\cdots\text{C}=\text{O } n\rightarrow\pi^*$ interaction in 3-[2-(dimethylamino) phenyl] propanal (DMAPhP) by varying the electronic substituents at the *para* position of the $n\rightarrow\pi^*$ donor group from the electron-withdrawing groups (EWGs) to the electron-donating groups (EDGs). We have also shown its role in folding flexible propanal side-chain in DMAPhP. The folding of the molecule by $n\rightarrow\pi^*$ interaction observed in this study is found to be similar to that present in the secondary structures of proteins due to hydrogen bonding interactions. Interestingly, stabilizing the global minimum of DMAPhP by $n\rightarrow\pi^*$ interaction demonstrates its importance in providing conformational preferences in molecular systems. The critical finding of this study is that the theoretical redshift obtained in the carbonyl stretching frequency of the DMAPhP is purely by $n\rightarrow\pi^*$ interaction, as the carbonyl group is not involved in hyperconjugation with any neighboring heteroatom, which is common in any ester or amide.

Chapter 7 deals with the theoretical study of the intermolecular modulation of $\text{N}\cdots\text{C}=\text{O } n\rightarrow\pi^*$ interaction in the complexes of *p*-substituted pyridines (*p*-R-Py) with formaldehyde,

formyl chloride, and acetaldehyde. Variation of the substituents at the *para* position of the pyridine ring from the EWGs to the EDGs results in a systematic increase in the strength of $n \rightarrow \pi^*$ interaction. The strength of this interaction is also modulated by tuning the electron density towards the carbonyl bond by substituting the hydrogen atom of formaldehyde with the chloro and methyl groups. The modulation of this interaction due to the electronic substitutions at the $n \rightarrow \pi^*$ donor and $n \rightarrow \pi^*$ acceptor sites in the complexes is monitored by probing the relevant geometrical parameters and electronic parameters. These intermolecular complexes are primarily stabilized by $N \cdots C=O$ $n \rightarrow \pi^*$ interaction.

Chapter 8 involves the overall finding of this thesis and presents a summarized perspective of the understanding of $n \rightarrow \pi^*$ interaction. In a nutshell, it has been shown that the strength of $n \rightarrow \pi^*$ interaction can be tuned intra and intermolecularly in various molecular systems. Some of the preliminary applications of $n \rightarrow \pi^*$ interaction have been studied in this thesis. The understanding and detection of $n \rightarrow \pi^*$ interaction using spectroscopic tools will have implications in drug designing with conformational specificity and molecular recognition based on the specific non-covalent interactions. This chapter also presents the future directions of this thesis, including some of the potential molecular systems and the preliminary results obtained from the quantum chemistry calculations.

List of Publications

13. Joy Chatterjee, Abhijit Chatterjee, Riteeka Tanwar, **Prakash Panwaria**, Sajid Saikia, Madan Ambhore, Pankaj Mondal, and Partha Hazra*, Engineering the triplet harvesting pathways and photon up-conversion properties of novel Cu(I)-iodide complexes by tuning Cu-Cu distance (*Manuscript under revision*).

12. **Prakash Panwaria*** and Alope Das*, $N\cdots C=O$ $n\rightarrow\pi^*$ Interaction: Gas-phase electronic and vibrational spectroscopy combined with quantum chemistry calculations, (*Manuscript under review*).

11. Moushakhi Ghosh, Nasrina Parvin, **Prakash Panwaria**, Srinu Tothadi, Rangarajan Bakthavatsalam, Arshad Theramram, and Shabana Khan*, Diverse structural reactivity pattern of a POCOP ligand with coinage metals, *Dalton Trans.* 2024, (*Just accepted*).

10. Joy Chatterjee, Raj Kumar Koninti, **Prakash Panwaria**, and Partha Hazra*, Elucidating excited state intramolecular double-proton transfer process of [2,2'-Bipyridyl]-3,3'-diol within pores of mesoporous silica nanoparticles, *Chem. Phys. Impact* **2023**, 7, 100285-100294.

9. **Prakash Panwaria** and Alope Das*, Modulation of $n\rightarrow\pi^*$ Interaction in the complexes of *p*-substituted pyridines with aldehydes: A theoretical study, *J. Phys. Chem. A* **2023**, 127, 6081-6090.

8. **Prakash Panwaria** and Alope Das*, Effect of substituents on intramolecular $n\rightarrow\pi^*$ interaction in 3-[2-(dimethylamino) phenyl] propanal: A computational study, *J. Phys. Chem. A* **2023**, 127, 3339-3346.

7. **Prakash Panwaria**, Marcos Juanes, Kamal Kumar Mishra, Rizalina Saragi, Kshetrimayum Borish, Imanol Usabiaga, Ander Camiruaga, Jose A. Fernandez*, Alberto Lessari*, and Alope Das*, Microhydration of phenyl formate: Gas-phase laser spectroscopy and quantum chemistry calculations, *ChemPhysChem*, **2022**, e202200330, 1-9.

6. **Prakash Panwaria** and Alope Das*, Understanding $n\rightarrow\pi^*$ non-covalent interaction from different experimental and theoretical approaches, *Phys. Chem. Chem. Phys.* **2022**, 24, 22371-22389 (*Invited perspective, selected for 2022 PCCP HOT article, published at Inside Front Cover*).

5. Debashis Mondal, Manzoor Ahmad, **Prakash Panwaria**, Avisikta Upadhyay, and Pinaki Talukdar*, Anion recognition through multivalent C–H hydrogen bonds: Anion induced foldamer formation and transport across phospholipid membrane. *J. Org. Chem.* **2022**, *87*, 10-17.
4. Kamal Kumar Mishra, Kshetrimayum Borish, Gulzar Singh, **Prakash Panwaria**, Surajit Metya, Mallur Srivatsan Madhusudhan*, and Alope Das*, Observation of an unusually large IR redshift in an unconventional S–H⋯S hydrogen-bond. *J. Phys. Chem. Lett.* **2021**, *12*, 1228-1235.
3. **Prakash Panwaria** and Alope Das*, Exploring non-covalent interactions by jet-cooled electronic and vibrational spectroscopy; Book chapter in Modern techniques of spectroscopy: Basics, Instrumentation and Applications, *Springer Nature*, **2021** [ISBN 978-981-33-6083-9].
2. Moushakhi Ghosh, **Prakash Panwaria**, Srinu Tothadi, Alope Das*, and Shabana Khan*, Bis (silanetellurone) with C–H⋯Te interaction. *Inorg. Chem.* **2020**, *59*, 17811-17821.
1. Santosh Kumar Singh[‡], **Prakash Panwaria**[‡], Kamal Kumar Mishra, and Alope Das*, Sterics as well as n→π* interaction controls the conformational preferences of phenyl acetate: Gas-phase spectroscopy and quantum chemical calculations. *Chem. Asian J.* **2019**, *14*, 4705-4711 ([‡]*Equal contribution*).

Chapter 1: Introduction of $n \rightarrow \pi^*$ non-covalent interaction



Partly adapted from: **P. Panwaria** and A. Das*, Understanding the $n \rightarrow \pi^*$ non-covalent interaction using different experimental and theoretical approaches. *Phys. Chem. Chem. Phys.* **2022**, 24, 22371-22389

1.1 Non-covalent interactions

Non-covalent interactions are crucial in determining the specific structures and functions of biomolecules, drugs, supramolecular assemblies, and materials.¹⁻¹² An in-depth understanding of these non-covalent interactions is worthwhile for better drug designing and molecular recognition of drugs. Different classes of non-covalent interactions, such as hydrogen bonding,¹⁻²⁰ halogen bonding,²¹⁻²⁵ chalcogen bonding,²⁵⁻²⁹ π - π stacking,³⁰⁻³³ cation- π ,³⁴⁻³⁷ and anion- π ³⁸⁻⁴¹ interactions have been studied in the literature. Amongst all of these interactions, hydrogen bonding is ubiquitous and well-established in the literature.^{1, 2} From a natural bond orbital perspective, hydrogen bonding ($X-H\cdots Y$) is considered as delocalization of the lone pair electron density of an electronegative atom Y to the σ^* orbital of X-H bond. Hydrogen bonding is further classified into conventional and unconventional hydrogen bonding based on the electronegativity of the X and Y atoms. In the case of conventional hydrogen bonding, both X and Y atoms are strongly electronegative. On the other hand, either X or Y or both are weakly electronegative in the case of unconventional hydrogen bonding.^{14-17, 42} Another non-covalent interaction, which has become popular in recent times, is $n\rightarrow\pi^*$ interaction. This non-covalent interaction has been described below in great detail.

1.2 $n\rightarrow\pi^*$ interaction

$n\rightarrow\pi^*$ interaction, which is an orbital interaction, is quite analogous to hydrogen bonding in terms of electron density delocalization between the donor and acceptor orbitals.⁴³⁻⁴⁵ This interaction involves delocalization of the lone pair electron density of nitrogen, oxygen, and sulfur atoms to the π^* orbitals of $C=O$, $C\equiv N$, and aromatic rings.⁴³⁻⁴⁵ $n\rightarrow\pi^*$ interaction has been proven as an important non-covalent interaction due to its prevalence in polyesters, peptides, peptoids, proteins, drugs, and materials.⁴³⁻⁶⁹ However, the $n\rightarrow\pi^*$ interaction has not been appreciated much earlier by the scientific community, probably due to its weak strength and counterintuitive nature.⁴³⁻⁴⁵ This weak interaction is categorized into two classes based on the π^* orbital of the acceptor group, i.e., $n\rightarrow\pi_{Ar}^*$ and $n\rightarrow\pi_{Am}^*$ (Figure 1.1). $n\rightarrow\pi_{Ar}^*$ (aromatic) interaction involves delocalization of the lone pair electron density into the π^* orbital of the aromatic ring while the $n\rightarrow\pi_{Am}^*$ (amide) interaction is about the delocalization of the lone pair electron density into the π^* orbital of the carbonyl group. A few geometrical parameters which characterize the $n\rightarrow\pi^*$ interaction in a molecular system or a complex are the distance (d) and angle (θ and α) between the donor and acceptor groups and the pyramidalization (Δ) of the carbon atom of the acceptor group (Figure 1.1). For the $n\rightarrow\pi_{Ar}^*$ interaction, the distance from a donor atom to the center of the aromatic ring should be in the range of 2.8-3.8 Å, and the

angle between the plane containing the donor atom and the acceptor aromatic ring should be less than 90° .⁴³ The $n \rightarrow \pi^*_{Am}$ interaction follows the Bürgi-Dunitz trajectory of a nucleophilic attack to an electrophilic center. In this case, the distance (d) from the donor atom ($Y = O, N$, and S) to the carbonyl carbon, i.e., $Y \cdots C=O$ should be less than $3.2 \text{ \AA}$, and the angle $\angle Y \cdots C=O$ (θ) should be in the range of $109 \pm 10^\circ$.⁴³

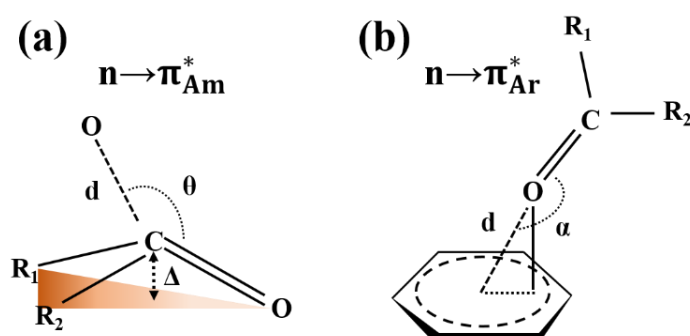


Figure 1.1. Classification of the $n \rightarrow \pi^*$ interaction with the representation of the geometrical parameters such as distance (d), angle (θ and α), and pyramidalization (Δ). Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

The $n \rightarrow \pi^*$ interaction was first observed in protopine (alkaloid) by Mottus and co-workers using UV-Vis and IR spectroscopy as well as chemical reactions.⁷⁰ Leonard and co-workers studied the $n \rightarrow \pi^*$ interaction in detail using similar approaches and laid its foundation around the same time.⁷¹⁻⁸⁵ Later, Bürgi *et al.* resurfaced the $n \rightarrow \pi^*$ interaction while studying the reaction coordinate of the nucleophilic attack on the carbonyl group.^{86, 87} Various types of $n \rightarrow \pi^*$ interaction involving nitrogen, oxygen, sulfur, and selenium atoms as $n \rightarrow \pi^*$ donors and $C=O$, $C \equiv N$, $>C=C<$, and aromatic rings as $n \rightarrow \pi^*$ acceptors have been explored in the literature.^{43, 45, 52} The prevalence of the $n \rightarrow \pi^*$ interaction in proteins and small molecules has been shown by analyzing their crystal structures in the protein data bank (PDB) and Cambridge structural database (CSD), respectively.^{63, 88} Most of the preliminary investigations on the $n \rightarrow \pi^*$ interaction involve the study on the stability of the collagen triple helix having three polyproline strands made of repeated units of $-X-Y-Gly-$, where X is proline (Pro), and Y is proline or 4(*R*)-hydroxyproline (Hyp).⁸⁹⁻⁹¹ The collagen triple helix structure is primarily stabilized due to $C=O \cdots C=O$ $n \rightarrow \pi^*$ interaction without any intrastrand hydrogen bonding. The PDB analysis shows that $\sim 34\%$ of residues of proteins involve the $C=O \cdots C=O$ $n \rightarrow \pi^*$ interaction.⁸⁸ Raines and co-workers contributed significantly to the understanding of the $n \rightarrow \pi^*$ interaction using NMR spectroscopy and quantum chemistry calculations in several molecular models containing proline derivatives. Later, Das and co-workers presented isolated

gas-phase IR spectroscopic evidence of the $n \rightarrow \pi^*$ interaction in small molecules, model peptides, and drugs.^{43, 61, 92, 93}

1.3 $n \rightarrow \pi^*$ interaction from solution-phase UV-Vis and IR spectroscopy

In 1953, Mottus and co-workers discovered the $n \rightarrow \pi^*$ interaction in protopine (Figure 1.2) comprised of two safrole rings (chromophores) separated by a ten-membered ring with a nitrogen atom and a carbonyl group and named it "*nitrogen bond*."⁷⁰ The UV-Vis spectrum of protopine showed only one absorption band, indicating the similar nature of both safrole rings, which is only possible when the carbonyl groups are not in conjugation with the safrole ring. The IR spectrum of protopine showed the absorption feature in the carbonyl region at 1658 cm^{-1} , redshifted by 32 cm^{-1} from acetophenone (1690 cm^{-1}), showing the weakening of the carbonyl bond due to $N \cdots C=O$ interaction.⁷⁰ IR spectrum of the perchlorate salt of the protopine showed transparency in the carbonyl stretching region and showed a strong absorption band in the O–H stretching region at 3385 cm^{-1} , concluding the covalent bond formation between the nitrogen atom and carbonyl carbon, resulting in the O–H bond formation (Figure 1.2). No IR absorption band was observed either in the O–H or C=O stretching region upon the treatment of protopine with methyl iodide due to the formation of the methoxy group (Figure 1.2), confirming close contact between nitrogen atom and carbonyl carbon in the ten-membered ring, i.e., $N \cdots C=O$ interaction.⁷⁰

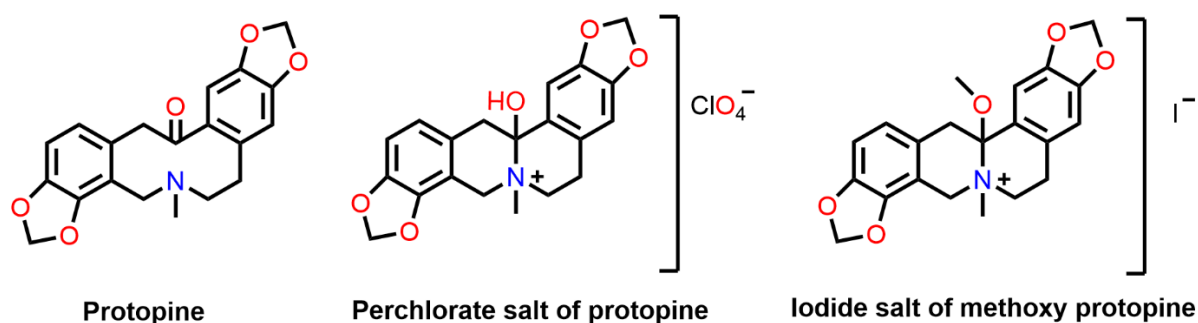


Figure 1.2. Molecular structures of protopine and its perchlorate and iodide salt. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

Leonard and co-workers studied $N \cdots C=O$ interaction using UV-Vis and IR spectroscopy and by utilizing chemical properties such as pK_a values in different solvents of cyclic aminoacylone.^{74, 76} It is a class of cyclic compounds with tertiary amine and ketone with a hydroxyl group present at the α -carbon atom of the ketone group. They also investigated 1-alkyl-1-azacyclononan-5-ol-6-ones (**1** shown in Figure 1.3) to study the steric effect on the $N \cdots C=O$ interaction.^{74, 76} They assumed that $R_1R_2R_3N \cdots C=O$ would exist as charge-separated

species like $R_1R_2R_3N^+-C-O^-$ similar to enol and acids ($R_1R_2R_3C-C=O \leftrightarrow R_1R_2R_3C^+=C-O^-$) due to the presence of the $N \cdots C=O$ interaction.⁷⁴ Hence, these molecules should also show a decrease in the pK_a values by varying the solvent from 66% dimethylformamide (DMF) to water. A similar trend in the pK_a values confirmed the presence of the charge-separated species (Table 1.1).⁷⁴ When the bulkiness of the alkyl group (Figure 1.3) was increased from methyl (**1a**) to ethyl (**1b**) and *iso*-propyl (**1c**), the $N \cdots C=O$ interaction decreased gradually. Interestingly, this interaction disappeared when the alkyl group was replaced by *tert*-butyl (**1d**), manifested by the increment in the pK_a values by varying solvent from 66% DMF to water.⁷⁴

Table 1.1. pK_a values for 1-alkyl-1-azacyclononan-5-ol-6-ones in different solvents

Compound	pK_a values in solvents		
	66% DMF	H ₂ O	ΔpK_a
1a	10.6	9.2	-1.4
1b	10.2	9.2	-1.0
1c	6.9	8.1	+1.2
1d	6.4	7.6	+1.2

The IR spectrum of the perchlorate salt of compounds **1a**, **1b**, and **1c** was found to be similar to the perchlorate salt of protopine in terms of the absence of the carbonyl stretching band and the presence of the strong absorption band of the O–H groups.^{70, 74} It was concluded that a covalent bond was formed between the nitrogen atom and carbonyl carbon ($R_1R_2R_3N^+-C-OH$ species) due to the $N \cdots C=O$ interaction in **1a**, **1b**, and **1c**.⁷⁴ However, the $N \cdots C=O$ interaction was absent in **1d** (*tert*-butyl) due to an excessive increase in the sterics, and there was no covalent bond formation between the nitrogen atom and carbonyl carbon. As a result, the IR spectrum of the perchlorate salt of **1d** showed the peak for the carbonyl stretching region.⁷⁴

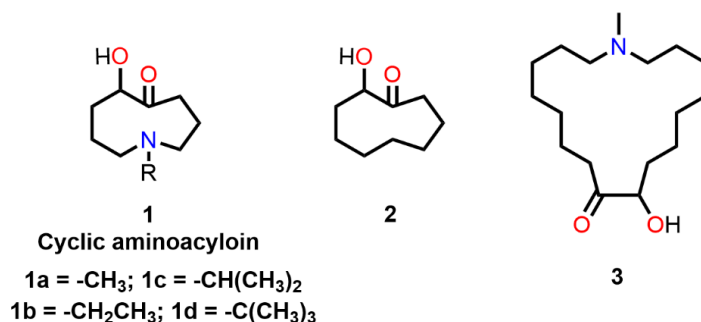


Figure 1.3. Molecular structures of **1**, **2**, and **3**. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

Leonard and co-workers further tried to find the effect of ring size on the $N\cdots C=O$ $n\rightarrow\pi^*$ interaction in cyclic aminoacyloin compounds using similar approaches. They found that a nine-membered ring is favorable for the presence of the $N\cdots C=O$ $n\rightarrow\pi^*$ interaction as the nitrogen atom and carbonyl group are diametrically opposite and have better orbital overlap (Figure 1.3).⁷¹ They used UV-Vis spectroscopy to probe the $N\cdots C=O$ interaction in the aminoacyloin compounds with respect to a reference compound, 2-Hydroxycyclononanone (**2** shown in Figure 1.3), which does not have any $N\cdots C=O$ donor and shows two bands at 217 and 264 nm in the UV spectrum.⁷⁶ On the other hand, a new electronic band was observed at 228 nm for compound **1a** having $N\cdots C=O$ interaction, while the band at 264 nm was missing.⁷⁴ When the ring size was increased to make the interaction unfavorable in 1-Methyl-1-azacycloheptadecan-9-ol-10-one (**3** shown in Figure 1.3), similar bands at 216 and 270 nm similar to compound **2** were observed in the UV-Vis spectrum.⁷⁶ UV absorption maximum (nm) for each band in molecules **1a**, **2**, and **3** are given in Table 1.2. Sarma and co-workers provided a detailed discussion of the literature reports on the $N\cdots C=O$ interaction in a series of aminoacyloin compounds studied through UV-Vis, IR, and NMR spectroscopy.⁵² The bands at 217 and 264/270 nm for compounds **2** and **3** were assigned as the $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ electronic transitions of the carbonyl group, respectively. In the case of the compound **1a**, the $n\rightarrow\pi^*$ transition band was shifted to 228 nm due to the $N\cdots C=O$ interaction, which was termed as the $n\rightarrow\pi^*$ interaction by Sarma and co-workers.⁵² Leonard and co-workers also studied the $O\cdots C=O$ and $S\cdots C=O$ type of $n\rightarrow\pi^*$ interactions.⁸¹

Table 1.2. UV absorption maxima (nm) of molecules **1a**, **2**, and **3**

Compound	Band 1	Band 2	Band 3	$n\rightarrow\pi^*$
1a	217	228	-	Yes
2	217	-	264	No
3	216	-	270	No

1.4 $n\rightarrow\pi^*$ interaction in the crystal structures of proteins and other small molecules

X-ray crystallography has become crucial in studying intra and intermolecular non-covalent interactions. The $n\rightarrow\pi^*$ interaction has also been identified by studying the crystal structures of various molecular systems in detail. Bürgi *et al.* observed the $N\cdots C=O$ short contact in the crystal structures such as cryptopine, protopine, and clivorine (Figure 1.4).⁸⁶ It follows a particular angle of $\sim 107^\circ$, and the acceptor carbon atom deviates from the plane formed by R₁, R₂, and O atoms, and the degree of deviation decreases as the $N\cdots C$ distance increases.⁸⁶

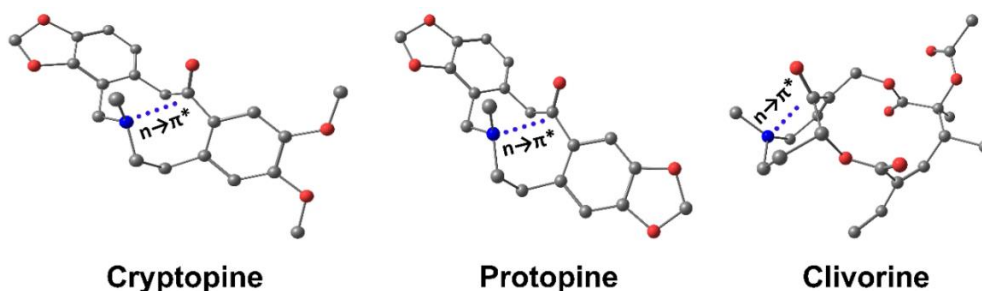


Figure 1.4. Optimized structures of cryptopine, protopine, and clivorine calculated at the B3LYP-D3/def2-TZVP level. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

The $n \rightarrow \pi^*$ interaction is present in various biologically relevant molecules such as 4S-aminoproline,⁹⁴ oligoproline,⁹⁵ poly(lactic acid),⁹⁶ homoserine lactones,⁹⁷ aspirin,^{57, 65} salicin,⁴⁷ and metal complexes.^{43, 98} Breton and co-workers studied the $n \rightarrow \pi^*$ interaction in several 2-(dimethylamino)biphenyl-2'-carboxaldehydes derivatives.⁹⁹ Wallis and co-workers observed the $N \cdots C=O$ $n \rightarrow \pi^*$ interaction in a series of 1-dimethylaminonaphthalene-8-ketones (shown in Figure 1.5a) and found that the $N \cdots C$ distance increases (Figure 1.5b) as the R group increases from methyl to *tert*-butyl.¹⁰⁰ The alkyl group pushes the electron density towards the carbonyl carbon (+I effect), reducing its electrophilicity and, ultimately, the strength of the $n \rightarrow \pi^*$ interaction.¹⁰⁰ On the other hand, when the R group is substituted by the $-\text{CF}_3$ group, $N \cdots C$ separation (Figure 1.5b) decreases, which proves that the strength of the $n \rightarrow \pi^*$ interaction increases due to the EWG at the $n \rightarrow \pi^*$ acceptor and vice-versa.¹⁰⁰

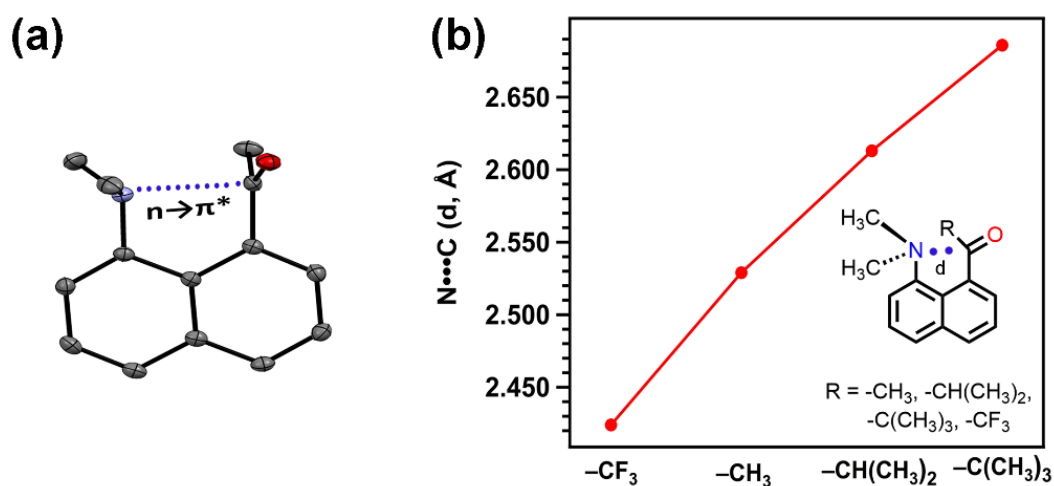


Figure 1.5. a) Crystal structure of 1-dimethylaminonaphthalene-8-ethanone; and b) Plot of the distance between the nitrogen atom and carbonyl carbon for various 1-dimethylaminonaphthalene-8-ketones in their crystal structures. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

The ubiquitous presence of the $n \rightarrow \pi^*$ interaction in the crystal structures of proteins was confirmed by the PDB survey performed by Raines and co-workers.⁴⁴ They chose a search criterion of distance ≤ 3.2 Å (sum of van der Waals radii of oxygen and carbon atoms) between the oxygen atom of the donor carbonyl group and the carbon atom of the ($O \cdots C$) acceptor carbonyl group while the angle $O \cdots C=O$ was chosen in the range of $99^\circ \leq \theta \leq 119^\circ$ (Bürgi-Dunitz trajectory) for performing the CSD and PDB analyses.⁴⁴ They found that the $n \rightarrow \pi^*$ interaction is present in 5-97% of residues of all the 1731 protein crystal structures.⁴⁴ It has also been observed that the carbonyl groups in the backbone of proteins can act as both donor and acceptor simultaneously, termed as reciprocal $n \rightarrow \pi^*$ interaction. Sarma and co-workers carried out CSD analysis for the reciprocal $n \rightarrow \pi^*$ interaction with the search parameter of $O \cdots C$ distance ≤ 3.2 Å and separation of at least three covalent bonds between the carbonyl groups (1,5 type interaction).⁶³ They found the reciprocal $n \rightarrow \pi^*$ interaction in 249 crystal structures with the $C \cdots O$ distance ≤ 3.0 Å. In 117 crystal structures, a chiral carbon atom or heteroatoms were present, similar to peptides and proteins. Out of the 2269 protein crystal structures in the protein database, 2184 structures showed reciprocal $n \rightarrow \pi^*$ interaction, and most of the crystal structures were found to be in the polyproline II (PP II) or turn regions.⁶³

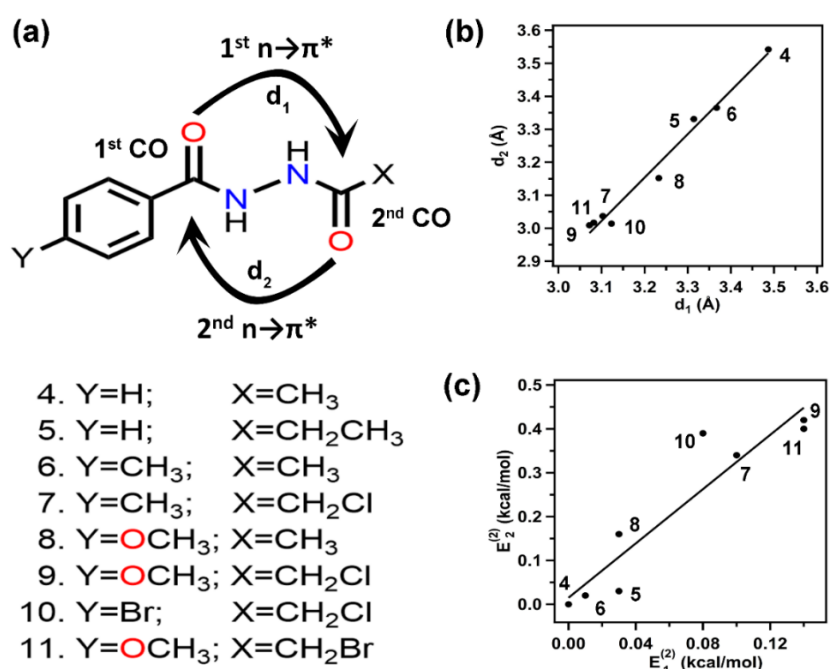


Figure 1.6. a) Various substituted N, N' -diacylhydrazines; Plots showing the correlation between b) $O \cdots C$ distances (d_1 and d_2); and c) $E^{(2)}$ energies of second and first $n \rightarrow \pi^*$ interaction in compounds 4-11. $E^{(2)}$ energies in the crystal structures are calculated from NBO analysis at the B3LYP/6-311+G(2d,p) level. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

They also studied the reciprocal $n \rightarrow \pi^*$ interaction in the substituted N, N' -diacylhydrazine.⁶³ It should be noted that both the amide bonds in the N, N' -diacylhydrazine were found in the *trans-trans* conformation. It has been found that EWG at the X position enhances the electrophilicity of the second carbonyl group and increases the first $n \rightarrow \pi^*$ interaction. Henceforth, it increases the electron donor capability of the second carbonyl; hence, the second $n \rightarrow \pi^*$ interaction also increases.⁶³ Similarly, the EDG at the Y position pushes the electron density towards the first carbonyl group, making the first $n \rightarrow \pi^*$ interaction more feasible. Figures 1.6b-c show the plots for the $O \cdots C=O$ distances and natural bond orbital (NBO) second-order perturbative energies [$E^{(2)}$], respectively, for the reciprocal $n \rightarrow \pi^*$ interactions in the compounds **4-11**.⁶³

1.5 $n \rightarrow \pi^*$ interaction from NMR spectroscopy

Collagen protein consists of three polypeptide chains, forming a right-handed triple helix. Each helical strand comprises a sequence of $(-X-Y-Gly)_n$, where X = Pro and Y = Hyp. Pro residue undergoes post-translational enzymatic modification and forms Hyp residue in the presence of the prolyl hydroxylase enzyme.¹⁰¹ Peptide bonds of Pro and Hyp residues are found in *trans* (*Z*) or *cis* (*E*) conformations (Figure 1.7). Interconversion from *trans* to *cis* conformation along the C–N bond is considered the rate-limiting step. It has been proved by studying 4(*R*)-fluoro-L-proline (Flp) and –Pro–Hyp–Gly– that stereoelectronic inductive effects at the 4-position of proline rings influence the conformation of these residues.¹⁰² NMR spectroscopy revealed the reason behind the stability of the collagen triple helix and showed that the *trans* conformation is favored due to the $C=O \cdots C=O$ $n \rightarrow \pi^*$ interaction over the *cis* conformation. The 1H NMR spectrum shows two different signals corresponding to the *cis* and *trans* conformation of the prolyl peptide bond at room temperature. The upfield shift of the 1H NMR signal corresponds to the *trans* conformation, whereas the downfield shift of the 1H NMR signal corresponds to the *cis* conformation. The integration of both signals gives the population of both conformations, which will provide the equilibrium constant ($K_{trans/cis}$) for the *cis-trans* isomerization by taking the ratio of the population of the *trans* and *cis* conformation.^{51, 103, 104} The equilibrium constant of the *cis-trans* isomerization determines the strength of the $n \rightarrow \pi^*$ interaction in the *trans* conformers as this interaction is absent in the *cis* conformation. A Van't Hoff/Eyring plot can be drawn by taking these ratios at the different values of the temperature, which can be linearly fitted in the equation given below, in order to calculate the $\Delta H^\ddagger$ and $\Delta S^\ddagger$.

$$\ln (K_{trans/cis}) = (-\Delta H^\ddagger/R)(1/T) + (\Delta S^\ddagger/R)$$

Where $-\Delta H/R$ is the slope of the linear fit, and $\Delta S/R$ is the intercept.

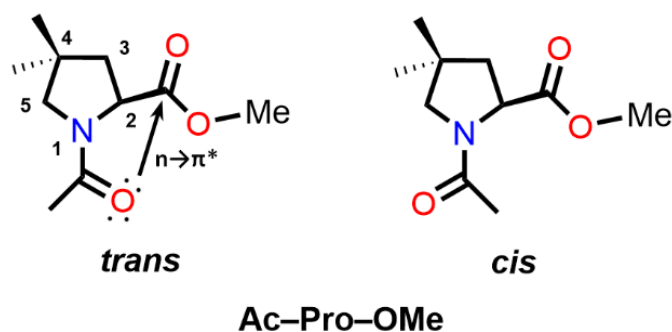


Figure 1.7. *Trans* and *cis* conformations of Ac-Pro-OMe. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

The stereoelectronic effect at the 4-position determines the *exo* and *endo* puckering of the proline ring. The *exo* puckering brings both the carbonyl groups closer in favor of the $C=O \cdots C=O$ $n \rightarrow \pi^*$ interaction, and hence, there is an increase in the $K_{trans/cis}$ ratio.¹⁰⁵ Various Ac-Yaa-OMe proline substitution has been studied to determine the stereoelectronic effect on $K_{trans/cis}$ of the proline peptide bond where Yaa is Flp, Hyp, Pro, 4(*S*)-fluoro-L-proline (flp), and 4(*S*)-hydroxy-L-proline (hyp). The order of $K_{trans/cis}$ in various Yaa proline substitutions is Flp (6.7) > Hyp (6.1) > Pro (4.6) > flp (2.5) > hyp (2.4). Melting temperature, which dictates the collagen stability, is around 45 °C for (Pro-Flp-Gly)₇ and <2 °C for (Pro-flp-Gly)₇, which can be correlated with the $K_{trans/cis}$ values of Ac-Flp-OMe and Ac-flp-OMe residues. Hence, the $K_{trans/cis}$ values, which correlate with the $n \rightarrow \pi^*$ interaction, have an important role in collagen stability. It has been proved from the NMR studies that there is little effect of the hydrogen bond in the stability of collagen due to the presence of the Hyp residue by studying Ac-Mop-OMe [Mop = 4(*R*)-methoxyproline].¹⁰⁶ The $K_{trans/cis}$ ratio of the Ac-Mop-OMe (6.7) is more than the Ac-Hyp-OMe (6.1), measured in 94:6 D₂O/CD₃OD solvent. It crystallizes in *trans* conformation with the *exo*-puckering of the proline ring.¹⁰⁶ Raines and co-workers made a seminal contribution in elucidating the nature of $n \rightarrow \pi^*$ interaction.⁵⁵ They replaced the $n \rightarrow \pi^*$ amide donor with thioamide for differentiating the charge-charge interaction with $n \rightarrow \pi^*$ interaction, as the former one will be diminished due to the less electronegative sulfur atom than the oxygen atom, and $n \rightarrow \pi^*$ interaction will be enhanced due to soft base nature of the sulfur atom.⁵⁵ Thus, the sulfur atom of thioamide serves as a better $n \rightarrow \pi^*$ donor (compounds **12** and **13** shown in Figure 1.8). The possibility of the dipole-dipole interaction was also ruled out by inducing a stereoelectronic effect at the 4*R*-position (4*S*) of the proline ring, which resulted in *exo* (*endo*) puckering and brought both the carbonyl groups close to (away from) each other (compounds **14-17** shown in Figure 1.8).⁵⁵ The $K_{trans/cis}$ ratio of various substitutions

proved that the interaction between $C=O \cdots C=O$ is due to $n \rightarrow \pi^*$ interaction, not the charge-charge or dipole-dipole interaction.⁵⁵

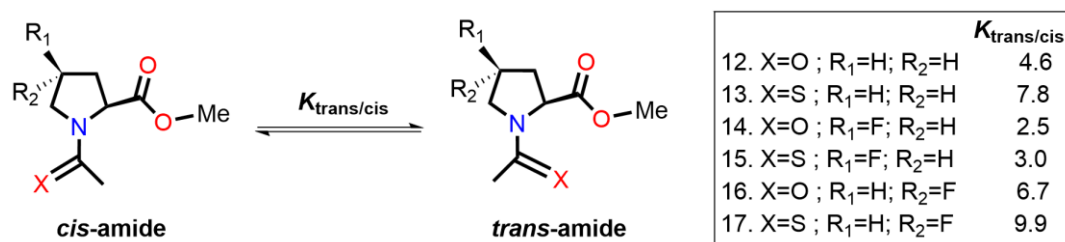


Figure 1.8. *Cis* and *trans* amide of various substituted Ac–Yaa–OMe proline. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

Raines and co-workers have also studied $n \rightarrow \pi^*$ interaction using amides as the $n \rightarrow \pi^*$ acceptor, as amino acid residues are linked with the $-C(=O)-N<$ linkage rather than $-C(=O)-O-$ linkage.¹⁰⁷ The electrophilicity of esters is more than that of amides, whereas the dipole moment of esters is less than that of amides. Greater $K_{trans/cis}$ values (Figure 1.9) for the esters than the amides suggest that $n \rightarrow \pi^*$ interaction is not dipolar; instead, it is an orbital overlap interaction.¹⁰⁷ We have discussed earlier that replacing the amide donor with the thioamide donor results in an increment in the $K_{trans/cis}$ ratio due to the enhanced orbital overlap. In the case of the amide as the $n \rightarrow \pi^*$ acceptor, a similar trend was observed by replacing the amide donor with the thioamide donor. When both the donor and acceptor were replaced by thioamide, the $K_{trans/cis}$ ratio was the highest.

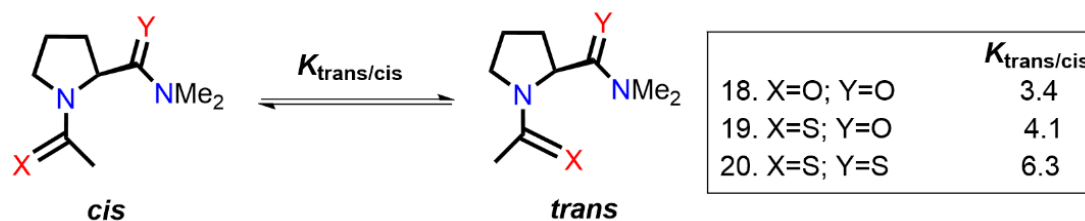


Figure 1.9. $n \rightarrow \pi^*$ interaction with $-C(=O)-N<$ as the $n \rightarrow \pi^*$ acceptor. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

So far, we discussed that the *trans* conformation is favorable in the *exo* puckering of the proline ring (Figure 1.10a). However, intramolecular hydrogen bond formation by the group at the 4*S* position with the oxygen atom of the carbonyl group of the methyl ester makes the *trans* conformation stable even in *endo* puckering of the proline ring (Figure 1.10b).^{94, 108} Hydrogen bond donating substituents at the 4*S*-position which induce the *endo* puckering of the proline ring, such as $-NH_3^+$ (5.7/3.5 in D_2O), $-NHAc$ (5.8/5.2 in $CDCl_3$), $-NHBOC$ (5.5/3.5 in $CDCl_3$), and $-OH$ (4.7/4.2 in $CDCl_3$) have more $K_{trans/cis}$ (values of 4*S*/4*R* substitution are provided in

parentheses) due to hydrogen bond. However, the $-N_3$ (1.9/3.9 in $CDCl_3$) substitution that cannot form a hydrogen-bond has lesser $K_{trans/cis}$ at the 4S-position.

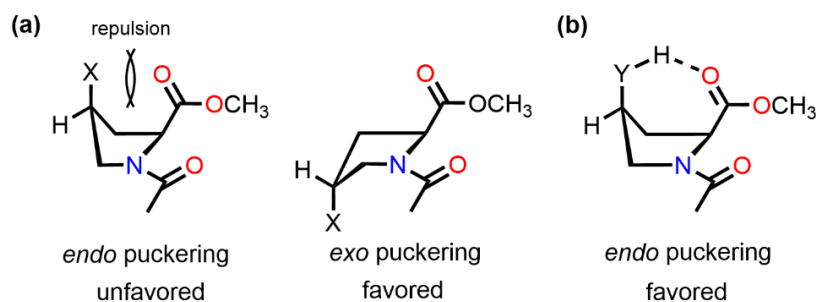


Figure 1.10. a) *Endo* and *exo* puckering in Ac-Pro-OMe; and b) Stabilization of *trans* conformation in endo puckering in Ac-Pro-OMe. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

It has been proved that the $n \rightarrow \pi^*$ interaction can dictate the conformational preference of the molecular systems. Sarma and co-workers have studied *N, N'*-diacylhydrazine, which is used as an insect growth regulator.⁶³ This compound exists in four rotameric conformations [*trans-trans* (*t-t*), *trans-cis* (*t-c*), *cis-cis* (*c-c*), and *cis-trans* (*c-t*)] based on the orientation of the amide bond. It has been discussed earlier that the *t-t* conformation of diacylhydrazines ($R_3 = R_4 = H$) is stable among others due to the reciprocal $C=O \cdots C=O$ $n \rightarrow \pi^*$ interaction (Figure 1.11a).⁶³

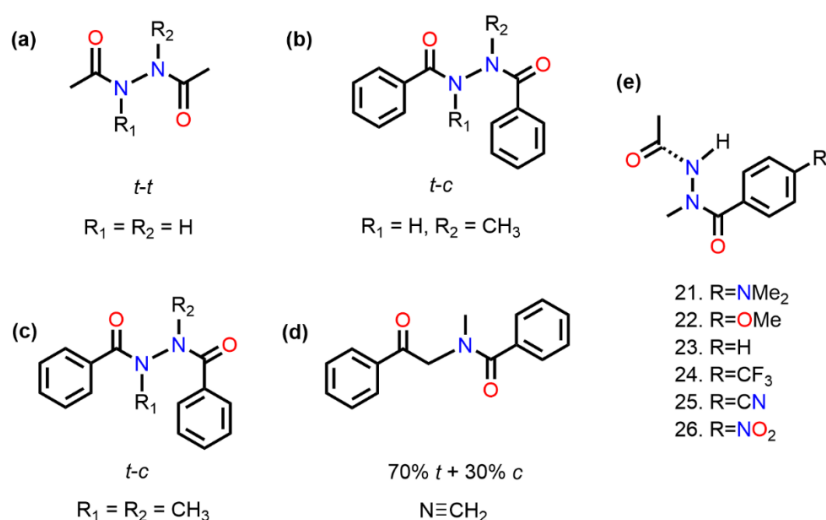


Figure 1.11. Chemical structures of various *N, N'*-diacylhydrazine. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

Meanwhile, preference for the amide bond changes drastically from *t-t* to *t-c* due to the carbon bonding ($N \cdots C-X$) interaction when one of the N-H groups is methylated.⁶³ A question

should be raised about the fate of the amide bonds on the preference of the *t-c* conformation due to the $n \rightarrow \pi^*_{Ar}$ interaction if C–X is substituted by an aromatic ring. An exclusive presence of the *t-c* conformations was observed through ^1H NMR spectroscopy and X-ray crystallography when one of the N–H groups was methylated (Figure 1.11b).⁵⁸ The probability of stabilization of these conformations due to the N–H $\cdots\pi$ hydrogen bond was ruled out when another N–H was also methylated (Figure 1.11c), and the *t-c* conformation was still favored.⁵⁸ However, when the nitrogen atom ($n \rightarrow \pi^*$ donor) was replaced by the $-\text{CH}_2$ group (Figure 1.11d), a mixture of 70% *trans* and 30% *cis* conformation was observed. Thus, the importance of the $n \rightarrow \pi^*$ interaction in stabilizing the *t-c* conformation of *N, N'*-diacylhydrazine was established.⁵⁸ Sarma and co-workers also tuned the strength of the $n \rightarrow \pi^*$ interaction by modifying various electronic substituents at the *para* position (**21–26** in Figure 1.11e) and observed the spectroscopic signature of this interaction.⁵⁸ The nitrogen atom of the $n \rightarrow \pi^*$ donor has also been found to be involved in the $-\text{NH}-\text{C}(=\text{O})-$ conjugation of the amide bond along with the $n \rightarrow \pi^*$ interaction. Hence, the increase in the strength of the $n \rightarrow \pi^*$ interaction makes the nitrogen lone pair less available for the $-\text{NH}-\text{C}(=\text{O})-$ conjugation, and thus, the N–H stretching frequency gets redshifted.⁵⁸ It has been found from the NBO analysis that the $E^{(2)}$ values of the $n \rightarrow \pi^*$ interaction decrease as the distance between the nitrogen atom and carbon increases from EWGs to EDGs (Figure 1.12a).

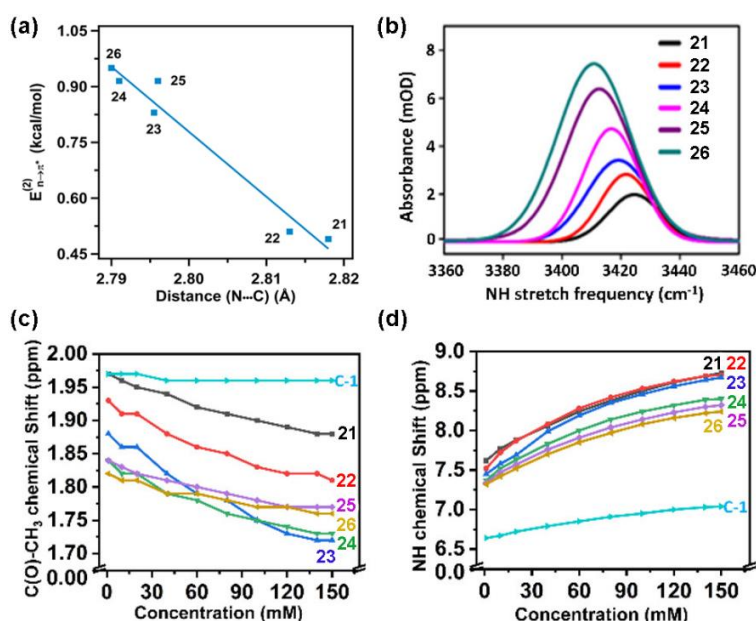


Figure 1.12. a) Plot of $E^{(2)}$ energies versus N $\cdots$ C distance of **21–26**; b) N–H stretching frequencies of **21–26**; and c-d) Plot of the chemical shift of CH_3 and NH protons versus concentration of **21–26** and acetohydrazide. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

It has been observed that the N–H stretching frequency is redshifted for the --NO_2 substituent having larger $E^{(2)}$ values of the $\text{n}\rightarrow\pi^*$ interaction (Figure 1.12b). Moving from the EWG to the EDG, the strength of the $\text{n}\rightarrow\pi^*$ interaction decreases, and thus, the N–H stretching frequency gets blueshifted.⁵⁸ From the NMR spectroscopy, the chemical shift values of the N–H and --CH_3 protons of the hydrazine compounds showed an upfield shift.⁵⁸ The conjugation in the --NH--C(=O)-- group, which decreases with the increment of the $\text{n}\rightarrow\pi^*$ interaction, weakens the anisotropic effect of the --N=C-- double bond and leads to the upfield of the chemical shift of the N–H and --CH_3 protons (Figures 12c and 12d).⁵⁸ The strength of the $\text{n}\rightarrow\pi^*$ interaction was found to increase along with the upfield shift of the --CH_3 protons, while the chances for the involvement of the N–H group in the intermolecular hydrogen bond formation were enhanced by increasing the concentration of the compound.⁵⁸ Moreover, in the ^1H NMR spectrum of acetohydrazide (lacking the $\text{n}\rightarrow\pi^*$ interaction), the absence of the upfield shift of the --CH_3 protons confirmed that the observed chemical shift of the protons in the hydrazine compounds was due to the $\text{n}\rightarrow\pi^*$ interaction.⁵⁸

1.6 $\text{n}\rightarrow\pi^*$ interaction from gas-phase studies

Heretofore, we discussed the $\text{n}\rightarrow\pi^*$ interactions studied in the solution-phase and crystal structures of several molecular systems, where perturbations arose from intermolecular interactions due to solvent or crystal packing forces affecting the strength of the $\text{n}\rightarrow\pi^*$ interaction. On the contrary, isolated gas-phase spectroscopy, free from any such perturbations arising from the surrounding environment, is an ideal means for understanding the intrinsic nature and strength of the weak $\text{n}\rightarrow\pi^*$ interaction. In the NMR spectroscopy, the $\text{n}\rightarrow\pi^*$ interaction in the *trans* conformation compared to the *cis* conformation of the proline derivatives was elucidated based on the $K_{\text{trans/cis}}$ values.^{45, 52} However, the $K_{\text{trans/cis}}$ values obtained from the NMR spectroscopy do not directly correlate with the quantitative strength of the $\text{n}\rightarrow\pi^*$ interaction. Gas-phase calculations and experiments go hand in hand to directly probe the strength and nature of this interaction. It would not be an exaggeration to say that it would be very difficult to comprehensively understand various non-covalent interactions and relative stability of different conformations of the molecules or complexes present in the experiment without quantum chemistry calculations. Thus, it is necessary to discuss the theoretical approaches generally used to understand the $\text{n}\rightarrow\pi^*$ interaction.

1.6.1 Understanding of the $\text{n}\rightarrow\pi^*$ interaction from gas-phase calculations

Quantum chemistry calculations such as natural bond orbital (NBO), quantum theory of atoms-in-molecules (QTAIM), non-covalent interaction index (NCI), and energy decomposition analysis (EDA) assist significantly in understanding the weak $n \rightarrow \pi^*$ non-covalent interaction.

1.6.1.1 Natural bonding orbital analysis (NBO)

NBO analysis¹⁰⁹ enables us to visualize the Lewis structure of the molecule by converting the delocalized molecular orbitals into localized natural bond orbitals. NBO analysis can be performed using the NBO6.0 program package to determine the second-order perturbative energy $[E^{(2)}]$ value of the $n \rightarrow \pi^*$ interaction, representing its qualitative strength.¹¹⁰ It involves delocalization of the lone pair electron density into the π^* orbital, i.e., the overlap of these two orbitals. The $E^{(2)}$ values are calculated using the equation $q_n F(n, \pi^*)^2 / (\epsilon_{\pi^*} - \epsilon_n)$, where q_n is the occupancy of the lone pair (n) orbital, $F(n, \pi^*)$ is the elements of off-diagonal Fock matrix consisting of these orbitals, and ϵ_n and ϵ_{π^*} are the diagonal elements depicting the orbital energies. Orbital overlap between the lone pair orbital and the π^* orbital can be visualized using the chemcraft visualization software.^{111, 112}

NBO analysis is also used to determine other electronic parameters, such as the occupancies of various orbitals and the Wiberg bond index (WBI) to determine the bond order of the carbonyl bond involved in the $n \rightarrow \pi^*$ interaction. WBI is calculated by the sum of squares of the off-diagonal density matrix consisting of C and O atoms of the carbonyl bond, determining the electron population overlap between them.¹¹³ NBO deletion analysis acts as confirmatory evidence for the presence of the $n \rightarrow \pi^*$ interaction. It selectively deletes the $n \rightarrow \pi^*$ interaction from a molecular system by deleting the Fock matrix elements for this interaction and again calculates the occupancies of the orbitals involved in the interaction. After deleting the $n \rightarrow \pi^*$ interaction, the lone pair and π^* orbital occupancies will increase and decrease, respectively, as there will be no delocalization of the electron density from the lone pair orbital to the π^* orbital. Natural steric analysis (NSA)^{110, 114, 115} implemented in the NBO6.0 program package was performed to determine local steric repulsion between two occupied orbitals in a molecular system. This calculation uses pairwise natural localized molecular orbitals (NLMOs) as an approximation.

1.6.1.2 Quantum theory of atoms in molecule (QTAIM)

QTAIM analysis helps in the identification of the specific non-covalent interaction present in a molecular system by generating the bond-critical points (BCPs) between the two atoms involved in the interaction.¹¹² QTAIM analysis can be performed using Multiwfn software.¹¹⁶⁻

¹¹⁸ It also generates the ring/cage critical points whenever a ring/cage is formed *via* covalent or non-covalent bonding. At the BCP, various QTAIM parameters, such as electron density [$\rho(r)$, a.u.], Laplacian of electron density [$\nabla^2\rho(r)$, a.u.], and the second eigenvalue of the Hessian matrix (λ_2 , a.u.) signify the strength of non-covalent interaction. $\rho(r)$ at the BCP determines the accumulation of electron density due to the non-covalent interaction and hence determines the strength of the interaction. The Sign of λ_2 determines whether the interaction is attractive (negative) or repulsive (positive). The numerical value of λ_2 determines the strength of the interaction. Sometimes, QTAIM analysis fails to generate the BCP for the non-covalent interaction despite its presence in the molecular systems. However, it has been proved that the absence of BCP does not guarantee the absence of the non-covalent interaction.¹¹⁹

1.6.1.3 Non-covalent interaction index (NCI)

NCI index analysis is performed using Multiwfn software.¹¹⁶⁻¹¹⁸ It offers qualitative ideas about the non-covalent interactions present in molecular systems. NCI isosurface plot follows the color code from blue to red for the attractive to repulsive interaction. At the same time, the NCI plot of the reduced density gradient (RDG) of the electron density versus [$\text{Sign}(\lambda_2)\rho(r)$] generates RDG minima for each non-covalent interaction, whether it is attractive or repulsive. RDG minima corresponding to the right side of the plot are for repulsive interaction, and RDG minima toward the left (≤ 0) are for attractive interaction. RDG minima, where both RDG and $\rho(r)$ are small, corresponds to the non-covalent interaction region.

1.6.1.4 Nature of the interaction energies of the complexes

The interaction energies of the complexes can be fragmented into several components, which helps in understanding the nature of the interaction. Absolutely localized molecular orbital energy decomposition analysis (ALMO-EDA) developed by Khaliullin *et al.*^{120, 121} and symmetry-adapted perturbation theory (SAPT)¹²² at the SAPT2+3 level using QChem 5.3 package¹²³ can be used to determine the various components of the binding energies of the complexes. ALMO-EDA decomposes the interaction energy into electrostatic interaction (ES), Pauli repulsion (REP), dispersion (DISP), polarization (POL), and charge transfer (CT) components. The SAPT decomposes the interaction energy into the ES, REP, DISP, and POL components. These analyses provide a qualitative idea about the nature of the non-covalent interaction present in the molecular complexes.

Altamirano and co-workers have reported that the $n \rightarrow \pi^*$ interaction can compete with a strong hydrogen bond and override the hydrogen bond in 3-nitrophthalic acid

(3NFAc).¹²⁴ 3NFAc is a conformationally rich molecule because of the presence of the flexible dihedral angles of nitro and carboxylic acid groups. Among a few lowest energy conformers of 3NFAc, the A1 and E1 conformers show interesting results. The NBO results obtained from the MP2/cc-pVTZ level of calculation show that the $E^{(2)}$ value for the O–H $\cdots$ O hydrogen bond in E1 is 40.75 kJ/mol, while for the $n(\text{O})\rightarrow\pi^*(\text{C}=\text{O})$ interaction in E1 is 9.58 kJ/mol. On the other hand, A1 forms dual $n\rightarrow\pi^*$ interactions having $E^{(2)}$ values of 9.62 and 10.33 kJ/mol.¹²⁴ E1 is expected to be the global minimum due to a strong O–H $\cdots$ O hydrogen bond. However, it was found that A1 is the most stable conformer, which is 9.50 kJ/mol lower in energy than E1. They explored the unusual stability of these two conformers by calculating their overall steric contributions.¹²⁴ It has been found that the E1 is engaged in steric repulsion of 64.77 kJ/mol, which is much larger than that present in the A1.¹²⁴ Thus, the relatively more significant steric repulsion present in the E1 subdues the stabilization caused by the hydrogen bond. The BCPs in 3NFAc due to the $n\rightarrow\pi^*$ interactions suggest that this interaction is strong enough in this compound. Figures 1.13 shows the QTAIM molecular graphs and NCI RDG plots displaying the $n\rightarrow\pi^*$ interactions for the conformers A1 and E1.¹²⁴

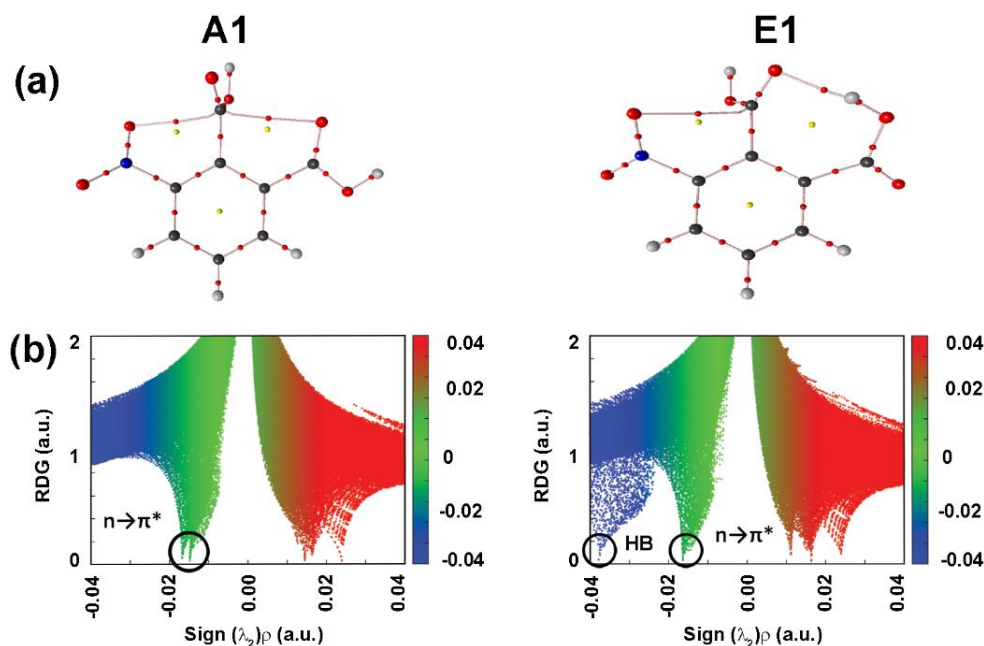


Figure 1.13. a) QTAIM molecular graphs; and b) NCI RDG plots of the A1 and E1. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

Das and co-workers studied a competition between the $n\rightarrow\pi^*$ interaction and N–H $\cdots$ N hydrogen bond in 1:1 complexes of 7-azaindole (7-AI) with 2,6 substituted fluoropyridines (FP) with the help of quantum chemistry calculations.¹²⁵ In these complexes, the nitrogen lone pair of 7-AI is delocalized into the π^* orbital of the FP ring, and the lone pair of the nitrogen

atom of the FP ring is involved in the hydrogen bond formation with the N–H group of the 7-AI. The binding energies of these complexes increase with the increase in the fluorination of the pyridine ring; hence, these results indicate the importance of $n \rightarrow \pi^*$ interaction.¹²⁵ It has been shown with the help of NBO analysis that the N–H $\cdots$ N hydrogen bond weakens with the strengthening of the $n \rightarrow \pi^*$ interaction upon increase in the fluorination of the pyridine ring.¹²⁵

1.6.2 Microwave spectroscopy

Rotational spectra of the molecules or complexes are measured with the help of microwave spectroscopy. The rotational spectra of the molecular systems provide various experimental parameters, such as rotational constants (A, B, and C) and centrifugal distortion constants (D_J , D_{JK} , D_K , d_1 , and d_2). At the same time, information obtained from the quantum chemistry calculations helps in assigning the rotational transitions observed in the rotational spectrum and determining the structures of various conformers of the molecules or complexes observed in the experiment. Thus, microwave spectroscopy is an important tool for accurately determining the structures of molecules or complexes, and various non-covalent interactions present there. Alonso and co-workers studied neurotransmitters such as β -alanine¹²⁶ and γ -aminobutyric acid (GABA),¹²⁷ biologically essential amino acids such as 4-hydroxyproline,¹²⁸ and drugs such as aspirin using microwave spectroscopy.⁶⁵ They found that the lowest energy conformers of all these molecules observed in the experiment are stabilized mostly by the $n \rightarrow \pi^*$ interaction. They also observed the $n \rightarrow \pi^*$ interaction in a Gly–Pro dipeptide.¹²⁹ Interestingly, it was found that the conformer having the $n \rightarrow \pi^*$ interaction is much more abundant than the conformer having the O–H $\cdots$ O hydrogen bond.¹²⁹ This finding shows the importance of the $n \rightarrow \pi^*$ interaction in the conformational preference of molecular systems. The conformer of the dipeptide observed in the experiment was found to have a similarity with that of the Gly–Pro unit present in the crystals of collagen mimetic peptides.¹²⁹ Pratt and co-workers have shown that the $n \rightarrow \pi^*$ interaction can fold the amino acids by bringing the $-\text{NH}_2$ and $-\text{COOH}$ groups together to form the lactam (C–N bond) by demonstrating the transformation of δ -aminovaleric acid to the δ -valerolactam (Figure 1.14).¹³⁰

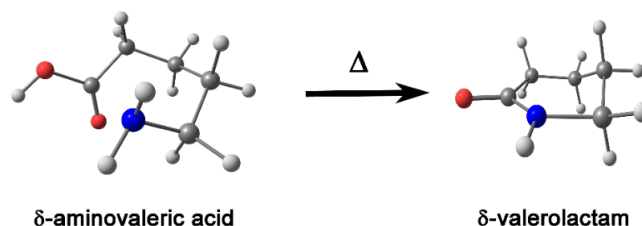


Figure 1.14. Conversion of δ -aminovaleric acid to δ -valerolactam. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

So far, we have discussed the molecular systems that have intramolecular $n \rightarrow \pi^*$ interaction, i.e., both the $n \rightarrow \pi^*$ acceptor and donor are present in the same molecule. To the best of our knowledge, the first experimental report for the observation of the intermolecular $n \rightarrow \pi^*$ interaction was presented by Kawashima and co-workers in the adducts of ethylene oxide (EO) and ethylene sulfide (ES) with carbon monoxide (CO) and carbon dioxide (CO₂).¹³¹ The oxygen lone pair of ethylene oxide/sulfide acts as the $n \rightarrow \pi^*$ donor, and the π^* orbital of CO and CO₂ acts as the $n \rightarrow \pi^*$ acceptor.¹³¹ Optimized geometries of these complexes with the $E^{(2)}$ values of the $n \rightarrow \pi^*$ interaction calculated at the B3LYP-D3/def2-TZVP level are provided in Figure 1.15. At the same time, Leopold and co-workers observed the intermolecular complex of pyridine (Py) with CO₂.¹³² They observed the planar structure of this complex (Figure 1.15) with the C₂ axis of symmetry, and no spectroscopic evidence was found for the internal rotation of the CO₂ molecule. This report was in line with the results obtained by Froudakis and co-workers using *ab-initio* calculations.¹³³

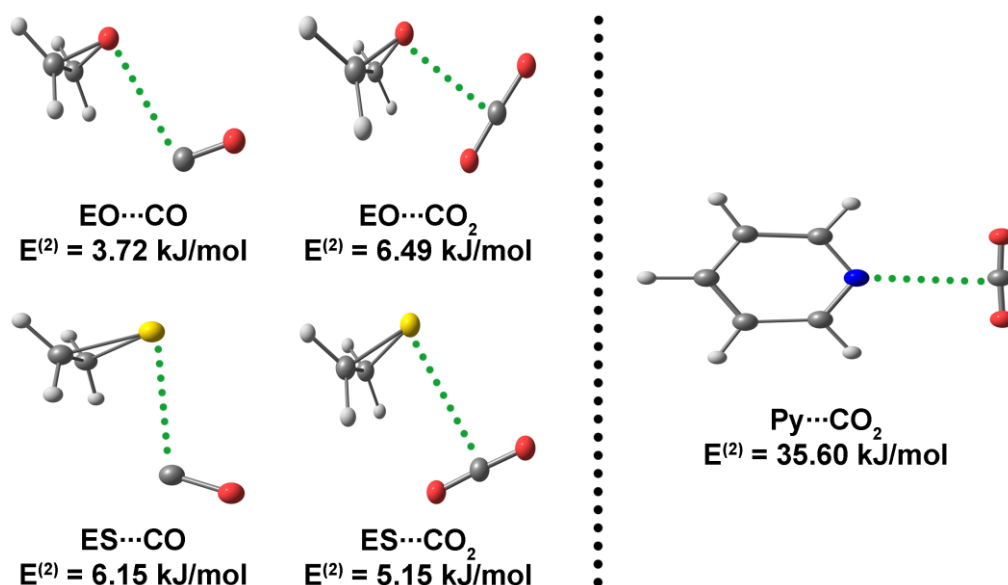


Figure 1.15. Optimized geometries of intermolecular complexes of Left panel: ethylene oxide/sulfide with CO and CO₂; and Right panel: Py...CO₂ with the $E^{(2)}$ values of $n \rightarrow \pi^*$ interaction calculated at the B3LYP-D3/def2-TZVP level.

Pate and co-workers observed the $n \rightarrow \pi^*$ interaction in β -propiolactone...(Water)₂ and β -propiolactone...(Water)₃ complexes (BPL...2W and BPL...3W) (Figure 1.16).¹³⁴ It should be mentioned that the $n \rightarrow \pi^*$ interaction is not solely responsible for stabilizing these complexes. The contribution of the $n \rightarrow \pi^*$ interaction in stabilizing the BPL complexes with water is marginal. These complexes are stabilized primarily by the O—H...O hydrogen bond (marked by blue dots) and have cooperativity effects with the $n \rightarrow \pi^*$ interaction (marked by green dots).¹³⁴

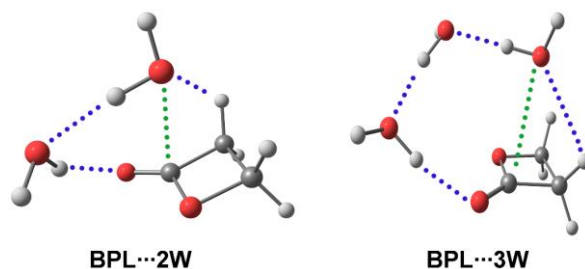


Figure 1.16. Optimized geometries of BPL...2W and BPL...3W complexes calculated at the B3LYP-D3/def2-TZVP level.

Lopez and co-workers studied complexes of pyridine with formaldehyde (HCHO), acetaldehyde (CH₃CHO), acetone (CH₃COCH₃), and butanone (CH₃CH₂COCH₃).¹³⁵⁻¹³⁷ Here, the lone pair orbital of the nitrogen atom, which is in the plane of the ring, acts as the $n \rightarrow \pi^*$ donor, while the π^* orbital of the carbonyl group acts as the $n \rightarrow \pi^*$ acceptor.¹³⁵⁻¹³⁷ Gou and co-workers studied a complex of acetophenone with CO₂ and found the dominance of the $n \rightarrow \pi^*$ interaction along with the secondary C–H(*sp*³)...O hydrogen bond.¹³⁸ They also observed the complex of benzaldehyde with HCHO. They found the presence of two conformers in a relative abundance of 3:1 with dominating $n \rightarrow \pi^*$ interaction along with a secondary C–H...O hydrogen bond.¹³⁹ Grabow and co-workers studied the HCHO complex with trifluoroacetone (CF₃COCH₃) and found an antiparallel structure in the experiment.¹⁴⁰ The $n \rightarrow \pi^*$ interaction (green dots) is a major stabilizing force in these complexes along with weak C–H...O hydrogen bond (blue dots). Optimized geometries of these complexes, along with the $E^{(2)}$ values for $n \rightarrow \pi^*$ interaction calculated at the B3LYP-D3/def2-TZVP level, are given in Figure 1.17.

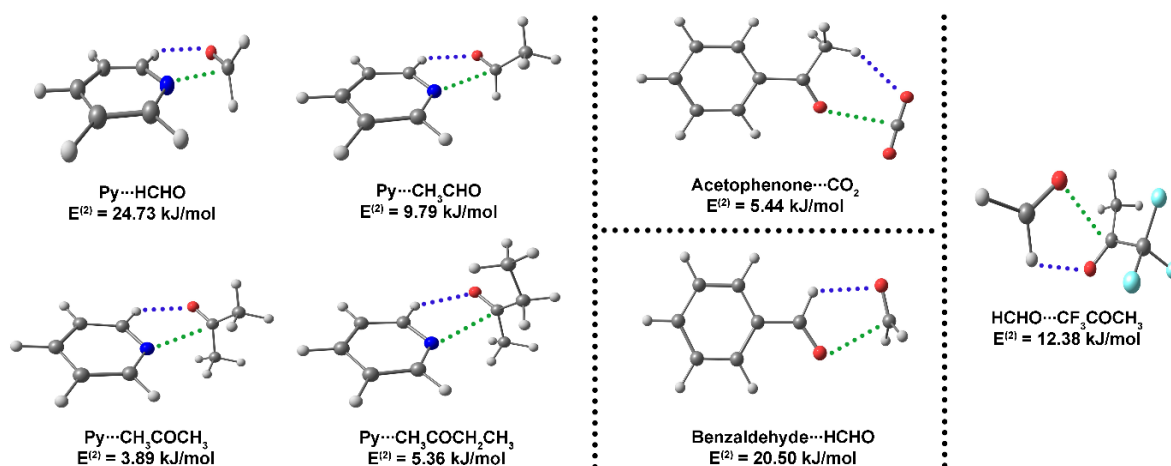


Figure 1.17. Optimized geometries of complexes of Left panel: pyridine complexes; Middle top panel: acetophenone with CO₂; Middle bottom panel: benzaldehyde with HCHO; and Right panel: HCHO with trifluoroacetone along with $E^{(2)}$ values of $n \rightarrow \pi^*$ interaction calculated at the B3LYP-D3/def2-TZVP level.

1.6.3 Electronic and vibrational spectroscopy

Microwave spectroscopy provides information about the presence and strength of the $n \rightarrow \pi^*$ interaction from the geometry of the molecules or complexes observed in the experiment. Further, mass-selective conformation-specific IR spectroscopy in the gas-phase can provide complementary information on the strength of the $n \rightarrow \pi^*$ interaction by probing the donor or acceptor groups involved in the interaction. Generally, a redshift in the vibrational frequency of the groups involved in the non-covalent interaction and enhancement in the intensity or broadening of the IR peaks indicate the presence of this interaction, especially the hydrogen bond. As the $n \rightarrow \pi^*$ interaction is generally very weak, it is not always straightforward to monitor the presence of this interaction through IR spectroscopy. In fact, there are a handful of reports of IR spectroscopy studies on the $n \rightarrow \pi^*$ interaction in the gas-phase. From our group, the indirect IR spectroscopic evidence of the weak $n \rightarrow \pi^*$ interaction was provided in the complexes of 7-azaindole...2,6-difluoropyridine (7AI...2,6-DFP) and 7-azaindole...2,3,5,6-tetrafluoropyridine (7AI...2,3,5,6TTFP) by probing the N–H stretching frequencies.⁴⁹ It is termed indirect evidence of the $n \rightarrow \pi^*$ interaction, as the N–H group is not directly involved in the interaction. In these complexes, the lone pair electron density of the nitrogen atom of the 7AI molecule is delocalized into the π^* orbital of the fluorosubstituted pyridines. At the same time, the N–H group of 7AI is hydrogen-bonded with the nitrogen atom of the pyridine ring.⁴⁹ Mass-selected electronic and conformation-specific IR spectra of these complexes were measured using the 1C-R2PI and RIDIR techniques, respectively.¹⁰ A large redshift of 265 cm^{-1} in the N–H stretching frequency was observed in the doubly hydrogen-bonded 7-azaindole...2-fluoropyridine complex (7AI...2-FP) with respect to that in the 7AI monomer (Figure 1.18a-b).⁴⁹ On the contrary, a redshift of 107 and 69 cm^{-1} in the N–H stretching frequency was observed in the 7AI...2,6-DFP and 7AI...2,3,5,6 TTFP complexes, respectively, which are stabilized by N–H...N and $n \rightarrow \pi^*$ interaction (Figure 1.18c-d).⁴⁹ The 7AI...2-FP complex is planar due to the N–H...N and C–H...N hydrogen bonds, while the N–H...N hydrogen bond in the 7AI...2,6-DFP and 7AI...2,3,5,6TTFP complexes is bent to favor for the $n \rightarrow \pi^*$ interaction.⁴⁹ The result shows the influence of the $n \rightarrow \pi^*$ interaction in governing the geometries of the complexes and the balance between the $n \rightarrow \pi^*$ interaction and N–H...N hydrogen bond.⁴⁹ The weakening of the N–H...N hydrogen bond and, thus, the reduction in the IR redshift in the N–H stretching frequency is affected by the presence of the $n \rightarrow \pi^*$ interaction.⁴⁹

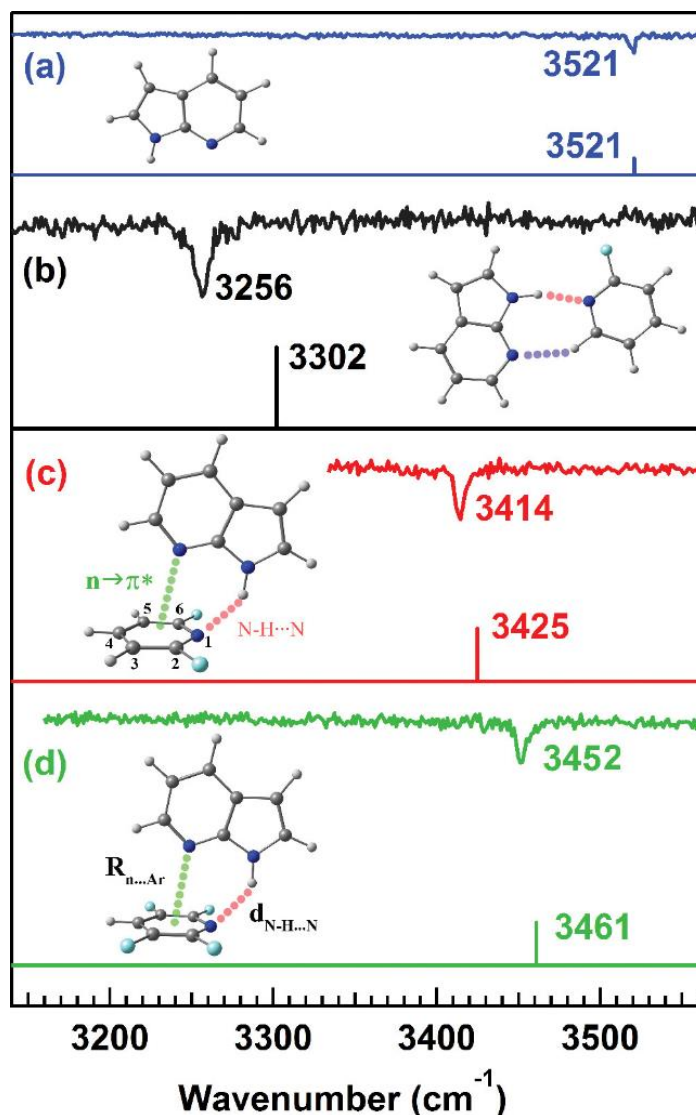


Figure 1.18. IR spectra of a) 7AI monomer; b) 7AI...2-FP complex; c) 7AI...2,6-DFP complex; and d) 7AI...2,3,5,6-TTFP complex in the N–H stretching frequency region with the stick spectra calculated at the M05-2X/cc-pVTZ level. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

Later, they also provided direct spectroscopic evidence of the $n \rightarrow \pi^*$ interaction by probing the carbonyl stretching frequency of phenyl formate in the gas-phase.⁹² Two conformers of phenyl formate were observed in the experiment. *Cis*-phenyl formate having the $n \rightarrow \pi^*$ interaction between the lone pair electrons on the oxygen atom of the carbonyl group and the π^* orbital of the phenyl ring is more stable by 5.52 kJ/mol than *trans*-phenyl formate lacking the $n \rightarrow \pi^*$ interaction.⁹² The gas-phase IR spectra (Figure 1.19) show that the carbonyl stretching frequency in *cis*-phenyl formate was redshifted by 31 cm^{-1} compared to *trans*-phenyl formate.⁹² The observed redshift in *cis*-phenyl formate was interpreted due to the $n \rightarrow \pi^*$ interaction (Figure 1.19) in the *cis* conformer as well as a subtle difference in various

hyperconjugative interactions involving the carbonyl group in both the conformers.⁹² A similar amount of redshift in the carbonyl stretching frequency of *cis*-phenyl formate with respect to that in *trans*-phenyl formate was also reported from 2D IR spectroscopy experiments.¹⁴¹

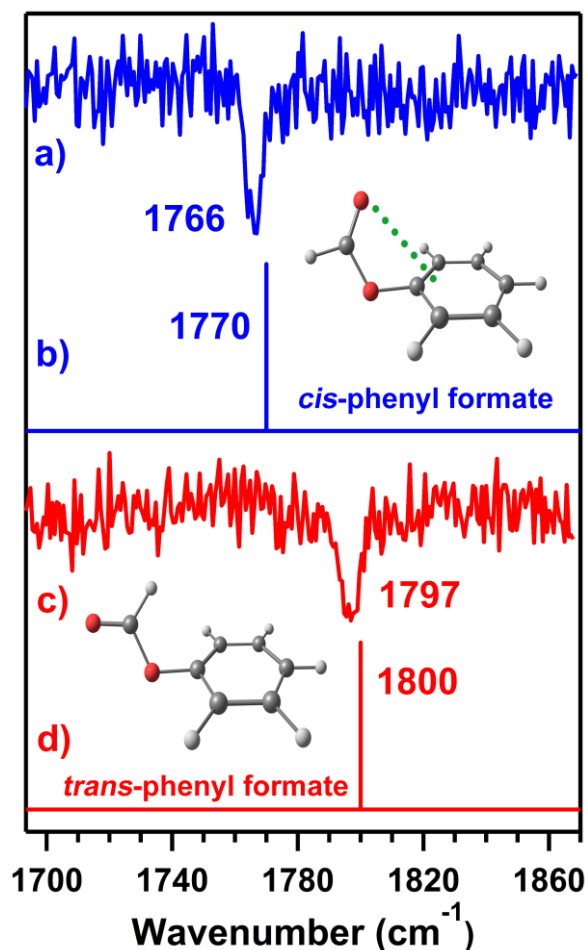
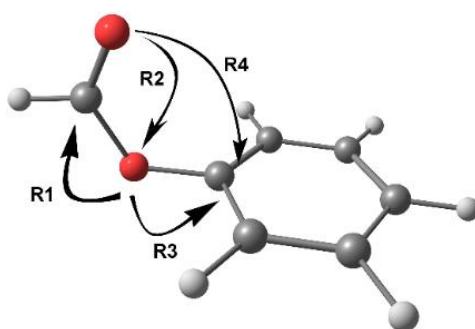


Figure 1.19. IR spectra of a) *cis*-phenyl formate; c) *trans*-phenyl formate; theoretical IR spectra of b) *cis*-phenyl formate; and d) *trans*-phenyl formate calculated at the M05-2X/aug-cc-pVDZ level. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.



Scheme 1.1. Arrow representation of various hyperconjugative interactions in one of the conformers of phenyl formate. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

Various hyperconjugative interactions present in phenyl formate have been shown in Scheme 1.1 by arrow representation, and the $E^{(2)}$ values in both the conformers are provided in Table 1.3.⁹² The R1 interaction, which reduces the carbonyl stretching frequency, involves the delocalization of the electron density mostly from the lone pair orbital of the etheral oxygen atom to the σ^* and π^* orbitals of the carbonyl group.⁹² However, there was also a relatively small contribution to the R1 interaction by the delocalization of the electron density from the σ orbital of the C–H bond to the σ^* orbitals of the carbonyl group. The R2 interaction augments the carbonyl stretching frequency by delocalizing the electron density from the lone pair orbital of the carbonyl oxygen atom to the σ^* orbital of the O–C and C–H bonds.⁹² The R3 interaction, which involves the delocalization of the lone pair electron density on the etheral oxygen atom to the σ^* and π^* orbitals of the aromatic ring, opposes the R1 interaction and hence favors the increase in the carbonyl stretching frequency.⁹² It can be found from Table 1.3 that the R1, R2, and R3 values are favorable for reducing carbonyl stretching frequency in the *cis* conformer compared to the *trans* conformer. The $n \rightarrow \pi^*$ interaction (R4), which is present only in the *cis* conformer, was found to be 4.69 kJ/mol from the NBO calculations.⁹²

Table 1.3. $E^{(2)}$ values in kJ/mol of various hyperconjugative interactions in the *cis* and *trans* conformers of phenyl formate, calculated at the M05-2X/aug-cc-pVDZ level

	Phenyl formate	
	<i>cis</i>	<i>trans</i>
R1	277.57	206.27
R2	296.48	302.13
R3	127.24	152.42

It should be noted here that the hyperconjugative interactions are quite larger than the $n \rightarrow \pi^*$ interaction. In contrast, the hyperconjugative interactions are present in both the conformers and the $n \rightarrow \pi^*$ interaction is present only in the *cis* conformer. While it is not straightforward to normalize the NBO values for different types of hyperconjugative interactions, it can be concluded that both hyperconjugative and $n \rightarrow \pi^*$ interactions contribute to the observed redshift in the carbonyl stretching frequency of *cis*-phenyl formate compared to *trans*-phenyl formate. Further, with the help of the NBO deletion, it has been shown that the hyperconjugative interactions, which favor the redshift in the carbonyl stretching frequency of *cis*-phenyl formate, are affected by $n \rightarrow \pi^*$ interaction.⁹² Table 1.4 shows the occupancy of the *p*-type lone pair on the carbonyl oxygen after the deletion of various interactions present in the

cis conformer. Occupancy of the donor and acceptor orbitals increases and decreases upon deletion of the interaction, respectively. Herein, we will be discussing specifically the effect of deletion of individual R2 and R4 interactions as well as both of those together, as these two interactions involve the delocalization of the lone pair electron density of the carbonyl oxygen. It can be noticed from Table 1.4 that the occupancy of the *p*-type lone pair on the carbonyl oxygen increases when R4 is deleted (Case II) in *cis*-phenyl formate, and this data confirms the presence of this interaction. It should be noted here that the occupancy on the carbonyl oxygen atom increases while both the R2 and R4 interactions are deleted with respect to the deletion of only the R2 interaction. It shows that the presence of the R4 interaction reduces the availability of the lone pair electron density for the R2 interaction, which is favorable for the redshift in the carbonyl stretching frequency.⁹²

Table 1.4. Occupancy of the *p*-type lone pair of the carbonyl oxygen after deleting various interactions in the *cis* conformer of phenyl formate calculated from the NBO deletion analysis at the M05-2X/aug-cc-pVDZ level

	Interactions	<i>cis</i> -phenyl formate
Case I	R1, R2, R3, R4 (Not deleted)	1.845
Case II	R4 (Deleted)	1.846
Case III	R2, R4 (Deleted)	1.988
Case IV	R2 (Deleted)	1.987

Das and co-workers also observed this interaction in a drug called salicin, which is an analogue of aspirin.⁴⁷ The chemical name of aspirin is 2-(hydroxymethyl)phenyl β -D-glucopyranoside, which is used as an analgesic, antipyretic, and anti-inflammatory drug.⁴⁷ Three conformers of salicin were observed in the gas-phase experiments using UV-UV hole-burning spectroscopy. Structural assignment of the experimentally observed conformers of salicin was done by recording their IR spectra in the O–H stretching frequency region and calculating their Franck-Condon spectra.⁴⁷ It can be noticed that all three conformers differ mostly in the orientation of the hydroxyl group of the –CH₂OH of the glucopyranoside ring (Figure 1.20). Here, the electron density of the lone pair orbital of the benzylic oxygen atom delocalizes into the π^* orbital of the aromatic ring. The strength of the $n \rightarrow \pi^*$ interaction calculated from the NBO analysis was almost similar in all three conformers (~ 4.75 kJ/mol).⁴⁷ It should be mentioned here that all three conformers of salicin have a subtle interplay with the hydrogen-bonding interaction of strength ~ 37.50 kJ/mol.⁴⁷

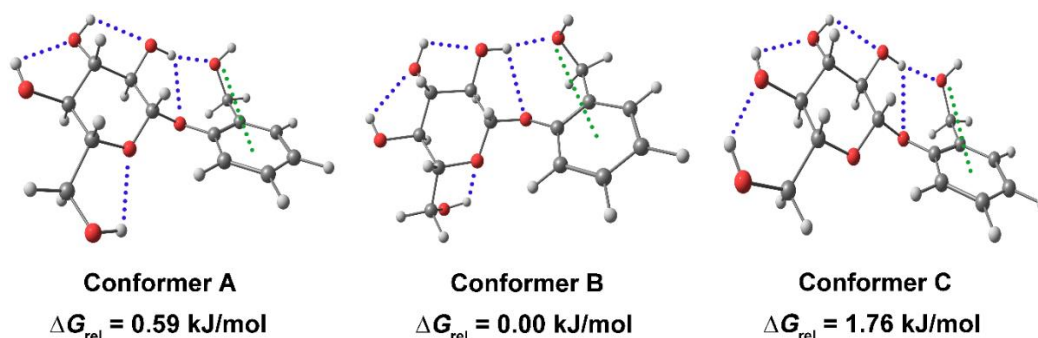


Figure 1.20. Experimentally observed conformers of salicin with their relative Gibbs free energies at the 10 K calculated at the M06-2X/6-311++G(d,p) level. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

They further studied capped 4*R*-hydroxyproline (2*S*,4*R*)-*N*¹-(benzyloxycarbonyl)-4-hydroxyproline methyl ester (Cbz-Hyp-OMe) and observed the presence of the C=O...C=O $n \rightarrow \pi^*$ interaction in the *trans* conformer.⁹³ Figure 1.21 shows the classification of its conformers in four different groups (P, Q, R, and S) based on the orientation of the amide bond and the benzene ring with their relative Gibbs free energies at 298 K with respect to global minimum conformation (I-*t*). This classification is also based on the *exo* and *endo* puckering of the proline ring. The structures of all the conformers are calculated at the M05-2X/aug-cc-pVDZ level.⁹³ Four conformers of the capped hydroxyproline were observed in the experiment using UV-UV hole-burning spectroscopy.⁹³ Two of these conformers were assigned as *trans* and another two as *cis* based on the IR stretching frequencies of the carbonyl groups (Figure 1.22a) and O-H group (Figure 1.22b).⁹³ The theoretical IR spectra of a few low energy conformers are provided with the experimental IR spectra presented in Figure 1.22. It can be observed that the conformers A and C have a similar carbonyl stretching frequency (amide and ester). However, conformer C shows a 35 cm⁻¹ redshift in the O-H stretching frequency with respect to conformer A. The carbonyl stretching frequencies of the conformers B and D are similar but different compared to the carbonyl stretching frequencies of the conformers A and C. Similarly, the O-H stretching frequency of the conformer D is redshifted by 34 cm⁻¹ with respect to the conformer B.⁹³ Thus, the O-H group in the conformers C and D are hydrogen-bonded while it is free in the conformers A and B. Further, the amide carbonyl ($n \rightarrow \pi^*$ donor) stretching frequency of the conformers A and C is redshifted by 14 cm⁻¹ from the conformers B and D. Similarly, the ester carbonyl stretching frequency ($n \rightarrow \pi^*$ acceptor) of the conformers A and C is redshifted by 5 cm⁻¹ from the conformers B and D.⁹³ Each of the experimentally observed conformers is assigned by more than one structure of Cbz-Hyp-OMe obtained from

the calculations due to the similarity in their energetics and IR stretching frequencies (Figure 1.22).⁹³

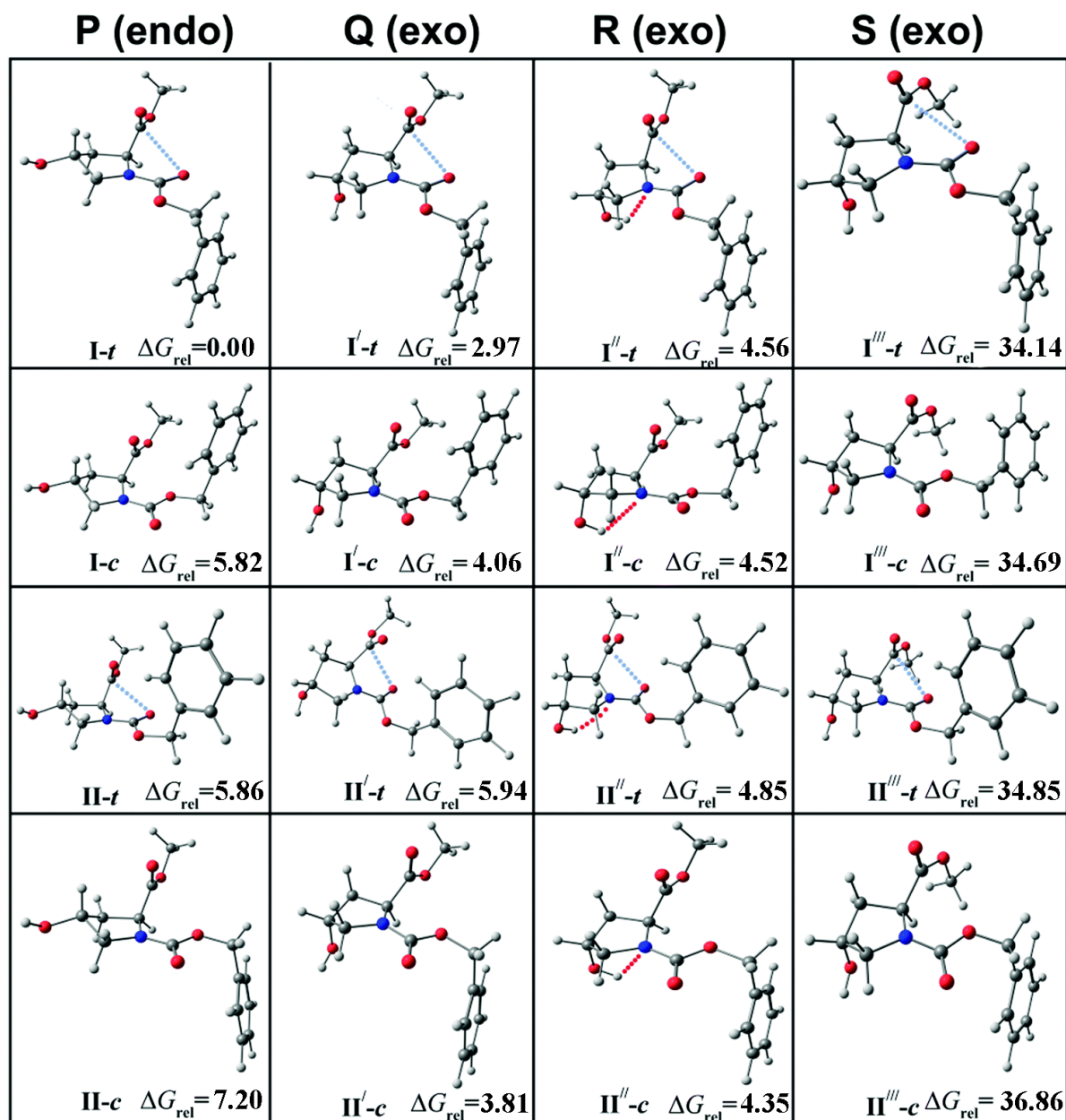


Figure 1.21. Optimized geometries of low-energy conformers of Cbz–Hyp–OMe calculated at the M05-2X/aug-cc-pVDZ level with the relative Gibbs free energies (ΔG_{rel} , kJ/mol) of various conformers at a temperature of 298 K with respect to the most stable conformer (I-t). “t” stands for *trans* and “c” stands for *cis*. Change in the orientation of the amide bond generates *trans* and *cis* conformers. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

The IR spectroscopy results, along with NBO analysis, demonstrate that the observed redshifts in the amide and ester carbonyl stretching frequencies in the conformers A and C are

due to the presence of the $n \rightarrow \pi^*$ interaction as well as the hyperconjugative interactions involving the carbonyl groups present there.⁹³

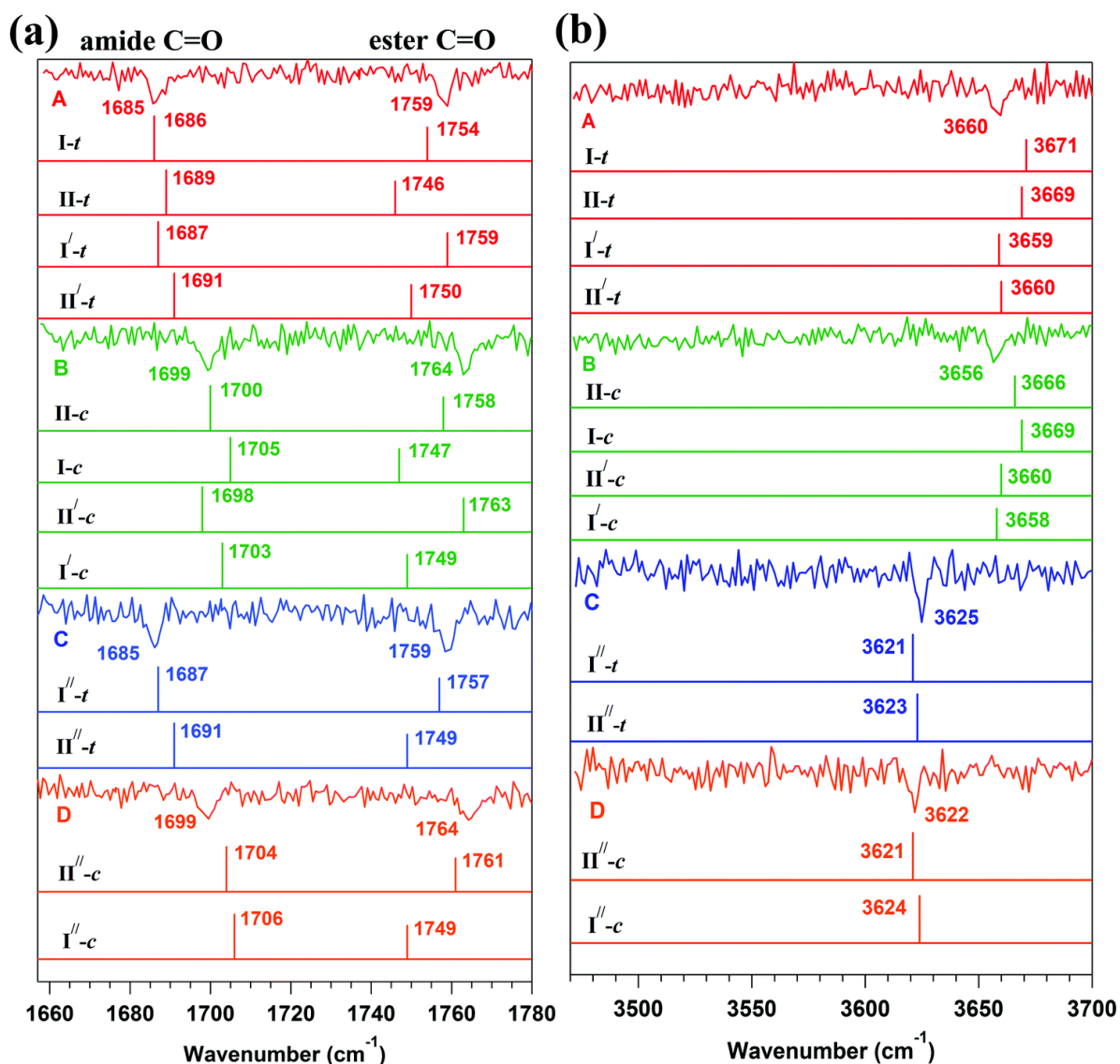


Figure 1.22. Experimental RIDIR spectra of conformers A, B, C, and D in the a) C=O; and (b) O–H stretching frequency regions with the theoretical stick IR spectra of groups P, Q, and R structures of Cbz–Hyp–OMe shown in Figure 1.21 calculated at the M05-2X/aug-cc-pVDZ level. I-t, II-c, etc., correspond to *trans* and *cis* conformers of Cbz-Hyp-OMe. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

The strength of the $n \rightarrow \pi^*$ interaction present in the *trans* conformers of the capped hydroxyproline is ~ 8.5 kJ/mol.⁹³ It was found that the $n \rightarrow \pi^*$ interaction in the *trans* conformers reduces the lone pair electron density of the amide carbonyl oxygen and thus enhances the hyperconjugation effect $R1_{amide}$, which favors the redshift in the amide carbonyl stretching frequency.⁹³ The $R1_{amide}$ interaction is about the overlap between the lone pair orbitals on the

etheral oxygen and nitrogen atom in the proline ring with the σ^* and π^* orbitals of the amide carbonyl group.⁹³ The overlap between the oxygen lone pair orbital on the amide carbonyl with the σ^* orbitals of the neighboring C–O and C–N bonds is termed $R2_{amide}$ interaction.⁹³ The $R1_{ester}$ and $R2_{ester}$ interactions involve the overlap between the lone pair orbital of the neighboring oxygen atom with the σ^* and π^* orbitals of the ester carbonyl group, while the $R2_{ester}$ interaction is about the overlap between the oxygen lone pair electrons on the ester carbonyl group and the σ^* orbitals of the neighboring C–O bond, respectively.⁹³ It can be noticed from Figure 1.23 that the $E^{(2)}$ values for $R1_{amide}$ are more for the *trans* conformers (having $n \rightarrow \pi^*$ interaction) than that for the *cis* conformer (lacking $n \rightarrow \pi^*$ interaction). It should also be noted here that the values for $R2_{amide}$, $R1_{ester}$, and $R2_{ester}$ are almost similar for the *trans* and *cis* conformers of the capped hydroxyproline.⁹³

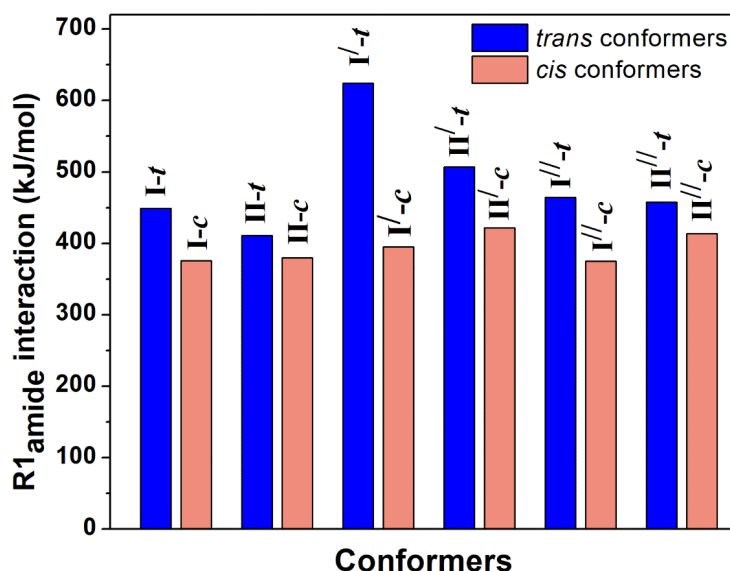


Figure 1.23. Bar diagram of $E^{(2)}$ values of $R1$ interaction for amide carbonyl group in *trans* and *cis* conformers of Cbz-Hyp-OMe calculated at the M05-2X/aug-cc-pVDZ level. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

1.7 Importance of the $n \rightarrow \pi^*$ interaction

Very recently, it has been demonstrated that the $n \rightarrow \pi^*$ interaction can have potential applications in different areas. These applications are discussed briefly in this section to establish the importance of this non-covalent interaction. One of the applications of the $n \rightarrow \pi^*$ interaction has been found in dynamic covalent chemistry, which has been utilized previously for studying the $C-H \cdots \pi$ and $\pi \cdots \pi$ stacking interactions.^{142, 143} You and co-workers studied the modulation of reactivity in a series of reactions of 2-X-2'-formylbiphenyl [1(X); X = OMe,

SMe, NMe₂, H, F, Cl, Br, and I] with an amine (Figure 1.24) to form imines [2(X)] by exploiting the $n \rightarrow \pi^*$ interaction present there between the lone pair electrons on the heteroatom of the X group and the CHO.¹⁴⁴ The formation of the imine molecules is stabilized by the $n \rightarrow \pi^*$ interaction as the electron density over imine carbon enhances and stabilizes the imine bond.

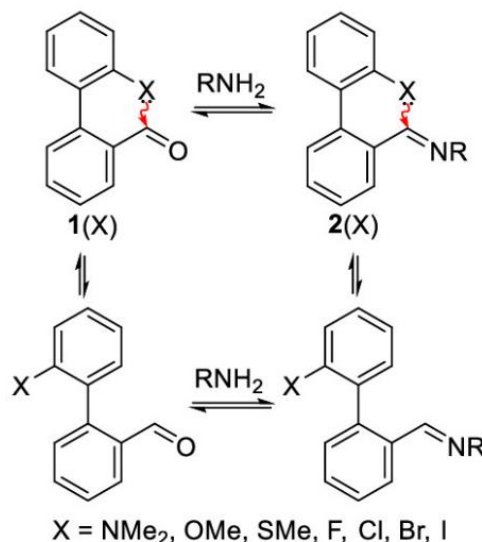


Figure 1.24. Representation of dynamic imine chemistry. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

Furthermore, You and co-workers studied the aldehyde exchange in the reaction of imine and aldehyde to understand the impact of the $n \rightarrow \pi^*$ interaction.¹⁴⁴ $n \rightarrow \pi^*$ interaction feeblies the nucleophilic attack of water on the imine [2(X)] by reducing its electrophilicity. It was found that the aldehyde exchange process in the step-wise formation of imine [2(X)] followed by the addition of aldehyde [1(H)] was prolonged. However, this exchange process (Exchange 1 shown in Figure 1.25a) was extremely fast when both the aldehydes [1(X) and 1(H)] were added simultaneously. The slow aldehyde exchange process was attributed to the absence of water molecules in the reaction environment, and this was confirmed by performing the kinetics in CD₃CN (180 days), 95:5 CD₃CN/D₂O (100 days), and 90:10 CD₃CN/D₂O (55 days).¹⁴⁴ However, this reaction was completed within one day when both the aldehydes [1(X) and 1(H)] were reacted simultaneously. To concretize the role of the $n \rightarrow \pi^*$ interaction (through space interaction shown in Figure 1.25c), they studied three sets of exchange reactions for different *p*-substituted imines and *p*-substituted aldehydes (Figure 1.25a).¹⁴⁴ It was found that the log K values for the exchange 2 type reactions (Figure 1.25b) were nearly zero for all the derivatives. It shows the undeniable role of the $n \rightarrow \pi^*$ interaction in the aldehyde exchange. NBO analysis corroborated these results as the relative Gibbs free energy values of aldehyde exchange showed a linear correlation with the $E^{(2)}$ values of the $n \rightarrow \pi^*$ interaction.

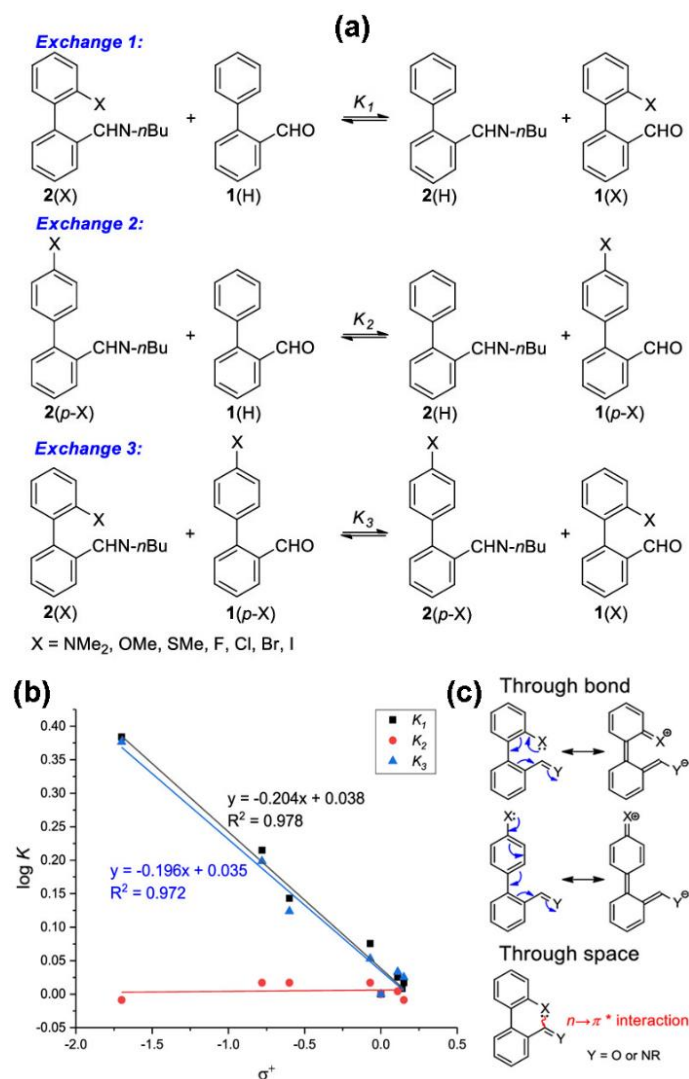


Figure 1.25. a) Different aldehyde exchange mechanisms; b) Plot of $\log K$ versus the σ^+ ; and c) representations of through space ($n \rightarrow \pi^*$ interaction) and through bond (resonance effect). Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

Raines and co-workers showed the role of the $n \rightarrow \pi^*$ interaction in the catalysis of hydrolysis of the Michaelis complex by HIV-1 protease.⁶⁸ Herein, Asp25 of one monomer abstracts the proton of the water molecule and attacks the carbonyl carbon of the scissile peptide bond. The oxygen atom of the same carbonyl group abstracts a proton from another Asp25' monomer, resulting in the regeneration of Asp25 and the formation of a gem-diol intermediate (Figure 1.26). There is a weak $n \rightarrow \pi^*$ interaction (2.76 kJ/mol) in the Michaelis complex, and the formation of a tetrahedral intermediate (gem-diol), upon attack of the water molecule, which is stabilized by stronger $n \rightarrow \pi^*$ interaction (8.41 kJ/mol).⁶⁸ $n \rightarrow \pi^*$ interaction assists in delocalizing the negative charge developed upon the attack of water molecules and helps in catalysis.⁶⁸

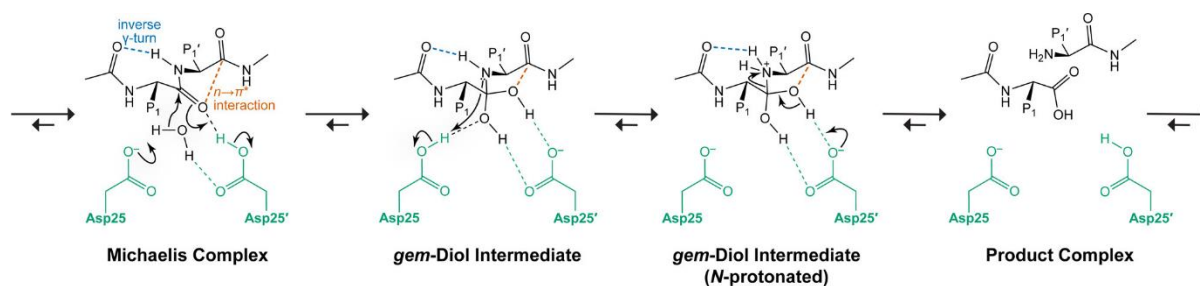


Figure 1.26. Mechanism of catalysis by HIV-1 protease. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

Shimizu and co-workers showed the utilization of the $n \rightarrow \pi^*$ interaction in stabilizing the transition state of the rotation of the $C_{aryl}-N_{imide}$ bond in N-phenylimide molecular rotors (Figure 1.27), resulting in the existence of these rotors in *syn* and *anti* conformers.¹⁴⁵

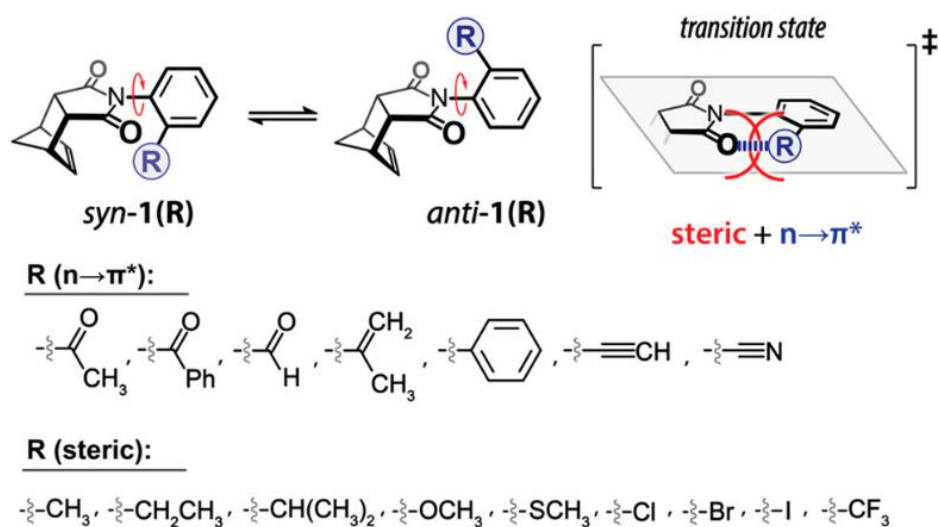


Figure 1.27. Equilibrium of *syn-anti* conformers of molecular rotors arising due to N-phenyl ring rotation. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

They measured the energy barrier of interconversion using ^1H NMR exchange spectroscopy in the temperature range of -60 to 130°C to obtain distinct peaks corresponding to *syn* and *anti* forms.¹⁴⁵ The free energy for the rotational barriers was calculated with the help of Eyring plots, which provided the enthalpy and entropy for the molecular rotors. There was a decrease in the energy barrier for the interconversion of the *syn-anti* forms when the $n \rightarrow \pi^*$ interaction was found between the oxygen atom of the imide and the π^* orbital involving the *ortho* group of the aromatic moiety (Figure 1.28a).¹⁴⁵ These energy barriers were further compared with the rotors lacking the acceptor π^* orbital (Figure 1.28a). Moreover, they took special care to maintain the bulkiness/sterics of the *ortho* group while comparing the different rotors with or without the acceptor π^* orbital.¹⁴⁵ A good linear correlation of the plot of energy

barrier versus steric values (B) for the R group (calculated from the Mazzanti's steric B-value parameter)^{146, 147} was observed for the rotors lacking $n \rightarrow \pi^*$ interaction where only steric effects were present and named it as steric trendline shown in Figure 1.28a.¹⁴⁵ The energy barrier is lowered from the steric trendline for the rotors having the π^* orbital in the *ortho* group, forming the $n \rightarrow \pi^*$ interaction, deviating from the steric trendline.¹⁴⁵ Moreover, for the rotors having the carbonyl group, the energy barrier is very low as the carbonyl group is polar and acts as a better acceptor for the electron density. The NBO orbital overlap for the $n \rightarrow \pi^*$ interaction in the transition state for one of the molecular rotors is shown in Figure 1.28b.¹⁴⁵

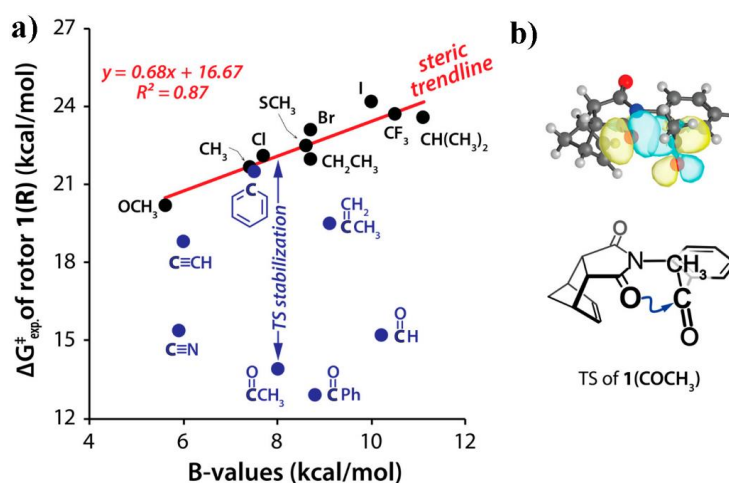


Figure 1.28. a) Rotational barriers for various rotors vs B-values of the R groups. Blue and black circles correspond to the rotors that can form $n \rightarrow \pi^*$ interactions and cannot form $n \rightarrow \pi^*$ interactions, respectively. b) NBO overlap for $n \rightarrow \pi^*$ interactions in the calculated TS (B3LYP-D3/6-311G*) of 1(COCH₃) and the ChemDraw presentation of TS (blue arrow shows $n \rightarrow \pi^*$ interaction). Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

Furthermore, they performed the NBO analysis of the transition states of the molecular motors at the ω B97M-V/6-311G* level.¹⁴⁵ They found a linear correlation of the experimentally calculated rotational barriers with the $E^{(2)}$ values of the $n \rightarrow \pi^*$ interaction (Figure 1.29a).¹⁴⁵ The overall results suggest that the $n \rightarrow \pi^*$ interaction stabilizes the transition states. A linear correlation was also observed in the plot of the rotational barrier with the distance between the oxygen atom ($n \rightarrow \pi^*$ donor) and the acceptor carbon atom of the π^* orbital (Figure 1.29b).¹⁴⁵ This observation confirms that the orbital-orbital overlap stabilizes the transition states of the molecular rotors increases.¹⁴⁵ They also observed the pyramidalization of the acceptor carbon atom, which is a signature of the presence of the $n \rightarrow \pi^*$ interaction. Hence, these rotors were successfully employed to lower the rotational barrier by ~ 9 kcal/mol.¹⁴⁵

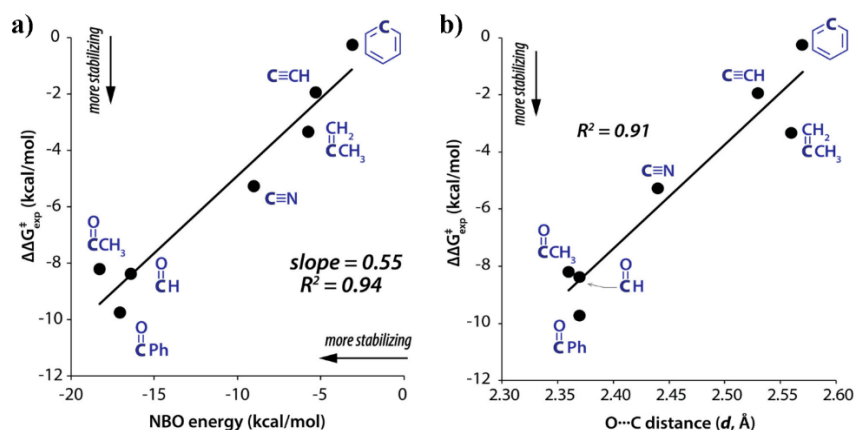


Figure 1.29. Rotational barriers for various rotors versus a) calculated NBO energies for the TS $n\rightarrow\pi^*$ interaction; and b) calculated donor-to-acceptor distance (d) in the TS, calculated at the $\omega\text{B97M-V/6-311G}^*$ level. Reproduced from Ref. 62 with permission from the Royal Society of Chemistry.

1.8 Aim of the thesis

As mentioned earlier, molecular-level understanding of the $n\rightarrow\pi^*$ interaction is more meaningful in the isolated gas-phase than in the solution-phase, as the environment perturbs this interaction in the latter case. However, reports on the $n\rightarrow\pi^*$ interaction using isolated gas-phase IR spectroscopy are scarce in the literature. Earlier from our group, the prevalence of the $n\rightarrow\pi^*$ interaction has been shown in several molecular systems, such as small molecules, drugs, and model peptides, and IR spectroscopic evidence has been presented.^{47, 49, 92, 93, 125} We continued advancing our understanding of the $n\rightarrow\pi^*$ interaction. In this thesis, we mainly focussed on the tuning of the strength of the $n\rightarrow\pi^*$ interaction by varying the electron density at the $n\rightarrow\pi^*$ donor or acceptor. We also aimed for the observation of the intramolecular and intermolecular $\text{N}\cdots\text{C}=\text{O}$ $n\rightarrow\pi^*$ interaction in the gas-phase IR experiments. We asked a few questions on the $n\rightarrow\pi^*$ interaction in the thesis, and the research work performed in this direction aimed to answer those questions.

Can $n\rightarrow\pi^*$ interaction govern the conformational preference of molecular systems?

Literature reports on the $n\rightarrow\pi^*$ interaction from the NMR spectroscopy discussed earlier showed the equilibrium between the *trans* and *cis* conformers with and without the $n\rightarrow\pi^*$ interaction, respectively.^{44-46, 148} Thus, integrating the chemical shifts for both the conformers gives an idea about the relative stability of the conformer having the $n\rightarrow\pi^*$ interaction over the other. Also, reports on the $n\rightarrow\pi^*$ interaction from the gas-phase microwave spectroscopy mostly involve the secondary non-covalent interaction.^{132, 135-137} Herein, we have shown that

the increase in the strength of the $n \rightarrow \pi^*$ interaction in the *cis*-phenyl acetate conformer and, at the same time, the increase in the steric repulsion in the *trans*-phenyl acetate conformer lacking the $n \rightarrow \pi^*$ interaction results in the exclusive observation of the *cis*-phenyl acetate. This shows that tuning of the $n \rightarrow \pi^*$ interaction in one of the conformers leads to the conformational selectivity over the other.

☞ **Can $n \rightarrow \pi^*$ interaction and hydrogen bonding coexist in the gas-phase involving the same lone pair electron density of the donor?**

Our group has shown earlier that the hydrogen bonding and the $n \rightarrow \pi^*$ interaction can coexist in a molecular system.¹²⁵ However, these non-covalent interactions in the defined molecular system involved different donor and acceptor groups. We thought to study the fate of the $n \rightarrow \pi^*$ interaction when the same lone pair electron density is delocalized for the hydrogen bonding and the $n \rightarrow \pi^*$ interaction. To study this, we synthesized phenyl formate...water complex in the gas-phase experiment. Here, we found that water made a strong hydrogen bond with the carbonyl oxygen of phenyl formate, bifurcating its lone pair electron density toward the hydrogen bond with water as well as the $n \rightarrow \pi^*$ interaction with the phenyl ring. Hence, both the interactions coexisted with each other in the complex. However, the strength of both the non-covalent interactions decreased to facilitate the presence of each other in a conformer.

☞ **Can $N \cdots C=O$ $n \rightarrow \pi^*$ interaction be probed using the gas-phase IR spectroscopy?**

Hitherto, to the best of our knowledge, $N \cdots C=O$ $n \rightarrow \pi^*$ interaction has not been studied using gas-phase IR spectroscopy. However, there are a few reports from gas-phase microwave spectroscopy on the $N \cdots C=O$ $n \rightarrow \pi^*$ interaction that coexists with a secondary $C-H \cdots O$ hydrogen bonding.^{131, 132, 135-137} Herein, we have studied this $n \rightarrow \pi^*$ interaction using gas-phase IR spectroscopy and showed that this interaction can stabilize the low-energy conformers of the potential energy surface of the ethyl 2-(2-(dimethylamino) phenyl) acetate. We have also shown the variable temperature ¹³C NMR spectroscopic evidence of the $N \cdots C=O$ $n \rightarrow \pi^*$ interaction in the same molecular system.

☞ **Can $N \cdots C=O$ $n \rightarrow \pi^*$ interaction resemble hydrogen bonding in terms of its applications in folding the flexible side-chain and stabilizing the molecular complexes?**

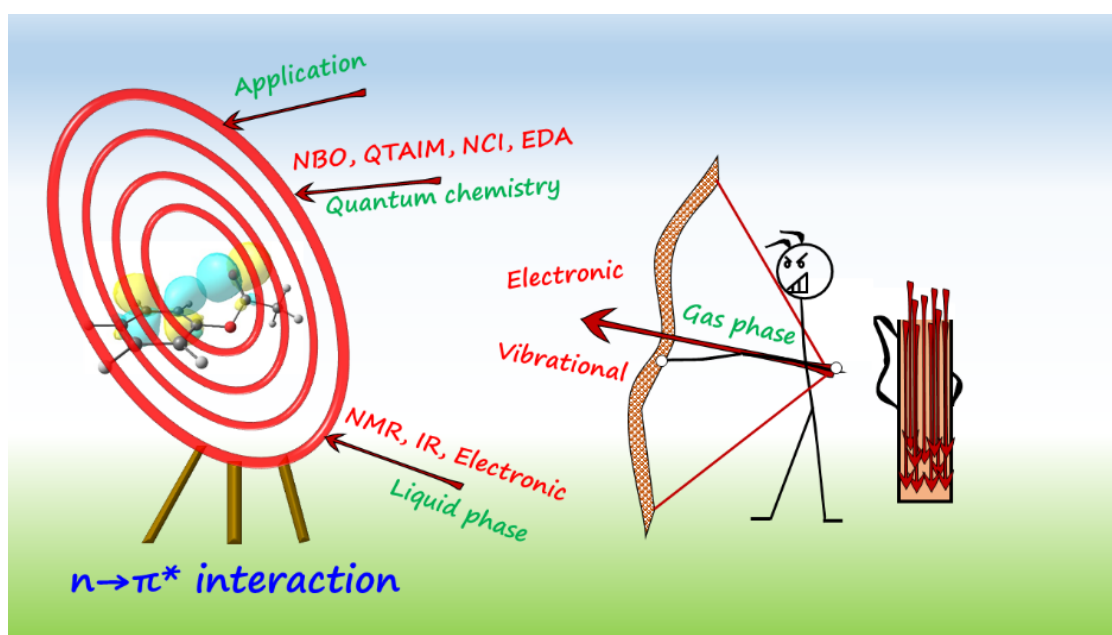
To the best of our knowledge, there is no report on $N \cdots C=O$ $n \rightarrow \pi^*$ interaction demonstrating the folding of flexible side-chains. Herein, we have shown that the $N \cdots C=O$ $n \rightarrow \pi^*$ interaction is responsible for the folding of the flexible propanal side-chain in 3-[2-(dimethylamino) phenyl] propanal. Furthermore, we have also shown that the $N \cdots C=O$ $n \rightarrow \pi^*$ interaction can

result in the stabilization of the molecular complexes of *p*-substituted pyridines with aldehydes. We have also shown that this interaction can be modulated by varying the electronic substituents on the $n \rightarrow \pi^*$ donor as well as the acceptor.

∅ **What is the role of the $n \rightarrow \pi^*$ interaction in the carbonyl stretching frequency, where the carbonyl group is free from hyperconjugative interaction from nearby heteroatoms such as oxygen and nitrogen atoms in the case of the ester and amide, respectively?**

The reports on the gas-phase IR spectroscopy studies on the $n \rightarrow \pi^*$ interaction provided by our group involve the carbonyl group in an ester, which includes the hyperconjugative interaction from the etheral oxygen atom of the ester and, hence, perturbing the carbonyl stretching frequency. This perturbation in the carbonyl stretching frequency arising from the hyperconjugative interactions can be avoided if the carbonyl group involved in the $n \rightarrow \pi^*$ interaction belongs to the aldehyde or ketones. In this scenario, the redshift observed in the carbonyl stretching will be purely due to the $n \rightarrow \pi^*$ interaction. Thus, we studied various molecular systems using quantum chemistry calculations and showed the contribution of the $n \rightarrow \pi^*$ interaction to the redshift of the carbonyl stretching frequency free from hyperconjugative interactions.

Chapter 2: Spectroscopic techniques coupled with the supersonic jet-cooled expansion and computational methods



2.1 Methodology

As discussed in Chapter 1, gas-phase spectroscopy goes hand in hand with quantum chemistry calculations. Thus, quantum mechanical calculations combined with high-resolution spectroscopic techniques are crucial to understanding the $n \rightarrow \pi^*$ interactions in various molecular systems. Accordingly, this chapter mainly deals with the methodologies utilized in this thesis and is divided into experimental and computational methods.

2.2 Experimental methodologies

The goal of this proposed thesis is the detailed study of the $n \rightarrow \pi^*$ interaction in small molecules or molecular complexes. Profound ridged potential energy surfaces with several conformations exist for these molecules or molecular complexes as these molecular systems have several degrees of freedom and multiple binding sites. Only a few low-energy conformations could be observed in the experimental condition. Observing specific conformation in the experiment relies upon the presence of the $n \rightarrow \pi^*$ interaction and the coexistence of other non-covalent interactions in the molecular system, if any. Understanding the functions of a molecule or complex at its molecular level is incredibly encouraged for knowing its complete primary structure. The exegesis of the fundamental structural requirements for molecules to exhibit biological activity is an active area of continuous research. Various methodologies such as mass spectrometry, X-ray crystallography, nuclear magnetic resonance (NMR) spectroscopy, and various jet-cooled spectroscopies, such as electronic, infrared, and microwave, have been used to observe the structure-function relationship. In this chapter, we will describe the supersonic jet-cooled expansion techniques, which enable us to study the molecules of interest at the microscopic level without having any perturbation from neighboring solute or solvent molecules. Here, we will understand the intrinsic nature of the $n \rightarrow \pi^*$ interaction, its strength, and its interplay with other non-covalent interactions.

We are familiar with the conventional UV-Vis electronic spectra (Figure 2.1a) measured in the solution-phase at room temperature, where excitation of the molecules occurs from various rotational/vibrational levels of the ground electronic state (S_0) to various rotational/vibrational levels of the excited electronic state (S_n). The absorption spectrum thus obtained generally has a broad background, is inconclusive about the vibronic structure of the molecular system, and lacks information about the presence of conformations in the experiment. The broad background is attributed to the electronic excitation arising from the significant population in the various rotational and vibrational energy levels of the S_0 state at room temperature. This broad background also emerges due to the collisional broadening. For

instance, if only the ground vibrational and rotational energy levels ($v''=0$ and $J''=0, 1, 2, \dots$) are populated, all the electronic transitions will occur from the ground vibrational/rotational energy levels ($v''=0$ and $J''=0, 1, 2, \dots$) of the S_0 state to the excited vibrational energy levels ($v'=0, 1, 2, \dots, n$) of the S_1 . This molecular arrangement in the S_0 state will give a vibrationally resolved electronic spectrum (Figure 2.1b) of the molecular system. Such molecular arrangement can be obtained by supersonic jet-cooled expansion of gaseous molecules.

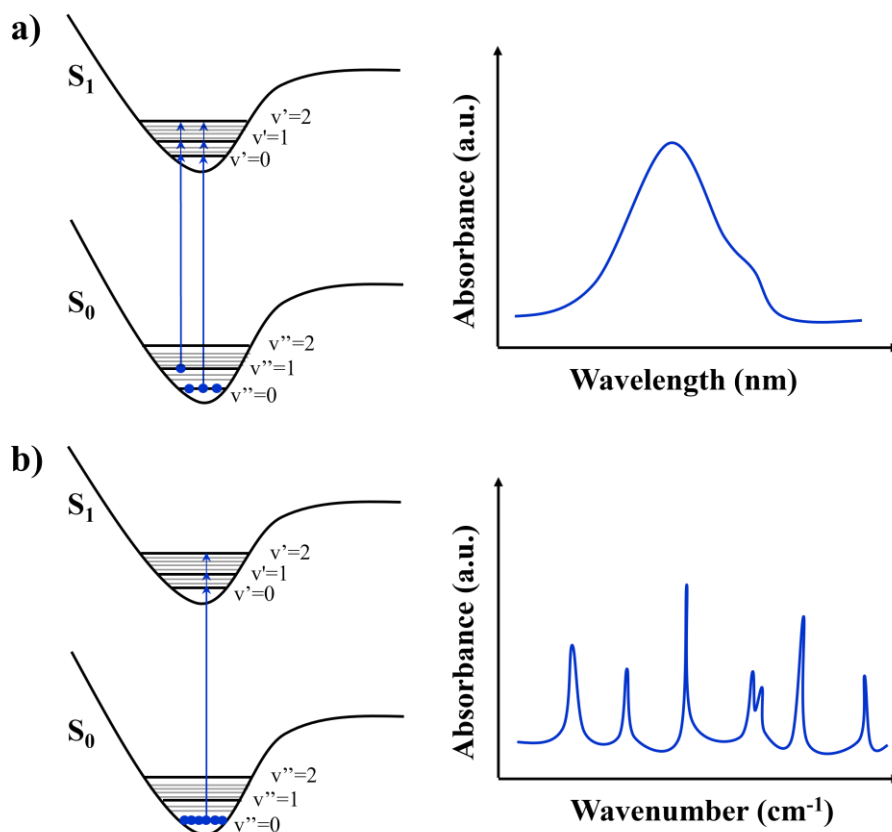


Figure 2.1. a) Electronic spectrum when various vibrational levels of ground electronic state (S_0) are populated; and b) High-resolution vibrationally resolved electronic spectrum when the ground vibrational level of the S_0 state is populated.

2.2.1 Supersonic jet-cooled expansion

The supersonic jet-cooling technique is central to the gas-phase laser spectroscopy of isolated molecules and weakly bound complexes held by various non-covalent interactions. An amalgamation of the supersonic jet-cooled technique with high-resolution tunable UV/Vis and IR lasers leads to well-resolved electronic and vibrational spectra of molecules and complexes. In comparing the molecular arrangement in the conventional UV-Vis absorption spectrum, mostly the lowest rotational ($J''=0$) and vibrational ($v''=0$) energy levels of the molecular system in the S_0 state get populated in a supersonic jet (Figure 2.1). Consequently, very high-resolution

electronic spectra featuring sharp vibronic bands of the molecules are obtained. The electronic spectrum obtained from this technique contains more information about the structure, conformation, and bonding of a molecule than the spectrum obtained from the solution-phase. The principles and applications of the supersonic expansion technique in molecular spectroscopy have been discussed in detail in the literature.^{10, 149-163} The sample molecules in the supersonic expansion remain in an isolated gas-phase without any collision with themselves and the solvent molecules. Additionally, the ultracold environment of the supersonic jet allows the formation of weakly bound complexes of different sizes and measurements of their high-resolution electronic and vibrational spectra, which are not possible in the solution-phase.

In supersonic expansion (Figure 2.2), the vapor of sample molecules seeded in a carrier/buffer gas of ~1500-4500 mbar pressure is expanded into a high vacuum chamber (10^{-6} mbar) via a small orifice of pulse valve with a diameter of 200-500 microns. The buffer gas (He, Ne, Ar, or a mixture of these gases in different proportions) should be monoatomic to obtain maximum cooling of the sample molecules, as monoatomic gases do not have rotational and vibrational degrees of freedom associated with them. Diatomic gases like nitrogen can also be used as buffer gas, but the cooling of sample molecules can vary due to their own vibrational and rotational degrees of freedom. When the diameter of the orifice (D) of the pulse valve is less than the mean free path (λ) of the sample molecules ($D < \lambda$), no collision takes place between the sample molecules and carrier gas at the nozzle orifice, this expanded beam is known as an effusive beam. The velocity distribution of the effusive beam remains the same before and after the expansion, and it follows the velocity-weighted Maxwell-Boltzmann distribution. On the other hand, when the diameter of the orifice is larger than the mean free path of the gas ($D > \lambda$) molecules, numerous collisions between sample molecules and carrier gas occur at the orifice, and the expanded beam is known as the supersonic molecular beam. Knudsen number (K_n) is defined as the ratio of the mean free path of the gas molecules to the diameter of the orifice. K_n is greater than one for the effusive beam and lesser for the molecular beam.¹⁶⁴ Supersonic expansion involves transforming internal energy associated with the randomized motion in the pre-expansion chamber to the directed mass flow along the beam axis after expansion and cooling the internal degrees of freedom of the sample molecules. It should be noted here that the molecules in the supersonic beam remain in the gas-phase even when the temperature of the sample molecule remains far lower than the freezing point of the sample. This is because the number density of the sample molecules in the supersonic beam rapidly decreases after a minimal distance from the orifice, and condensation cannot happen due to the lack of any significant three-body collisions.

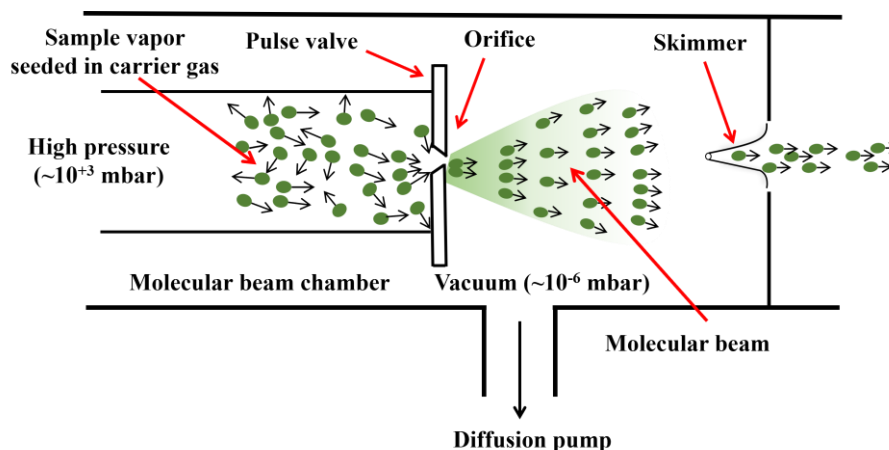


Figure 2.2. A schematic diagram of supersonic jet-cooled expansion.

The density of the molecules, i.e., the number of collisions, is maximum near the orifice and decreases with the distance (x) from the orifice. Thus, the cooling depends on the (x/D) ratio. The extent of cooling in the supersonic beam is expressed in terms of Mach number (M), which is the ratio of the velocity of molecules in the supersonic beam to the speed of the sound. This is called supersonic expansion, as the Mach number is more than one. The following equation gives the relationship between M and (x/D) : $M = A(x/D)^{\gamma-1}$, where γ is the ratio of the heat capacity (C_p/C_v) and A is a constant that depends on γ , and its value is 3.26 for a monoatomic gas. This cooling makes the velocity distribution of the gas narrower as the translational temperature of the molecules gets lowered in the sample molecule. The width of the velocity distribution defines the translational temperature of the gas. After expansion, molecules move as a directed mass flow, and thus, the maximum velocity of the distribution shifts towards a higher velocity (Figure 2.3).

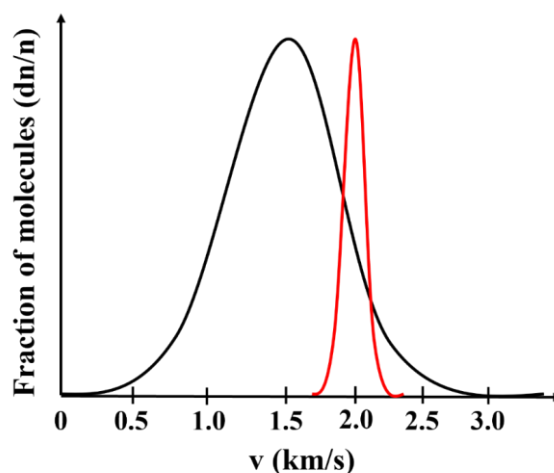


Figure 2.3. Velocity distribution of sample molecules in pre-expansion/effusive beam (black trace) and supersonic molecular beam (red trace).

As the expansion proceeds, the speed of sound decreases as it depends on the translational temperature. The relation gives the speed of the sound $(\gamma kT/m)^{1/2}$, where k is the Boltzmann constant, and m is the molecular mass of the molecule. These collisions significantly cool down the translational degrees of freedom, and their cooling rate is higher than the vibrational and rotational degrees. The rotational and vibrational degrees of freedom cool down when they equilibrate with the translational cold bath. This equilibration is faster for the rotational degrees of freedom than the vibrational; hence, rotational cooling is faster than the vibrational cooling. However, collision ceases downstream of the expansion, and hence, molecular density decreases, and further cooling of vibrational and rotational degrees is stopped. The translational temperature in the supersonic jet reaches ~ 0.1 K, and hence, translational degrees act as a cold bath for rotational and vibrational degrees. Rotational temperature equilibrates faster with the translational, so rotational temperature reaches ~ 2 -3 K, whereas vibrational temperature equilibrates much slower than rotational. Thus, vibrational cooling is not as complete as rotational cooling, and the vibrational temperature goes in the range of 15-50 K. Though the vibrational temperature in comparison to the rotational temperature is higher in a supersonic jet, higher vibrational levels are still not significantly populated. The vibrational temperature in the supersonic jet can be calculated experimentally when any hot band arises in the electronic spectrum of the molecule by $\frac{I_{0-0}}{I_{1-0}} = e^{\frac{-\Delta E}{kT_{vib}}}$ equation, where I_{0-0} is the intensity of adiabatic transition ($v''=0$ of S_0 state to $v'=0$ of S_1 state), I_{1-0} is the intensity of the hot band from $v''=1$ of S_0 state to $v'=0$ of S_1 state, ΔE is the vibrational energy of the $v''=1$, and k is Boltzmann constant. This equation assumes that the Franck-Condon factor for both transitions is equal. Supersonic expansion is isentropic under reversible adiabatic conditions, i.e., without any shock wave, shear force, heat source, or sink. Thus, the following equation of the ideal gas can be used to determine the temperature, pressure, and density of the expanding gas in the supersonic jet.

$$\frac{T}{T_0} = \left(\frac{P}{P_0}\right)^{\frac{\gamma-1}{\gamma}} = \left(\frac{\rho}{\rho_0}\right)^{\gamma-1} = \frac{1}{1 + \frac{1}{2}(\gamma-1)M^2}$$

Where T_0 , P_0 , and ρ_0 are the temperature, pressure, and density of the gas in the high-pressure reservoir, respectively, while T , P , and ρ are the same quantities of the expanded gas after supersonic expansion. It is likely from the equation mentioned above that the Mach number increases while the temperature, pressure, and density of the molecular beam decrease as we go downstream of the orifice. Anderson and Fenn in 1965 showed that the Mach number could

not keep increasing in downstream of the molecular beam. The equation above is for continuous gas flow, but the gas molecules are discrete particles. The density of the molecules decreases downstream of the orifice, and hence, the number of collisions between them decreases. Thus, the Mach number achieves a terminal value (M_T), which is given by the equation below,

$$M_T = 2.05\varepsilon^{-(1-\gamma)/\gamma} (\lambda/D)^{-(1-\gamma)/\gamma} = 133(P_0D)^{0.4} \text{ (for Argon)}$$

Where ε is the collisional effectiveness constant, it is evident from the above equation that the M_T is directly proportional to gas pressure in the reservoir and the diameter of the orifice. As the probability per unit of time for a molecule to make a binary collision is proportional to the pressure (P_0), the quantity P_0D is proportional to the total number of binary collisions. Hence, the M_T is directly proportional to the total number of binary collisions the molecule makes. The central coldest part of the molecular beam is extracted with the help of a delicate cone-shaped skimmer to perform spectroscopy. This is placed in front of the expanding supersonic beam at a distance of $\sim 5\text{-}6$ cm. It is required to extract the coldest part of the beam to make it supersonic, else it will be termed a free jet. The molecular density decreases downstream of the expansion, and hence, further rotational and vibrational cooling ceases. The central part of the molecular beam is isentropic under the adiabatic reversible flow conditions.

2.2.2 Bringing the sample in gas-phase for supersonic expansion

As discussed in the previous section, the vapor of a sample molecule of interest seeded in a buffer gas is expanded into a high vacuum through a small orifice to obtain supersonic cooling. However, sample molecules are generally solid or liquid at room temperature. Thus, thermal heating or laser desorption could bring the samples up in the gas-phase. On the other hand, highly volatile sample molecules must be cooled at low temperatures to control their vapor pressure and avoid flooding the vacuum chamber with a very high sample concentration. The solid and liquid sample molecules with a moderate vapor pressure at room temperature can be thermally heated to bring them into a gaseous state. These samples are heated to create enough vapor pressure to obtain a good signal amount in the supersonic jet-cooled experiment. The sample molecule is placed in a stainless steel container behind the pulse valve and heated using a resistive heater. The sample holder and pulse valve are often heated to obtain a stable signal amount. The pulse valve is generally heated by $15\text{-}20$ °C higher than the sample to avoid clogging the sample inside the pulse valve. The solenoid pulse valve has a heating limitation of only up to 120 °C. Several molecular systems cannot be heated at high temperatures due to their non-volatile nature, fragmentation, and denaturation in the case of biomolecules, such as

amino acids and peptides. Such molecular systems can be brought up in the gaseous state using pulse laser ablation or laser desorption, which has not been used in this thesis.

2.2.3 Difficulty in performing direct absorption spectroscopy in gas-phase jet-cooled experiment

Conventional UV-Vis spectrophotometry performed in the solution-phase measures the electronic spectrum of samples by recording absorbance of the intensity of the light passing through the sample under observation as a function of the frequency of the UV-Vis region. The absorbance depends on the sample concentration and the path length traveled by the UV-Vis radiation. The absorbance of the sample is given by $A = \epsilon cl$, where A is the absorbance of the sample, ϵ is the molar absorptivity or molar extinction coefficient of the sample, c is the concentration of the sample, and l (generally 10 mm) is the path length traveled by the UV light through the sample. Similarly, FTIR spectroscopy performed in solution-phase involves measuring the change in the intensity of the IR radiation after passing through the sample at a different frequency of the IR region. The number of molecules absorbed by the UV-Vis and IR radiation in the conventional UV-Vis and FTIR spectroscopy, respectively, is considerable. Hence, attenuation in the intensity of the incident light could be measured successfully. On the contrary, in supersonic jet-cooled expansion, the number density of the sample molecule is very low; also, the absorption path length is much less. Thus, it is impossible to measure the change in light intensity after passing through such a low number density sample. It is required to have more sensitive detection methods employed for the purpose.

2.2.4. Action spectroscopy in the supersonic jet

With the help of action spectroscopy (indirect detection), the effect of UV and IR radiation on the molecules can be studied despite limitations in measuring the attenuation of the intensity of the light passing through the sample. These action spectroscopic methods can involve various electronic states such as ground, excited, and ionic states. This may involve investigating the population of molecules in the ground state by fluorescence, ionization, dissociation, fragmentation, or other processes. There are various action spectroscopies in the literature involving the excited or ionic electronic states, such as resonance-enhanced multiphoton ionization (REMPI), laser-induced fluorescence (LIF) excitation spectroscopy, double resonance spectroscopy (UV-UV hole-burning and IR-UV hole-burning spectroscopy) and resonant ion-dip infrared spectroscopy (RIDIR), infrared ion-gain spectroscopy (IRIG), and fluorescence dip in infrared spectroscopy (FDIR) etc. In this thesis, we have used action

spectroscopies related to resonant photoionization followed by time of flight (TOF) detection, where molecular ions are separated based on their m/z ratio ($z=1$). The ion-detection method utilizes various spectroscopies, such as REMPI, RIDIR, IRIG, and UV-UV HB. It should be noted that despite the ion-detection method employed, the spectroscopies performed are for the S_0 state of the isolated neutral molecule, as the energy of the resonant UV photon provided varies from the ground electronic state to the first excited electronic state.

2.2.5 Resonance-enhanced multiphoton ionization and time of flight mass spectrometry (REMPI-TOF-MS)

As stated in the previous section, TOF ion-detection has been used in detail as an action spectroscopy to detect the changes in the sample molecule in the supersonic jet by the UV and IR radiation. TOF detection provides the mass-selection as the lighter ion reaches the detector faster than the heavier mass. The REMPI technique produces these ions and measures the electronic spectrum of the molecule in a supersonic jet. Resonance-enhanced multiphoton ionization and time-of-flight mass spectrometry have been coupled to study the isolated molecules and complexes bound by non-covalent interactions.

2.2.5.1 Resonantly enhanced multiphoton ionization (REMPI) spectroscopy

The REMPI (Figure 2.4) technique measures the electronic spectra of molecules and weakly bound complexes in the isolated gas-phase. In this technique, the first photon ($h\nu_1$) from a tunable ultraviolet (UV) laser excites the supersonically cooled molecules in the lowest vibrational level ($v''=0$) of the S_0 state to different vibrational levels of the S_1 state. Subsequently, the second photon ($h\nu_1$) of the same wavelength of the same laser ionizes the molecules to the ionic state (D_0), and the ion signal is detected as a function of the wavelength of the first photon of the laser. Thus, the REMPI spectrum is essentially an absorption spectrum for the $S_1 \leftarrow S_0$ electronic transition where ionization of the molecules *via* resonant S_1 state is monitored instead of directly measuring their absorption. This technique is called 1-color or (1+1) resonant 2-photon ionization (1C-R2PI) spectroscopy. In the REMPI, the total energy of the two photons has to be higher than the ionization potential of the molecular system. However, the 1C-R2PI method may not be suitable for measuring the electronic spectra if the sum of the energy of the two photons used for the $S_1 \leftarrow S_0$ electronic excitation and subsequent ionization is less than the ionization energy of the molecule. In that case, the second photon ($h\nu_2$) of higher energy from a different laser fixed at a specific wavelength is used to ionize the molecule while the wavelength of the first photon is tuned. This technique is called 2-color or

(1+1') resonant 2-photon ionization (2C-R2PI) spectroscopy (Figure 2.4). Sometimes, the total energy of the two photons is much higher than the ionization threshold of the molecule and results in the fragmentation of the molecular system in the ionic state. In these cases, the energy of the second photon from another laser is chosen so that the summation of the two photons' energy will be a few 100 cm^{-1} higher than the ionization threshold to prevent dissociation of the molecule or the complex in the ionic state. Here, the two laser beams should be temporally and spatially overlapped, and the pulse energy of the excitation laser should be as low as possible to avoid two-photon ionization from the first laser. The R2PI spectroscopy is coupled with TOF-MS to measure mass-selected electronic spectra of the molecules and complexes.

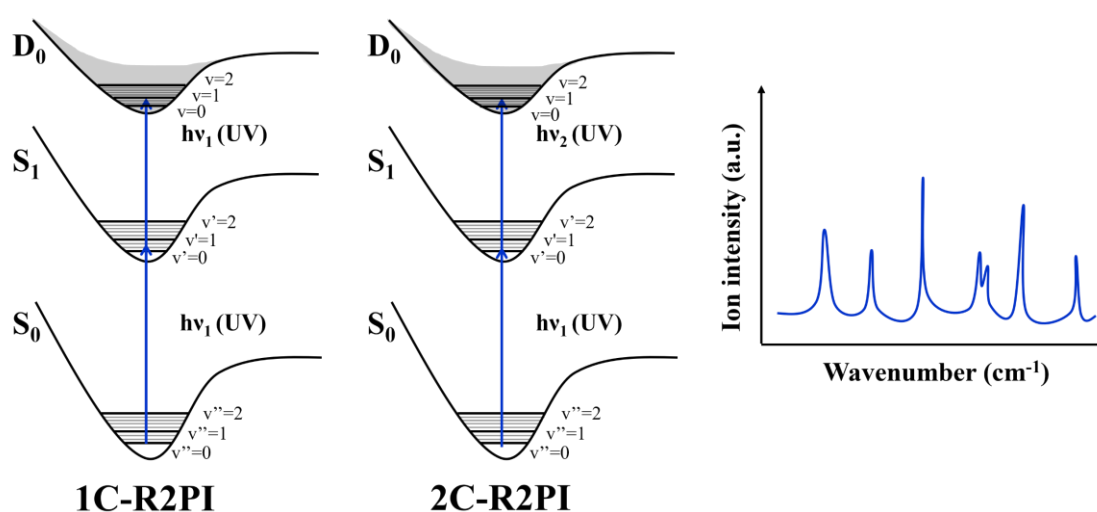


Figure 2.4. A schematic presentation of 1C-R2PI and 2C-R2PI spectroscopic techniques and an R2PI spectrum.

2.2.5.2 Time of flight mass spectrometry (TOF-MS)

In the TOF ion detection, the coldest part of the molecular beam selected through the skimmer is ionized by the REMPI technique, and the ions are accelerated by a uniform electric field with the same kinetic energy. These ions move in an electric field-free TOF tube and are detected by the microchannel plate (MCP) detector placed at a one-meter distance to separate ions of different masses based on their TOF. These TOF values depend on the mass-to-charge ratio (m/z) of the ions ($z=1$), providing the singly charged ions in this thesis work; these TOF values can be directly correlated with the mass. Lighter ions will have lesser TOF values than heavier ions as lighter ions reach the detector faster. The potential energy (U) of these positively charged ions having charge q in an electric field of potential V can be calculated by $U=qV$. The kinetic energy (K) of these accelerated ions of mass m and moving with velocity v in an electric field-free TOF tube can be calculated by $K=(1/2)mv^2$. While accelerating these ions, the

potential energy converts to kinetic energy; thus, $qV = (1/2)mv^2$. The accelerated ions travel distance d of the TOF tube in time t before reaching the detector, which can be calculated by $v = d/t$. We will get $t = (md^2/2qV)^{1/2}$ by substituting the velocity value in the kinetic energy equation. As the length of the TOF tube, the charge of the ion ($z=1$), and the electric field applied are constant for all the ionic particles, the TOF value of the ions will be proportional to the square root of the mass of the ions. Wiley-McLaren configuration (Figure 2.5)¹⁶⁵ TOF-MS has been used to improve the mass resolution of the molecular system under consideration. This design consists of three electrode plates, i.e., repeller plate, extraction grid, and accelerating grid. The positive potential applied at the repeller plate is higher than at the extraction grid, and these two electrodes are separated by distance s . The accelerating grid is grounded and is separated by the extraction grid at distance d . The REMPI technique produces the positively charged ion in the middle of the repeller plate and the extraction grid, and this region is known as the ionization region. Thus, these ions moved toward the extraction grid due to the electric field E_s between these electrode plates. These ions move toward the accelerating grid further with acceleration as they experience a higher electric field (E_d) applied between the extraction grid and the accelerating grid.

A pulsed UV laser beam of size $\sim 2\text{--}3$ mm produces a bundle of ions at different positions in space (initial spatial distribution). The ions closer to the repeller plate move faster than those closer to the extraction grid, resulting in initial velocity distribution, also known as initial kinetic energy distribution. The molecular ions of the same masses reach the detector at a slightly different time due to the initial spatial and velocity distribution, leading to decreased mass resolution. However, adjusting the dual source field, i.e., E_d and E_s , so that the ions start moving in the field-free region with the same position increases mass resolution. This fine adjustment of the dual-source field is known as energy focusing or space focusing. If these ions get deflected from their vertical path in the field-free region, they can be brought to the focal plane of the detector by tuning the X/Y electric field of the repeller plate and extraction grid. Thus, the Wiley-McLaren design increases the resolution of the TOF-MS by reducing the time spread of the ions of the same mass. The TOF mass spectrometer consists of three electrode plates, a field-free TOF tube, a ground plate, and an MCP detector. Suppose U_0 is the initial energy of the molecular ions, and it increases to U upon experiencing the electric field E_s and E_d . The energy of the ions can be calculated by $U = U_0 + qsE_s + qdE_d$. The total time-of-flight T for the ion of mass m and charge q is given by $T = T_s + T_d + T_D$. The time taken by the ion source to travel the ionization region is given by the formula (+ and – signs in the expression of T_s are the initial velocity oriented toward and away from the detector, respectively) $T_s = 1.02$

$[(2m)^{1/2}/qE_d [(U_0 + q_s E_s)^{1/2} \pm (U_0)^{1/2}]$. The time taken by the ion source to travel the acceleration region is given by $T_d = 1.02 [(2m)^{1/2}/qE_d [(U)^{1/2} - (U_0 + q_s E_s)^{1/2}]$ and the time taken by the ion source to travel the field-free drift tube with a distance D between the detector and accelerating grid is given by $T_D = 1.02 (2m)^{1/2} (D/2U)^{1/2}$.

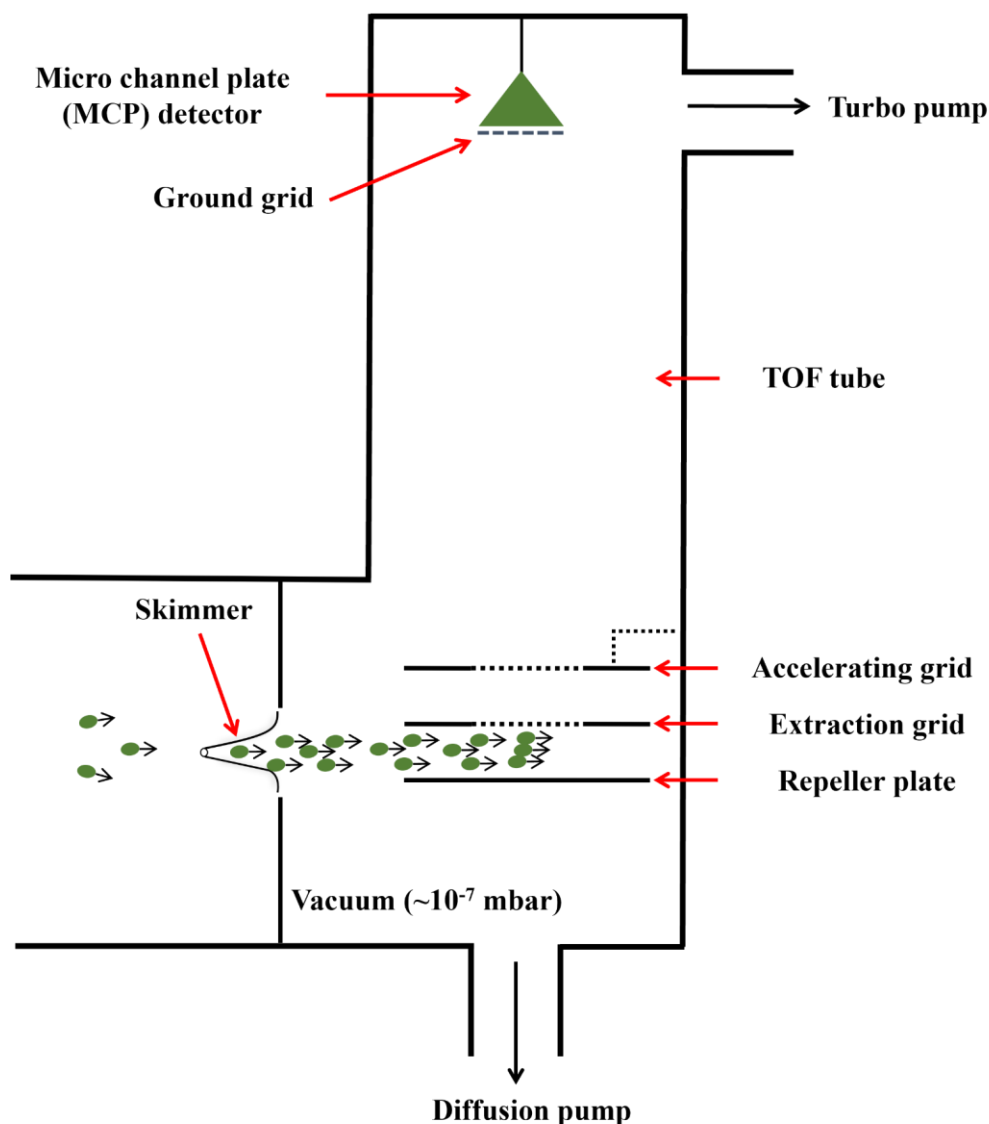


Figure 2.5. A schematic representation of a time-of-flight mass spectrometer.

In our experimental setup, the TOF-MS (Jordan TOF Products Inc.), the coldest part of the molecular beam, and the pulse UV laser beam are mutually perpendicular. A laser pulse ionizes this skimmed molecular beam at a right angle between the repeller plate and extraction grid, which are 1 cm apart. The ions move towards the extraction grid due to the potential difference between the repeller plate (+3060 V) and the extraction grid ($\sim +2750$ V). The ions are further accelerated between the extraction grid and the grounded accelerating grid (0 V).

After passing through the grounded accelerating grid, ions travel into a field-free ($E=0$) TOF tube of 1 m in length. These ions are detected by an 18 mm dual chevron-type MCP detector (-3000 V) placed at the end of the TOF tube. MCP detector generates electrons from its channel wall upon the entrance of the molecular ions at the detector. The potential at the other side of the MCP detector develops the electric field and thus accelerates the secondary electrons. The accelerated electrons move in the parabolic trajectory until they collide with the channel wall, producing further secondary electrons. Such enormous processes along the channel wall result in the cascade process, leading to the generation of millions of electrons that emerge from the rear end of the plate. The electronic signal generated from the detector due to the bombardment of ions is amplified through a preamplifier and visualized on the oscilloscope. The signal due to the ions of different masses appears at different times on the oscilloscope. This technique has an advantage over LIF, giving mass-selectivity of the sample molecules. With TOF-MS detection, studying various complex formations in a jet is possible, which is not straightforward in LIF due to a lack of mass-selectivity.

2.2.5.3 UV-UV hole-burning spectroscopy (UV-UV HB)

As discussed earlier, isolated gas-phase spectroscopy allows us to arrest the population of different conformations of the molecular system. The electronic spectrum measured by the REMPI technique provides the vibrationally resolved bands, which are otherwise broad in the solution-phase. These bands in the gas-phase electronic spectrum could arise due to more than one conformer in the experiment. Double resonance spectroscopy, i.e., UV-UV and IR-UV hole-burning (HB) spectroscopic techniques, discriminates the different conformers of molecular systems in the experiment. In this thesis, we have used the UV-UV HB technique, which is a pump-probe spectroscopy employing two spatially overlapped UV lasers. Here, the probe UV laser is fixed at one of the vibronic bands of the electronic spectrum (such as the bands marked with red and green colored asterisks in Figure 2.6), and another pump UV laser, which is fired 100 ns prior to the probe UV laser, is scanned throughout the electronic spectral region of the molecular system. The pump laser burns the population in the $v''=0$ of the S_0 state of the molecular system by electronic excitation, which is probed by the probe laser and can be observed as the depletion in the ion-signal of the molecular system. The pump laser shows the depletion in the ion signal for all those vibronic bands that share the ground state of the same conformer (conformer I). In contrast, none of the vibronic bands from the other conformer (conformer II) show ion-signal depletion. Afterwards, the probe UV laser can be fixed at another vibronic band, and the pump UV laser will be scanned again; it shows the depletion in

ion-signal for all those bands that belong to the other conformer. Figure 2.6 shows that the molecular system under consideration has two conformers in the experiment. Thus, the UV-UV HB technique provides the conformation-specific electronic spectrum and gives an idea about the number of conformations in the experimental condition of the molecular system.

In the case of IR-UV hole-burning spectroscopy, the IR laser is used as a probe laser and fixed at the stretching frequency of one of the functional groups present in that molecule. The pump UV laser is scanned throughout the electronic spectral region and shows the depletion for the vibronic bands, which belong to the same conformer.

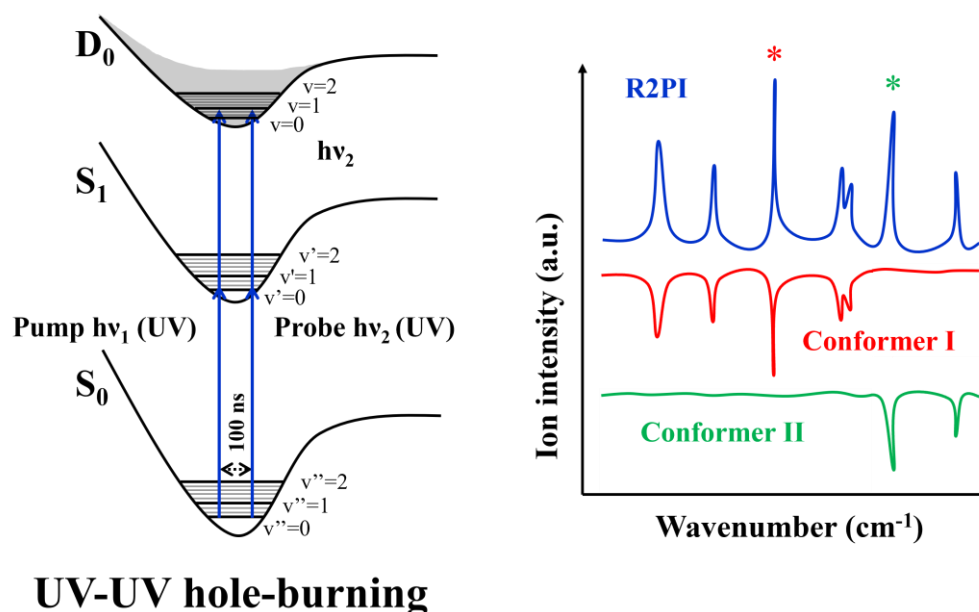


Figure 2.6. A schematic presentation of UV-UV hole-burning spectroscopy along with the UV-UV HB spectrum depicting the presence of two conformers (I & II) in the experiment.

2.2.5.4 Resonant Ion-dip Infrared Spectroscopy (RIDIR)

After obtaining the information about the number of conformations in the experiment from the UV-UV HB technique, conformational assignment is needed to study the $n \rightarrow \pi^*$ interaction. RIDIR spectroscopy (Figure 2.7) is used for conformational assignment by probing the various functional groups in the molecular system, such as C=O, N-H, O-H, etc. Herein, counter-propagating UV and IR laser beams are spatially overlapped, where the probe UV laser (pulse energy 0.2-0.3 mJ) is fixed to a particular vibronic band of the conformation-specific electronic spectrum (such as the bands marked with red and green colored asterisks in Figure 2.6). The pump IR laser (2-3 mJ) coming 100 ns prior to the probe UV laser is scanned in the region of the characteristic functional group. The pump IR laser excites the molecule from $v''=0 \rightarrow 1$ of the S_0 , resulting in its population burning whenever the IR laser frequency resonates with any

vibrational frequency of the functional group, thus depleting the UV ion signal. Thus, RIDIR spectroscopy provides the conformation-specific IR spectra of molecules and complexes.

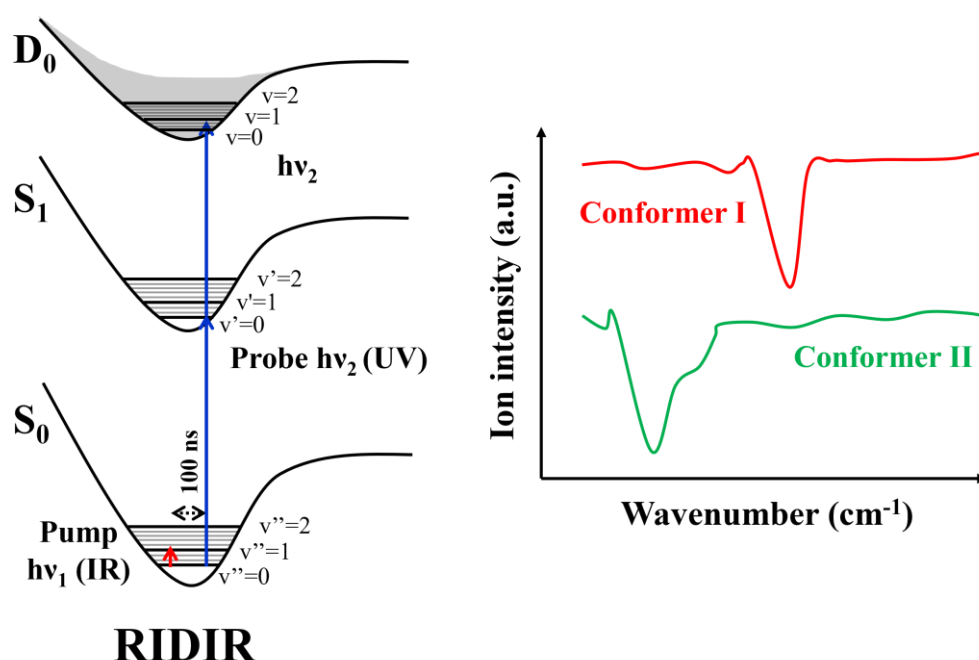


Figure 2.7. A schematic presentation of RIDIR spectroscopy along with the conformation-specific IR spectrum of conformer I and II.

2.2.5.5 Infrared Ion-Gain Spectroscopy (IRIG)

On the contrary to the RIDIR technique, IRIG spectroscopy provides the IR stretching frequency of the functional groups for all the conformers in a single spectrum. The IR laser in this technique is also fired 100 ns prior to the UV laser. However, in this technique, the UV laser is not fixed to any of the vibronic bands of the electronic spectrum but is somewhat fixed to the red side of the origin band where no vibronic band is present. Here, the IR laser excites the molecules from $v''=0 \rightarrow 1$ of the S_0 state, and these molecules are further ionized from $v''=1$ by two UV photons upon the firing of the UV laser instead of the $v''=0$ as was in the case of RIDIR spectroscopy. As the UV laser is fixed to the red side of the origin band, there is very little ion-signal of the molecular system, which increases when the IR laser frequency resonates with the vibrational frequency and results in the ion-gain of the signal. Upon the vibrational excitation by IR laser, the UV laser results in the excitation and ionization of all the conformers present in the experiment; thus, it is a non-conformer-specific spectroscopic technique. Also, as the scanning of the IR laser continues, it provides the IR frequency for all the conformers in a single spectrum. If an IRIG spectroscopy is performed on a molecular system having two conformers, as shown in Figure 2.6, having one N–H functional group, two sets of N–H IR

stretching frequencies will be observed in a single IRIG spectrum. Thus, IRIG spectroscopy indirectly gives the idea about the number of conformers present in the experiment.

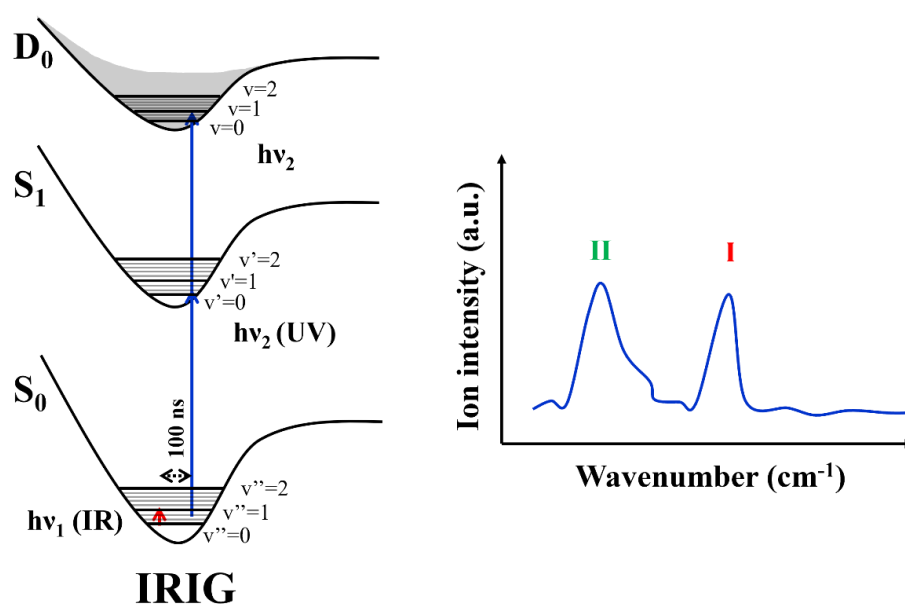


Figure 2.8. A schematic presentation of IRIG spectroscopy along with the IRIG spectrum of the molecular system under consideration having IR features of the conformers I and II.

2.2.6 Experimental set-up

The jet-cooled REMPI-TOF-MS set-up used to perform experiments in our laboratory at the Indian Institute of Science Education and Research (IISER) Pune, shown in Figure 2.9, is a home-built instrument. This set-up consists of two differentially pumped high-vacuum chambers connected *via* a skimmer (Beam Dynamic Inc.) of 2 mm diameter and 25 mm length. These chambers are named molecular beam and ionization chamber, based on the formation of the molecular beam due to supersonic expansion and ionization of the coldest part of the molecular beam extracted by the skimmer, respectively. The molecular beam chamber is pumped by a 10-inch diffstack oil diffusion pump (OD250, HindHivac), having a pumping speed of 2000 L/s. This diffusion pump is further backed by the oil roughing pump (FD-60, HindHivac) with a pumping speed of 17 L/s. In contrast, the ionization chamber is pumped by the 4.5 inch diffstack oil diffusion pump (OD-114, HindHivac), having a pumping speed of 280 L/s. It is further backed by an oil roughing pump with a pumping speed of 6 L/s. The pneumatic gate valves separate the diffusion pumps from the molecular beam and ionization chambers. The upper portion of the diffusion pump is fitted with copper baffles cooled with liquid nitrogen to prevent the diffusion pump oil from entering the vacuum chambers. The inner walls of the diffusion pumps are cooled by the cold water maintained at 18 °C. The typical base

pressure in the molecular beam and ionization chamber is 1×10^{-6} and 1×10^{-7} mbar, respectively. A commercial pulse solenoid valve (General valve, Series 9, 10 Hz repetition rate, opening time ~ 180 -200 μ s) of orifice diameter 200-500 microns operated by a pulse driver (IOTA ONE, Parker Instrumentation) is placed in the molecular beam chamber. It is used to create the pulses of the molecular beam, where numerous collisions at its orifice result in molecular cooling. The pulse valve is placed just after the stainless steel sample holder and is connected via a steel pipe mounted with an XYZ manipulator. This XYZ manipulator is used to align the orifice of the pulse valve with respect to the skimmer (separated by ~ 25 mm distance) to ensure the coldest part of the molecular beam is entering the ionization beam chamber to maximize the ion-signal.

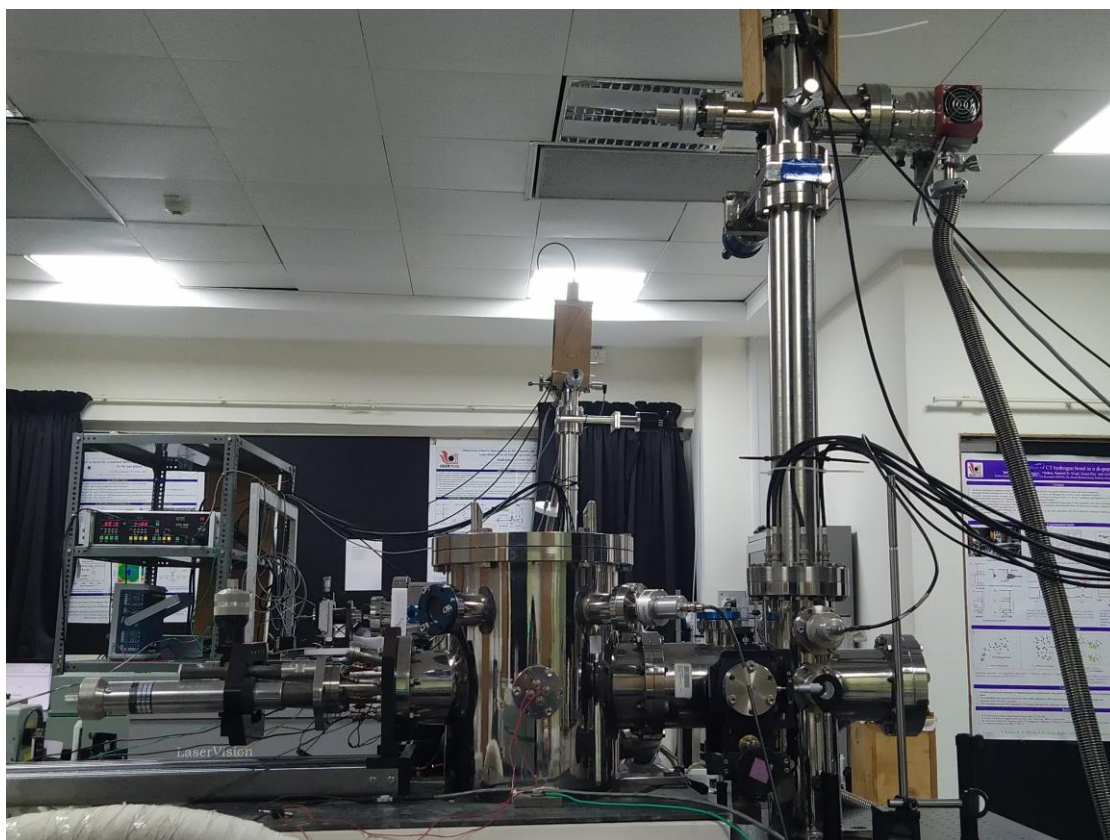


Figure 2.9. REMPI-TOF-MS experimental set-up at Indian Institute of Science Education and Research (IISER) Pune.

A schematic diagram of a generalized set-up for performing gas-phase laser spectroscopy experiments employing REMPI techniques coupled with supersonic jet-cooling has been provided in Figure 2.10. The sample is kept in the sample holder behind the pulse valve and heated at a particular temperature to obtain sufficient vapor of the sample for experimenting. Sometimes, a sample is kept outside the vacuum chamber if it is highly volatile so that it can be cooled at an optimum temperature to control the vapor pressure of the sample. A buffer gas

of He, Ne, Ar, or a mixture of these gases with different proportions with a pressure of 1500–4500 mbar is flown to carry the sample vapor for the supersonic expansion. The extracted coldest part of the molecular beam reaches the ionization region of the ionization chamber. A pulse UV laser with a 10 Hz repetition rate with a pulse width of 10 ns crosses the molecular beam at a right angle at the ionization region, resulting in ionization using the R2PI technique. An eight-channel digit delay generator (BNC, model 575) is used to temporally synchronize the opening and delay of the pulse valve with respect to the firing of the UV laser.

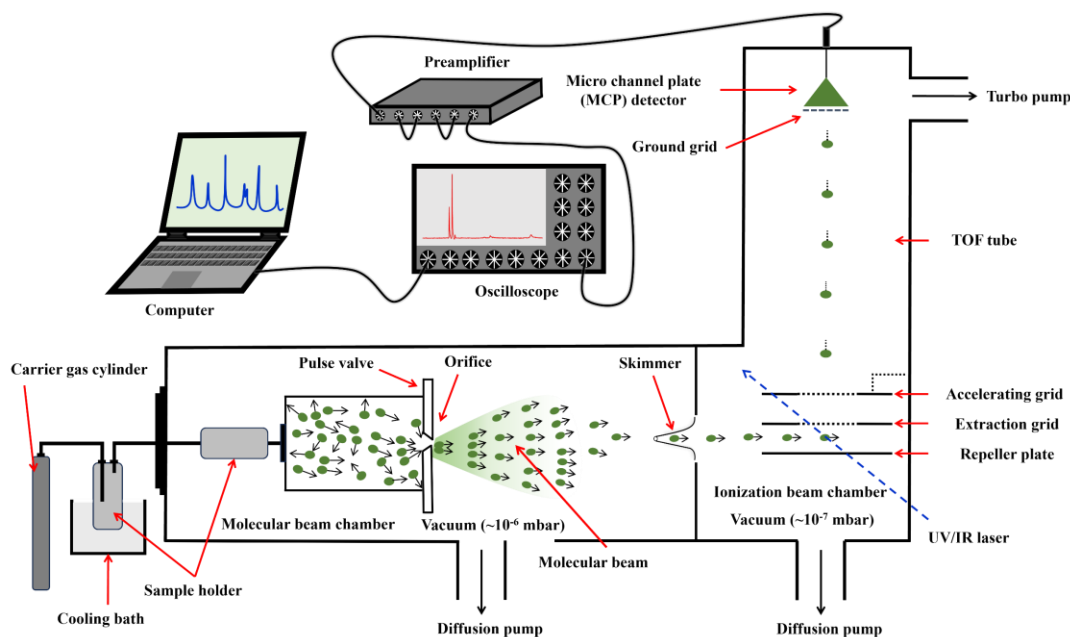


Figure 2.10. A schematic diagram of a REMPI-TOF-MS set-up for performing gas-phase laser spectroscopy experiments.

A two-stage ion source consisting of three electrode plates following the Wiley-McLaren design with a 1 m linear TOF tube is incorporated into the ionization chamber. The TOF tube is placed perpendicular to the axis of the molecular beam. The ions generated in the ionization region move in the direction perpendicular to both the molecular beam and the laser beam. The ions are finally detected by an MCP detector placed at the end of the TOF tube. The detector chamber is pumped by a turbomolecular pump with a pumping speed of 70 L/s, backed by a dry scroll pump (SH-110, Varian, pumping speed 1.5 L/s), and the operating pressure is maintained at $\sim 1 \times 10^{-7}$ mbar. A grounding mesh is placed just before the detector to ensure that the ions coming out of the accelerating grid travel the field-free region of the TOF tube with the same kinetic energy. These ions of different masses reach the detector at different times. This ion signal is amplified using a preamplifier (SRS, Model SR445A) and can be observed in the digital oscilloscope (Tektronix, 350 MHz, DPO 4034). The TOF-MS of the molecular

system is recorded at a single wavelength, and the mass-selected electronic spectrum is recorded by gating a particular mass channel on the oscilloscope and tuning the wavelength of the UV laser. The LabView-based program uses a USB interface to acquire data from the oscilloscope and simultaneously scan the laser wavelength.

2.2.7 Microwave spectroscopy

The rotational spectrum was recorded with a broadband supersonic-expansion chirped-pulsed Fourier transform microwave spectrometer operating in 2-8 GHz. Microwave spectroscopy was performed in the laboratory of Prof. Alberto Lesarri at the University of Valladolid, Spain, for the work presented in Chapter 4. The spectrometer uses the direct-digital design developed by Pate.¹⁶⁶ A transient excitation was produced with a 4 μ s chirp pulse created by an arbitrary waveform generator, which was later amplified to 20 W for probing the jet. The radiation excites the moving expansion perpendicularly, using a horn antenna. The subsequent time-domain free-induction decay is detected through a second collinear horn antenna, recorded with a digital oscilloscope (25 GS/s), and Fourier transformed to yield the frequency-domain spectrum. The pulsed molecular jet was created by expanding neon at 2.5 bar through an 800 micron circular nozzle into the evacuated expansion chamber, where the effective rotational temperature was estimated to be ~ 2 K. Phenyl formate was vaporized in a liquid heating reservoir at the exit channel at temperatures of 313-333 K while the H₂O vapor was added to the expanding gas through an external reservoir.

2.2.8 Tunable lasers

The details and optical schematic diagrams of the tunable UV and IR lasers used to perform these experiments have been discussed in detail in the following sections. These lasers are pumped with a Neodymium Yttrium Aluminium Garnet (Nd: YAG) laser (Continuum, Surelite II-10, 10 Hz repetition rate, 10 ns pulse width). The schematic diagram of the pump Nd: YAG laser is shown in Figure 2.11, consisting of a rear mirror, Pockel cell, quarter waveplate, dielectric polarizer, active medium, highly reflective mirror, output beam compensator, second harmonic generation crystal (required for pumping the dye laser). This active medium of Nd³⁺ doped with YAG of doping level varying between 0.9-1.4% is pumped by the flashlamp filled with Xenon gas at 1-3 atmosphere. This flashlamp and Nd: YAG rod is cooled by single distilled water. Q-switch starts lasing in the resonator once the laser gain reaches its peak and then opens the cavity to allow oscillation. It comprises a dielectric polarizer, Pockel cell, and quarter waveplate. Nd: YAG laser generates the fundamental wavelength output of 1064 nm

photons with a pulse energy of 650 mJ with horizontal polarization. These 1064 nm photons pump IR OPO/OPA systems. However, the dye laser (needed to produce UV photons) is pumped by the second harmonic doubled output of the Nd: YAG pump laser, i.e., 532 nm. The second harmonic generation (SHG) crystal is placed just after the output beam compensator at the end of the laser bench. This crystal produces the 532 nm beam (~350 mJ pulse energy) of vertical polarization with some residual photons of 1064 nm. Thus, the wavelength separation is done with the help of the Surelite separation package (SSP-1), comprising a set of dichroic mirrors. The first dichroic mirror is transparent towards 1064 nm while reflective for 532 nm. The dichroic mirrors steer the separated 1064 nm and 532 nm beams toward the output port. The residual 1064 nm can mix with the dye fundamental or with the doubled output of the dye fundamental in the UV tracker (UVT). If a residual 1064 nm beam is not needed, it is safely disposed of at the beam dump.

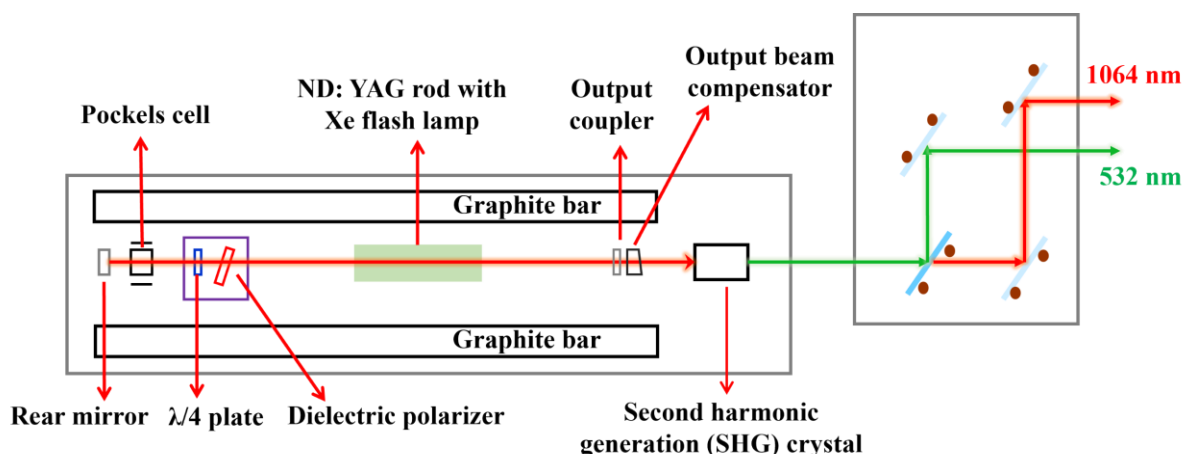


Figure 2.11. A schematic diagram of the pump Nd: YAG laser along with the surelite separator used to separate residual 1064 nm light from 532 nm light.

2.2.8.1 Dye laser

Herein, the organic dye solution dissolved in the HPLC-grade methanol is used as an active medium. Different types of organic dye, such as Fluorescein, Rhodamine 590, Rhodamine 610, Rhodamine 640, DCM, and LDS-698, are used to generate the laser beam of different wavelength ranges. These organic dyes have excellent photochemical stability, high quantum yield, and minimum intersystem crossing for better fluorescence. Most of these dye molecules have a broad range of emission profiles upon excitation by the 532 nm beam. The dye laser consists of a rectangular-shaped oscillator, pre-amplifier cells, and capillary-shaped final amplifier cells. The doubled output of the pump laser splits into two parts *via* a beam splitter (BS1). A 5% output of the pump laser reflected from this beam splitter is utilized in pumping

the oscillator dye cell. The rest of the output transmits to another beam splitter (BS2) by passing through four dichroic mirrors, where 10% of this residual output is reflected to pump the pre-amplifier dye cell, and 90% of this residual output is transmitted to pump the final amplifier dye cell via a prism.

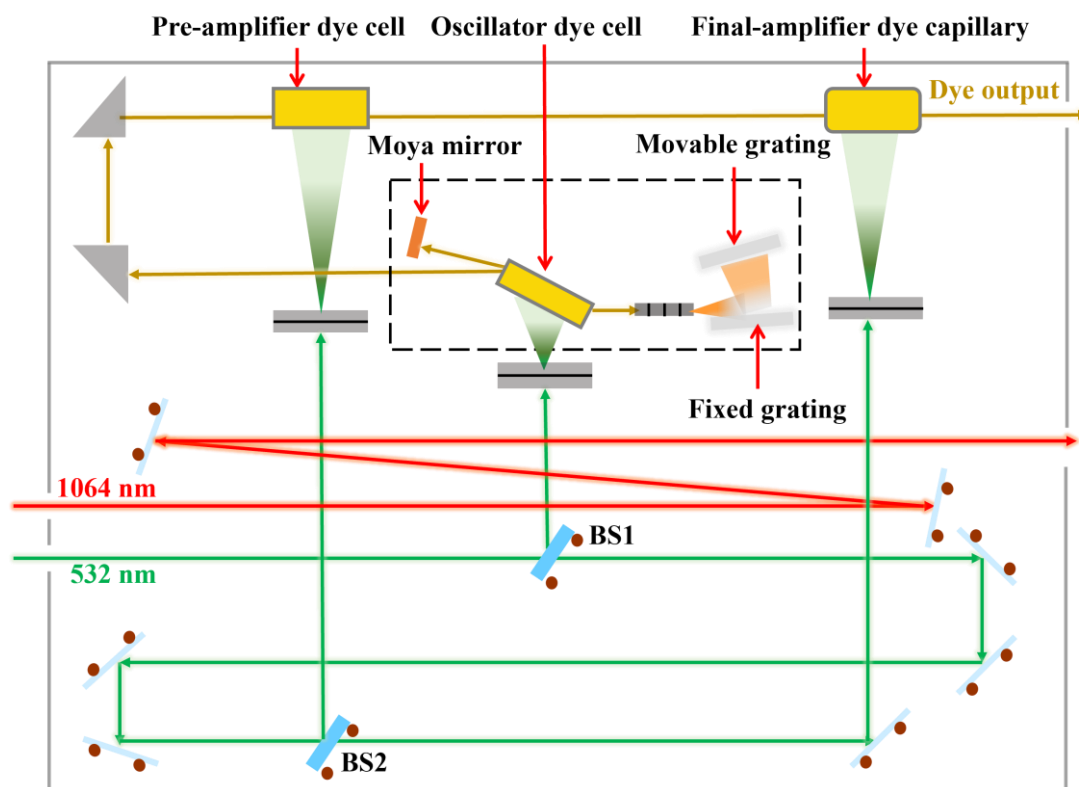


Figure 2.12. A schematic diagram of the dye laser (ND6000).

The oscillator assembly is kept in a casing with thermal isolation from the optical bench to maintain a constant temperature of 308 K for better frequency stability of the oscillator output. The oscillator cavity consists of a dye cell, beam expander (a set of four prisms), grating, sine drive mirror, and Moya mirror. A fraction of the pump laser output sequentially falls on the cylindrical lens (used for expanding the beam), spherical lens (used for making the elliptical beam), and oscillator dye cell. The pump beam excites the dye molecules and produces the fluorescence when these molecules come back to their ground state, which passes through the beam expander (used to expand the dye fluorescence so that it can cover the entire grating) and falls on the high-resolution dual grating (2400 lines/mm) for better wavelength selectivity. Using a beam expander, this utilization of grating surface is known as grazing-incidence grating tuning (a part of the Moya dye laser cavity). The two highly reflecting mirrors complete this laser cavity, the Moya mirror near the dye cell and the sine drive mirror placed after the grating. After diffracting from the grating, the dye fluorescence falls on the flat

rectangular silvered sine drive mirror. It rotates around the center of the grating for wavelength selection. The lasing from the oscillator cavity is coupled out by diffracting from the edge of the dye cell window. It should be noted here that the path of the oscillator laser output is neither in the path of the laser oscillation nor in the direction of fluorescence from the dye cell. The oscillator laser output passes through the pre-amplifier dye cell. 10% of the residual pump energy is focussed onto a pre-amplifier dye cell, which overlaps with the oscillator lasing, amplifying the laser power. The pre-amplifier output is passed through the final amplifier dye cell. 90% of the residual pump energy is focussed in the dye capillary and overlaps with the pre-amplifier output, producing the circular beam of dye laser output of 50-80 mJ pulse energy (varies for different dyes) with vertical polarization.

This dye fundamental (visible) is further passed into a UVT, where it is converted to the UV beam *via* frequency doubling or frequency mixing after frequency doubling using potassium dideuterium phosphate (KD*P) and β -barium borate (BBO) non-linear crystals. The dye fundamental reaches frequency doubling and frequency mixing crystals using dye turning prisms (DP) and polarization rotation prism assembly (PR). These frequency doubling and frequency mixing crystals are placed after the quartz compensating crystals to correct the path of the beam with the change in the wavelength of the dye laser. This UVT has two harmonic positioning stages; mixing crystal is always placed in stage 2, whereas doubling crystal can be placed in either of these stages. When only frequency doubled output is required, a frequency-doubling crystal is placed at stage 2. The output wavelength of the frequency doubling crystal is half of the dye fundamental. The residual dye beam and the horizontally polarized frequency doubled output emerge from this stage. Moreover, when frequency mixing after doubling output is required, doubling crystal is placed at stage 1. PR is used to change the polarization of the dye beam to the horizontal to match the polarization axis of the frequency doubled crystal at stage 1. The residual 1064 nm energy (horizontal polarization) from the SSP-1 reaches the frequency mixing crystal at stage 2 by steering the 1064 nm beam throughout the dye laser using two mirrors and inside UVT using two IR mirrors (IM) and two IR turning prisms (IP). This residual 1064 nm beam mixes with the doubled output of dye fundamental from stage 1 (vertical polarization) inside the mixing crystal. The wavelength of the mixing output after doubling (horizontal polarization) can be calculated by the formula $1/(\text{mixed output after doubling}) = 1/1064 + 1/(\text{doubled output of dye fundamental})$. This UV beam (doubled or mixed after doubled), the residual dye beam, and others exit the UVT using a turning prism or Pellin-Broca. This turning prism steers these beams into a set of four Pellin-Broca prisms placed just after the exit of UVT. This set of Pellin-Broca crystals helps separate the desired UV output of

horizontal polarization from these residual beams. It directs the UV output into the mirror, where it is sent to the vacuum chambers to utilize for the REMPI experiment.

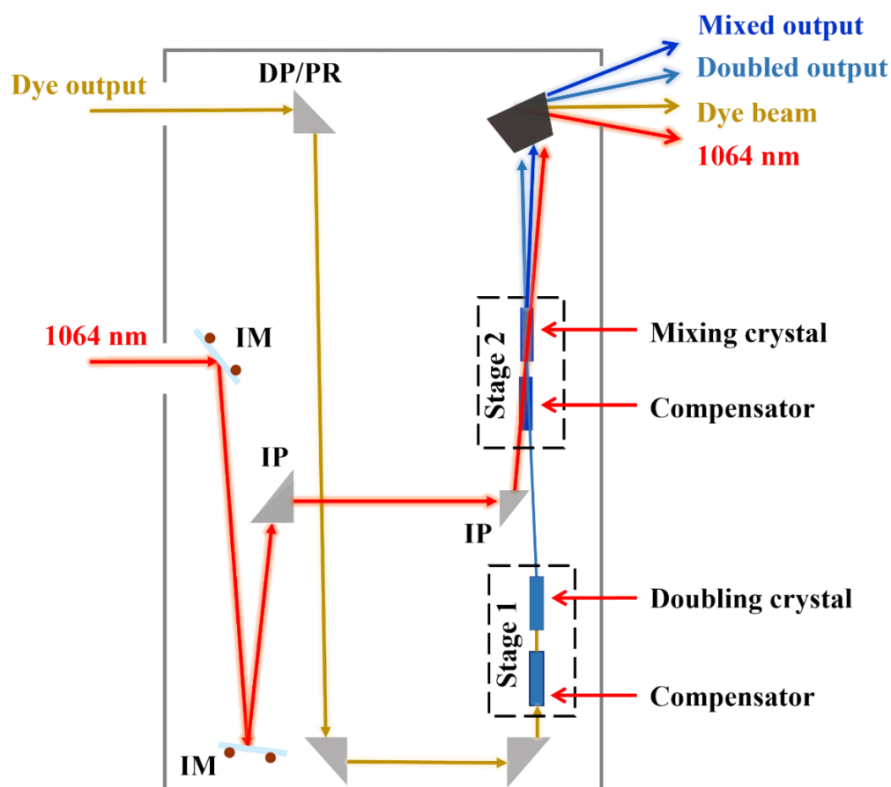


Figure 2.13. A schematic diagram of the UV tracker (UVT).

2.2.8.2 IR laser

The infrared laser (LaserVision) consists of two significant parts: an optical parametric oscillator (OPO) and an optical parametric amplifier (OPA). 1064 nm beam (horizontally polarized) from the pump Nd: YAG laser enters inside the IR laser using two highly reflecting mirrors used for fine alignment and passes through the telescope to adjust the beam profile, including beam resizing. A beam splitter (BS) divides this focussed beam into two parts. One-third of the pump beam energy is directed towards the half-wave plate attenuator (used to control the conversion efficiency) of the rotation stage just before the BBO crystal, where it doubled frequency (532 nm), which is passed into the OPO stage. The frequency doubled output beam is incident on the potassium titanyl phosphate (KTP) non-linear crystal via two highly reflecting mirrors and output coupler, resulting in the generation of two photons of near IR (710-880 nm) and intermediate IR (1.35-2.13 μm) via optical parametric oscillation. This crystal is mounted on a stepper motor, and tuning the angle of this crystal results in a change of the phase match angle, which results in the wavelength tuning. The photon of the near IR region is known as OPO signal, and of intermediate IR is known as OPO idler. The sum of

these photon energies is equal to the energy of the 532 nm photon, and these wavelengths can be determined by the formula $1/532 = 1/(\text{OPO signal}) + 1/(\text{OPO idler})$. This non-linear KTP crystal is placed in a cavity of highly reflective mirrors, such as the rear mirror and output coupler. Another additional mirror with silver coating reflects any leakage of the idler beam from the rear mirror. The output coupler results in the leakage of the OPO signal and OPO idler and results in the lasing output, which passes through the dove prism used for the collimation of the vertically elliptical beam and rotating it by 90° , making it horizontally elliptical beam. This horizontal elliptical beam passes through the MgF_2 waveplate used to change the polarization from vertical to horizontal and correct the slight scrambling due to the dove prism.

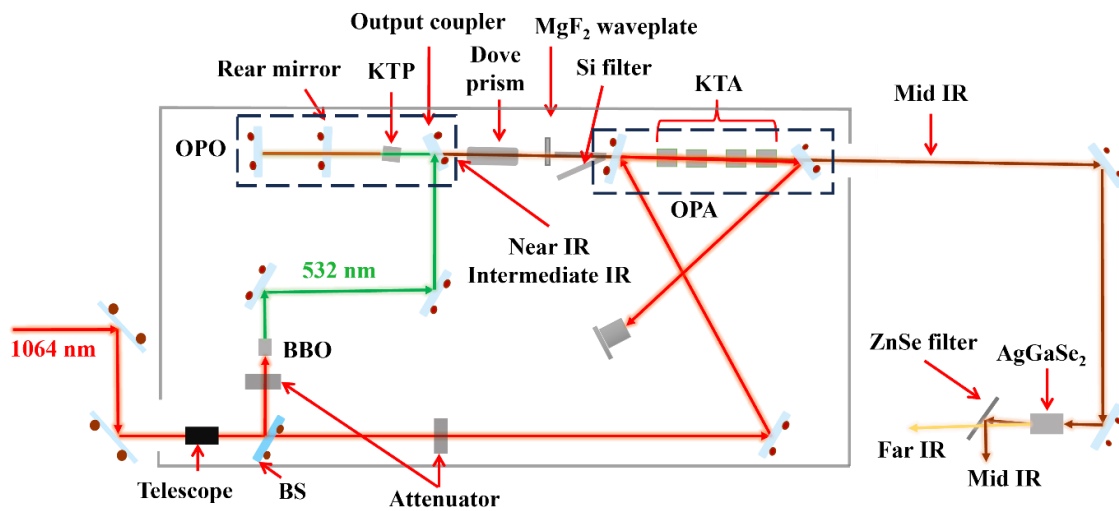


Figure 2.14. A schematic diagram of the IR laser comprised of OPO and OPA with far-IR generation set-up.

Two-third of the pump beam energy (OPA pump) passes through the half waveplate along with the 1064 nm attenuator, changing the polarization to vertical and controlling the 1064 nm pump energy for the OPA stage. It is further allowed to pass through the OPA stage using two 1064 nm steering mirrors (M3 and M4) along the direction of the OPO idler, which became an OPA signal for the OPA stage. The OPA stage consists of two pairs of potassium titanyl arsenate (KTA) non-linear crystals. Crystals from each pair rotate in opposite directions to compensate for any change in the path of the beam (similar to the quartz compensating crystal used in the doubling and mixing stage of the UVT discussed in the previous section). These KTA crystals are also mounted on the stepper motor, whose positions are aligned for the optimization of energy as well as for better phase matching angle. OPO output from the MgF_2 waveplate enters the OPA stage by passing through the final 1064 nm steering mirror (M4) and mixing it with the 1064 nm pump beam. In these crystals, the difference frequency mixing of

both these beams takes place and generates the photon of mid-IR (2.13-5.02 μm) with vertical polarization. The wavelength of the OPA output/idler can be calculated by the formula $1/(\text{OPA output}) = 1/1064 - 1/(\text{OPA signal})$ [OPA signal = OPO idler]. At the same time, the OPO signal also undergoes difference frequency mixing, hence amplifying the intermediate IR, i.e., OPO idler. The formula of $1/(\text{OPO idler}) = 1/(\text{OPO signal}) - 1/1064$ confirms the amplification of the intermediate IR photon. Any residual 1064 nm is filtered out using a 1064 nm separating mirror placed just after the OPA stage and falls on the beam dump. This 1064 nm separating mirror is transparent to the intermediate IR and mid-IR photons. Thus, the OPA signal and OPA idler are passed through the stack-of-plates silicon polarizer with vertical polarization, which passes only the OPA idler, i.e., mid-IR. The resolution of this IR laser is $\sim 2 \text{ cm}^{-1}$. These mid-IR photons exit from the IR laser and enter the ionization chamber *via* two gold-coated mirrors for performing the IR experiments to probe the vibrational frequencies of the various functional groups, such as O–H, N–H, C–H, and S–H.

An extension of a few more optics in the existing optical set-up of the generation of mid-IR is required to generate the far-IR photon after the generation of the mid-IR photons. A silicon filter is placed just after the MgF_2 waveplate to block the OPO signal so that only the OPO idler reaches the OPA stage. Furthermore, the stack-of-plates silicon polarizer is removed so that both the OPA signal and OPA idler can be mixed at silver gallium selenide (AgGaSe_2) crystal at the $\sim 2 \text{ m}$ distance of the exit port of the IR laser after passing through two gold-coated mirrors placed. This crystal is also placed on a stepper motor whose angle is tuned for a better phase-matching angle. The wavelength of the far-IR output with vertical polarization after difference frequency mixing inside the AgGaSe_2 crystal can be calculated by the formula $1/(\text{far-IR output}) = (1/\text{OPA signal}) - 1/(\text{OPA idler})$. This output is passed through the zinc selenide (ZnSe) filter placed at the 45° angle to reflect the residual pump beams towards the optical bench, which only allows the transmission of the far-IR beam. This far-IR beam enters the ionization chamber *via* two gold-coated mirrors from the opposite end of the UV laser.

2.2.9 Solution-phase studies (HRMS, NMR, IR, UV-Vis, Emission, and lifetime)

High-resolution mass spectra (HRMS) were recorded using an AB Sciex 4800 plus HRMS instrument. NMR spectra were recorded in CDCl_3 solvent using a Bruker 400 MHz spectrometer. The variable temperature NMR spectra were performed in CDCl_3 solvent in the 218-328 K range using tetramethylsilane as an internal standard. IR spectrum was recorded to determine carbonyl stretching frequency ($\nu_{\text{C=O}}$) in CCl_4 solvent using ALPHA-II ECO ATR, Bruker. The steady-state absorption spectrum was recorded using a UV-2600 UV-Vis

spectrophotometer, Shimadzu. The steady-state emission spectrum was recorded using a FluoroMax-4 spectrofluorometer (HORIBA Jobin Yvon, USA). Lifetime was measured using fluorescence decays collected using a TCSPC setup (HORIBA Jobin Yvon). Diode lasers (NanoLED-375L, IBH, UK) having an FWHM of 100 ps were used as the excitation sources for lifetime studies. These studies have been performed for the work presented in Chapter 5.

2.3 Quantum Chemistry Calculations

As discussed in Chapter 1, theoretical calculations and experiments go hand in hand to probe the strength and nature of the $n \rightarrow \pi^*$ interaction directly. Theoretical calculations can predict the conformation of the molecular system to be present in the experiment to a reasonable extent. Thus, a brief discussion over obtaining several conformations of the molecular systems *via* quantum chemistry calculation is necessary. Various theoretical analyses used to study the $n \rightarrow \pi^*$ interaction, such as NBO, QTAIM, and NCI, have already been discussed in Chapter 1.

2.3.1 Obtaining various ground state local minima of the potential energy surface

Various local minima (S_0) of the potential energy surface of a molecular system are obtained from the Marvin sketch program using the MMFF94 force field and by chemical intuition.¹⁶⁷ Dihedral angles are tuned for the flexible molecules to obtain any missing conformers from the Marvin sketch program. For the complexes, various local minima were obtained by complexation at the active binding sites of various conformations of the monomer at which another molecule can bind through the $n \rightarrow \pi^*$ interaction or other non-covalent interactions. It provides a pool of the various possible local minima of any molecule or complexes.

2.3.2 Confirmation of the actual local minima of conformers

Two types of calculation, such as wavefunctional theory and density functional theory (DFT), have been used to optimize the ground state geometry of the conformers. Various functionals, such as HF, MP2, B3LYP, Grimme's dispersion corrected B3LYP (B3LYP-D3), including Becke-Jones damping correction in B3LYP-D3 [B3LYP-D3(BJ)], M05-2X, M06-2X, B97-D, B97-D3, and ω B97X-D along with several basis sets, such as 6-31+G(d), 6-311++G(d,p), aug-cc-pVDZ, aug-cc-pVTZ, and def2-TZVP have been used to perform these calculations. The conformers obtained from the Marvin sketch program and chemical intuition are optimized at the HF/6-31+G(d) level and grouped based on the structure and energetics with an energy limit of 0.3 kJ/mol so that any probable conformer should not be missed. These selected conformers are further optimized at the other calculation levels. These calculations are performed using an ultrafine numerical integration grid and tight convergence criterion in the Gaussian 09 program

package.¹⁶⁸ The harmonic vibrational frequencies of all the conformers of the molecular system are calculated to ensure true minima corresponding to the optimized geometries and to compare them with the experimentally observed IR frequencies of the detected conformers. The relative energies of the various conformations are obtained with respect to the most stable conformer of the molecular system. The zero-point energy (ZPE) correction is employed to correct these energies. The binding energies or interaction energies of the complex are calculated by subtracting the ZPE-corrected energy of all the monomers involved in the formation of the complex from the ZPE-corrected energy of the complex. The basis-set superposition error (BSSE) further corrects this binding energy. The basis functions of these monomers also overlap as the monomers involved in the complex interact due to the non-covalent interactions. Hence, practical basis functions over the interacting sites of the nearby monomer increase, resulting in the shortening of the intermolecular distances between these interacting sites and affecting the strength of non-covalent interactions involved. The counterpoise method given by Boys and Bernadi is used to perform BSSE correction.¹⁶⁹

2.3.3 Excited state calculations

Excited state (S_1) geometries of the molecular systems have been optimized using the configuration interaction singles approach (CIS) and time-dependent density functional theory (TD-DFT) calculations available with the Gaussian program package.¹⁶⁸

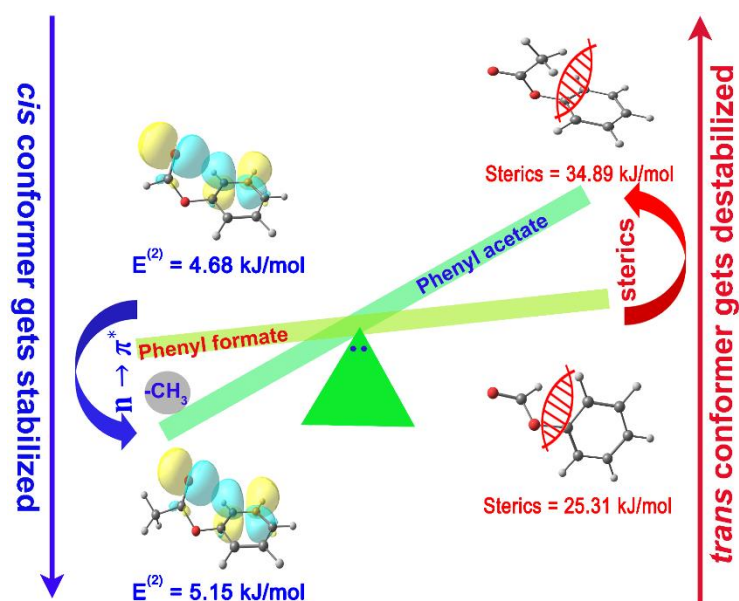
2.3.4 Transition state calculation

Transition state (first-order saddle point) geometries for the interconversion of conformers are calculated using the quadratic synchronous transit (QST2) approach. These geometries are ensured by the presence of one imaginary frequency along the coordinate of the interconversion. The relaxed potential energy scan (PES), which is performed to find the transition state, also provides the energy barrier of the interconversion.

2.3.5 Incorporating solvent effects using solvent continuum

Ground state geometry optimizations are also performed in the solution-phase using the polarizable continuum model (PCM) employing the integral equation formalism variant (IEFPCM) available in the Gaussian 09 program package.^{170, 171} Solution-phase calculations were done using various solvents such as H_2O (polar protic), CH_2Cl_2 (polar aprotic), and CCl_4 (non-polar). These studies have been performed for the work presented in Chapters 6 and 7.

Chapter 3: Steric as well as $C=O \cdots \text{aromatic } n \rightarrow \pi^*$ interaction controls the conformational preferences of phenyl acetate



Adapted from: S. K. Singh[‡], P. Panwaria[‡], K. K. Mishra, A. Das*, Steric as well as $n \rightarrow \pi^*$ interaction controls the conformational preferences of phenyl acetate: Gas-phase spectroscopy and quantum chemical calculations. *Chem. Asian J.* **2019**, *14*, 4705-4711 ([‡]*Equal Contribution*).

3.1 Motivation of this work

As discussed in detail in Chapter 1, the first gas-phase IR spectroscopic evidence of the $n \rightarrow \pi^*$ interaction in phenyl formate was provided by our group earlier.⁹² Two conformers were observed in the experiment, *cis*-phenyl formate and *trans*-phenyl formate, classified based on the orientation of the carbonyl group with respect to the aromatic ring. *Cis*-phenyl formate has the carbonyl group toward the aromatic ring, and *trans*-phenyl formate has the carbonyl group away from the aromatic ring, thus making the *cis*-phenyl formate favorable for the $n \rightarrow \pi^*$ interaction from the lone pair orbital of the carbonyl oxygen to the π^* orbital of the aromatic ring. The presence of the $n \rightarrow \pi^*$ interaction in *cis*-phenyl formate was confirmed by the redshift observed in the carbonyl stretching frequency of the *cis*-phenyl formate compared to the *trans*-phenyl formate lacking this interaction. Further, it was thought that if the formyl hydrogen of the phenyl formate could be substituted by the methyl group, i.e., phenyl acetate, it would push the electron density toward the carbonyl group because of its +I effect. This electron push from the methyl group will increase the availability of the electron density over the carbonyl oxygen. Thus, the delocalization of the lone pair electron density to the π^* orbital of the aromatic ring will be increased. In this chapter, we will be studying the effect of the methyl group on the strength of the $n \rightarrow \pi^*$ interaction and other parameters, which reduces the conformational heterogeneity of the phenyl acetate.

3.2 Introduction

In general, electronic and steric effects play a central role in the conformational preferences of molecules and complexes.^{51, 59, 172-175} Electronic effects include various non-covalent interactions, hyperconjugation, and inductive effects. Steric effects, which arise due to repulsion between different groups in molecules, can also influence the conformational preferences of molecules. Increasing the steric effect in molecular systems by incorporating bulky substituents reduces conformational diversity and selectively promotes a conformer for optimum structure and function of biomolecules, supramolecular assemblies, and drugs.

The strength of the $n \rightarrow \pi^*$ interaction can be tuned by introducing EDG and EWG on the $n \rightarrow \pi^*$ donor and acceptor groups of the molecular systems. Substitution of the EDG on the $n \rightarrow \pi^*$ donor increases the strength of the $n \rightarrow \pi^*$ interaction by increasing the electron density over the carbonyl oxygen. In contrast, the EWG on the $n \rightarrow \pi^*$ donor decreases the strength of the $n \rightarrow \pi^*$ interaction by pulling the electron density away from the carbonyl oxygen.^{51, 66, 97} The substituent on the $n \rightarrow \pi^*$ donor can also introduce steric repulsion in one of the conformers by rendering conformational preference of the other. The substituent can have additional

electronic effects on the carbonyl moiety through hyperconjugation.^{44, 47, 50, 51, 55, 60, 99, 125, 176} Many reports in the literature show the electronic and steric control of conformational populations of molecular systems.^{45, 60, 91, 172, 177, 178} However, the study of conformational homogeneity or specificity controlled by the $n \rightarrow \pi^*$ interaction and steric effect is scarce in the literature. Recently, Zondlo and co-workers have demonstrated through NMR spectroscopy and quantum chemistry calculations of acyl *N*-cap proline derivatives that preferences toward a defined conformation can be modulated through steric and electronic control of the $n \rightarrow \pi^*$ interactions by varying the bulkiness of the acyl substitution present there.⁵¹ Blackwell and co-workers have also reported that $n \rightarrow \pi^*$ interaction and steric repulsion can regulate the *cis* and *trans* isomerization ratios of peptoid oligomers.⁶⁶ Raines and co-workers have shown that the preferences of the *trans* conformation of the amide bonds in peptides and proteins are due to both $n \rightarrow \pi^*$ interaction (electronic) and steric effects.^{45, 107, 179, 180}

In this chapter, we will discuss the conformational preference of phenyl acetate by introducing a methyl group at the $n \rightarrow \pi^*$ donor (carbonyl group) employing gas-phase electronic and vibrational spectroscopy coupled with quantum chemistry calculations. The present spectroscopic investigation on phenyl acetate focuses on studying the conformational preferences induced by the effect of methyl substitution on the strength of the $n \rightarrow \pi^*$ interaction, steric repulsion, and hyperconjugation simultaneously. In the case of phenyl formate reported earlier, both the *cis* and *trans* conformers were observed in the experiment.⁹² Conversely, the current chapter shows the exclusive observation of the *cis* conformer having the $n \rightarrow \pi^*$ interaction. The *trans* conformer of phenyl acetate with the methyl group projected towards the phenyl ring is absent in the experiment. The present research on understanding the conformational preferences due to the steric effects and non-covalent interaction may have significant implications for designing materials, biomolecules, and drugs with desired conformational specificity for their optimum structures and functions.

3.3 Results and Discussion

Before starting the gas-phase experiments, we tried to look for the theoretical conformational landscape of phenyl acetate. Figure 3.1 shows the structures and ZPE-corrected relative energetics of the *cis* and *trans* conformers of phenyl acetate and phenyl formate optimized at the M05-2X/aug-cc-pVDZ level. It can be observed that the conformational landscape of phenyl acetate is similar to that of the phenyl formate, where the *cis* conformer is stable as compared to the *trans* conformer.⁹² These conformers have been classified based on the orientation of the carbonyl group with respect to the phenyl ring. In both cases, the *cis*

conformer with the carbonyl group oriented toward the phenyl ring is more stable relative to the *trans* conformer having the carbonyl group away from the phenyl ring. However, the stability of the *cis* conformer over the *trans* is much more in phenyl acetate (13.51 kJ/mol) than in phenyl formate (5.52 kJ/mol).

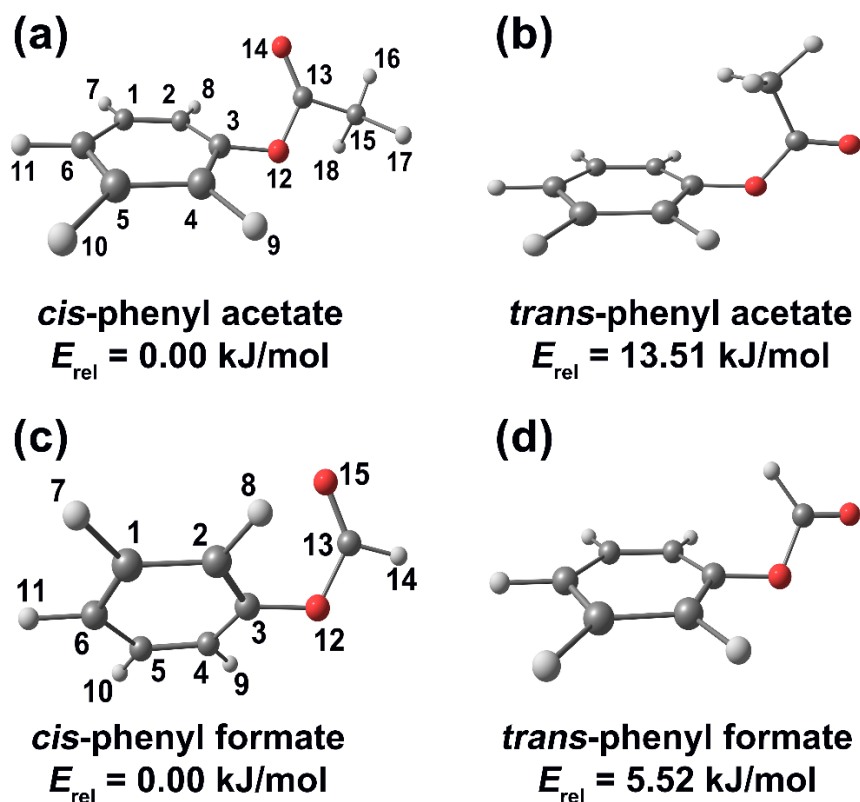
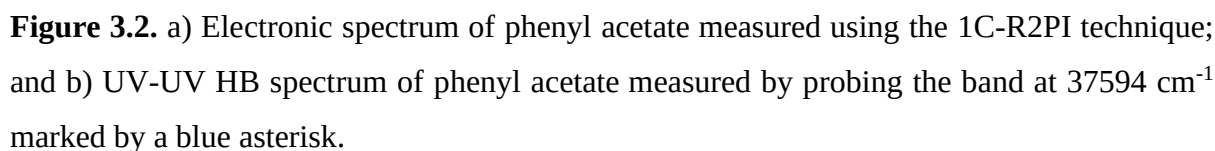


Figure 3.1. Optimized structures of the a) *cis* and b) *trans* conformers of phenyl acetate; optimized structures of the c) *cis* and d) *trans* conformers of phenyl formate, optimized at the M05-2X/aug-cc-pVDZ level. E_{rel} represents the ZPE corrected relative energies of the conformers with respect to the *cis* conformer. The atom numbering scheme is shown in the structure of the *cis* conformer.

Phenyl acetate ($\geq 98\%$, Sigma Aldrich) was heated at 333 K and seeded in Ar carrier gas at 3 bar pressure for supersonic expansion. The molecular beam of phenyl acetate was ionized using the 1C-R2PI technique to obtain the electronic spectrum through the variation of the wavelength of the UV laser. Figure 3.2a displays the electronic spectrum of phenyl acetate with its origin band (0_0^0) for the $S_1 \leftarrow S_0$ transition at 37550 cm^{-1} . The electronic spectrum shown in Figure 3.2a perfectly matches the previously reported phenyl acetate electronic spectrum measured by the LIF technique.¹⁸¹ The spectrum measured upto $\sim 300\text{ cm}^{-1}$ above the electronic origin band exhibits multiple sharp bands of appreciable intensity. Konaka and co-workers assigned all the bands in the electronic spectrum due to the electronic transition of a single



Prakash Panwaria

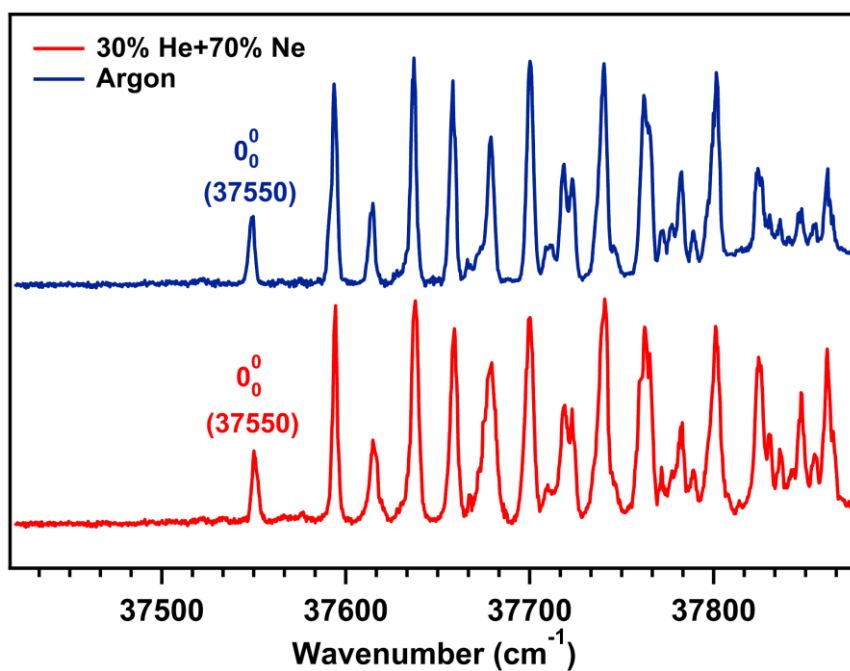


Figure 3.3. Electronic spectra of phenyl acetate measured in Ar (blue trace) and 30%He-70%Ne gas mixture (red trace).

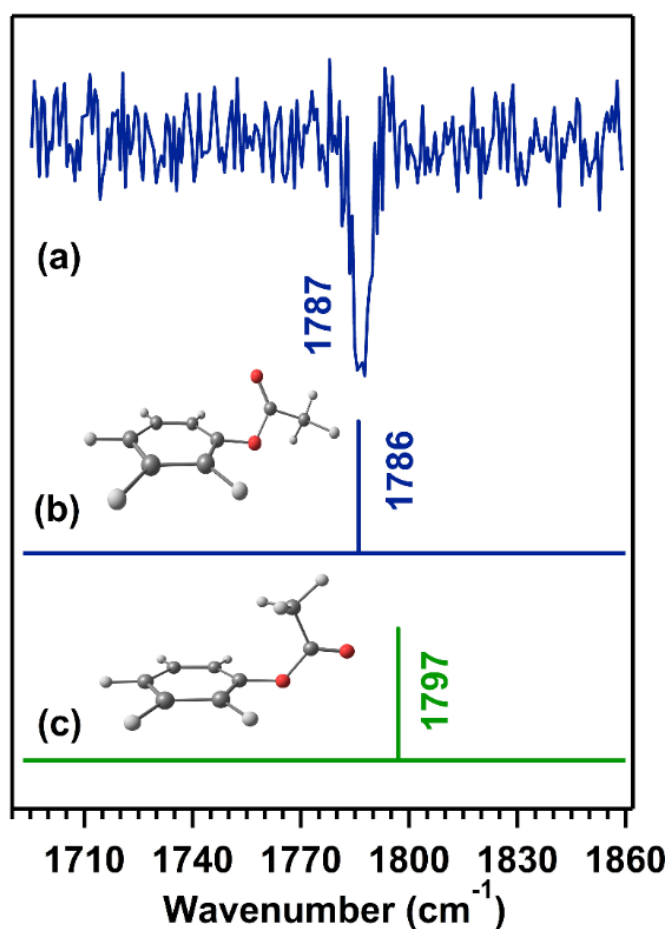


Figure 3.4. a) IR spectrum of phenyl acetate in the carbonyl stretching region obtained by probing the band at 37594 cm^{-1} in the electronic spectrum; and b-c) M05-2X/aug-cc-pVDZ

level calculated IR stick spectra of the phenyl acetate conformers, scaled by 0.9556 with respect to the *trans*-phenyl formate.⁹²

The structure of the observed conformer of phenyl acetate has been determined using RIDIR spectroscopy with the help of quantum chemistry calculations. Figure 3.4a shows the IR spectrum of phenyl acetate measured in the carbonyl stretching region by probing the band at 37594 cm⁻¹ in the electronic spectrum. Theoretical IR spectra of the *cis* and *trans* conformers of phenyl acetate calculated at the M05-2X/aug-cc-pVDZ level are displayed in Figures 3.4b and 3.4c, respectively. The harmonic carbonyl stretching frequencies have been scaled using a factor (0.9556) obtained by the ratio of the experimentally observed carbonyl stretching frequency to the M05-2X/aug-cc-pVDZ level calculated carbonyl stretching frequency of the *trans*-phenyl formate.⁹² The trend in relative energies and carbonyl stretching frequencies of phenyl acetate conformers are consistent at the different DFT levels (Table 3.1). Thus, the experimentally observed carbonyl stretching frequency at 1787 cm⁻¹ very well agrees with the calculated carbonyl stretching frequency of *cis*-phenyl acetate, confirming the observation of *cis*-phenyl acetate in the experiment.

Table 3.1. ZPE-corrected relative energies (E_{rel} , kJ/mol) and scaled carbonyl stretching frequencies ($\nu_{\text{C=O}}$, cm⁻¹) of the *cis* and *trans* conformers of phenyl acetate at the different DFT levels

DFT levels	<i>cis</i> -phenyl acetate		<i>trans</i> -phenyl acetate	
	E_{rel}	$\nu_{\text{C=O}}$	E_{rel}	$\nu_{\text{C=O}}$
M05-2X/aug-cc-pVDZ	0.00	1786	13.51	1797
ω B97X-D/aug-cc-pVDZ	0.00	1783	11.72	1794
M06-2X/aug-cc-pVDZ	0.00	1782	13.31	1795
M05-2X/6-311++G(d,p)	0.00	1783	15.98	1795
M05-2X/aug-cc-pVTZ	0.00	1781	14.94	1794

Table 3.2. Observed and calculated S_1 state vibrational frequencies (cm⁻¹) of *cis*-phenyl acetate conformer. S_1 state vibrational frequencies are calculated at the CIS/6-31+G(d) level

Observed ^a	Calculated	Assignment	Description
0.0		0 ₀ ⁰	
44	45	48 ₀ ¹	Ph-O torsion

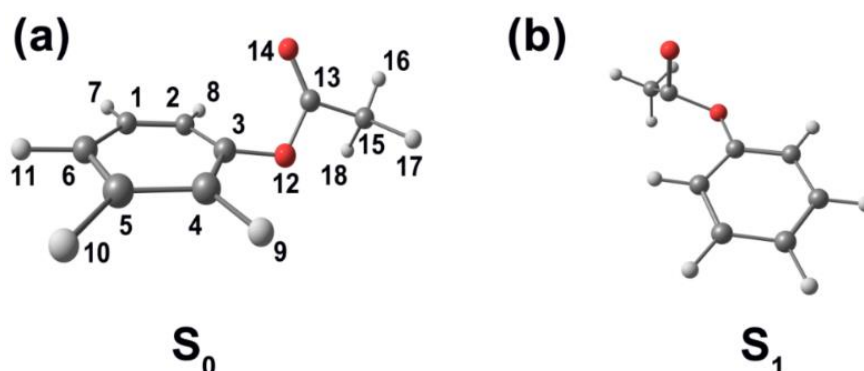
65	75	47_0^1	C=O-O torsion
87		48_0^2	
109	108	46_0^1	Methyl torsion
129	135	$48_0^3/47_0^2/45_0^1$	Ring bend (boat) + C-O-C bend
151		$47_0^1 48_0^2/46_0^1 48_0^1$	
162		-	
169		48_0^4	
174		$47_0^2 48_0^1$	
191		$47_0^3/47_0^1 48_0^3$	
212	207	$44_0^1/47_0^2 48_0^2$	Ring twist
223		$48_0^5/46_0^2$	
228	230	43_0^1	Ring bend (chair)
233		$47_0^1 48_0^4$	
239		$47_0^3 48_0^1$	
252		$47_0^2 48_0^3$	
275		$43_0^1 48_0^1$	
281		$47_0^3 48_0^2$	
287		$47_0^1 48_0^5$	
298		$43_0^1 47_0^1$	
306		$47_0^4 48_0^1$	
312		$43_0^1 48_0^2$	

^aRelative to the 0_0^0 band observed at 37550 cm^{-1} . The Mulliken notation has been used to number the vibrational modes.

The vibronic bands observed in the electronic spectrum have been tentatively assigned based on the S_1 state vibrational frequencies of the *cis*-phenyl acetate calculated at the CIS/6-31+G(d) level.⁹² Detailed assignments of the bands and a description of the modes have been

provided in Table 3.2, while the band assignments are also shown with the electronic spectrum. The S_1 state calculation reveals that bands in the electronic spectrum are mostly due to the fundamentals, overtones, and combination modes of Ph–O torsion (mode 48) of 44 cm^{-1} and O–C=O torsion (mode 47) of 65 cm^{-1} .^{92, 181} Although the modes 48 and 47 are the most active ones, the bands for the fundamental mode of methyl torsion (46_0^1) of 109 cm^{-1} , ring twist (44_0^1) of 207 cm^{-1} , and ring bend (43_0^1) of 228 cm^{-1} are also observed in the electronic spectrum. A comparison of relevant geometrical parameters and structures of the observed *cis*-phenyl acetate in the S_0 and S_1 states calculated at the M05-2X/6-31+G(d) and TD-M05-2X/6-31+G(d) levels, respectively, are provided in Table 3.3, respectively. The comparison indeed shows that there is a significant geometry change in the S_1 state compared to the S_0 state along the Ph–O torsion ($\angle\text{C}_4\text{--C}_3\text{--O}_{12}\text{--C}_{13}$) and O–C–O torsion ($\angle\text{C}_3\text{--O}_{12}\text{--C}_{13}\text{--O}_{14}$) modes.

Table 3.3. Geometrical parameters of the *cis* and *trans* conformers of phenyl acetate in the S_0 and S_1 state by TD-DFT calculation at the M05-2X/6-31+G(d) level along with the structures of *cis*-phenyl acetate with atom numbering



	<i>cis</i> (S_0)	<i>cis</i> (S_1)	<i>trans</i> (S_0)	<i>trans</i> (S_1)
C=O (Å)	1.202	1.298	1.199	1.232
C=O...ring center (Å)	3.721	4.111	-	-
^a Θ	49.0^0	99.5^0	-	-
$\angle\text{C}_3\text{--O}_{12}\text{--C}_{13}$	119.1^0	119.3^0	120.8^0	115.0^0
$\angle\text{O}_{12}\text{--C}_{13}\text{--O}_{14}$	123.8^0	104.5^0	118.3^0	118.1^0
^b $\angle\text{C}_3\text{--O}_{12}\text{--C}_{13}\text{--O}_{14}$	0.1^0	85.9^0	0.0^0	116.6^0
^c $\angle\text{C}_4\text{--C}_3\text{--O}_{12}\text{--C}_{13}$	59.1^0	24.3^0	91.7^0	145.9^0

^a Θ is the angle between the plane containing the carbonyl and the aromatic plane; ^b $\angle\text{C}_3\text{--O}_{12}\text{--C}_{13}\text{--O}_{14}$ is the O–C–O torsional angle; ^c $\angle\text{C}_4\text{--C}_3\text{--O}_{12}\text{--C}_{13}$ is the Ph–O torsional angle.

It is quite intriguing to note that both the *cis* and *trans* conformers have been observed in phenyl formate, which is an aromatic ester analogous to phenyl acetate.⁹² However, the

trans-phenyl acetate is absent in the experiment, confirmed by UV-UV HB and IR spectroscopy. Interestingly, the population of the *trans*-phenyl formate was albeit found to be very small compared to *cis*-phenyl formate based on the intensity of the vibronic bands observed in their electronic spectrum. Observation of various conformers of molecules in the experiment, i.e., the intensity of their spectroscopic transitions, greatly depends on the distribution of their Boltzmann population, conformational relaxation,⁹² and absorption cross-section. Figure 3.5 shows the Boltzmann population of the *cis* and *trans* conformers of phenyl acetate and phenyl formate, calculated from the relative change in their Gibbs free energies (ΔG^0) in the temperature range of 10-298 K using the formula given below.

$$\text{Boltzmann population (\%)} = \frac{n_2}{n_2 + n_1} * 100 = \frac{e^{\frac{-\Delta G_2}{k_B * T}}}{e^{\frac{-\Delta G_2}{k_B * T}} + e^{\frac{-\Delta G_1}{k_B * T}}} * 100$$

Where n_1 , n_2 , ΔG_1 and ΔG_2 are the population and the change in Gibbs free energy for the first and second conformers, respectively. We find that the population of *trans*-phenyl acetate is negligible up to 150 K and increases slowly to only 0.2% at 298 K. On the other hand, the population of *trans*-phenyl formate is 0% up to 90 K, and it increases quite rapidly to 7.2% at 298 K. Thus, the absence of *trans*-phenyl acetate in the experiment can be explained by negligible Boltzmann population even at 298 K.

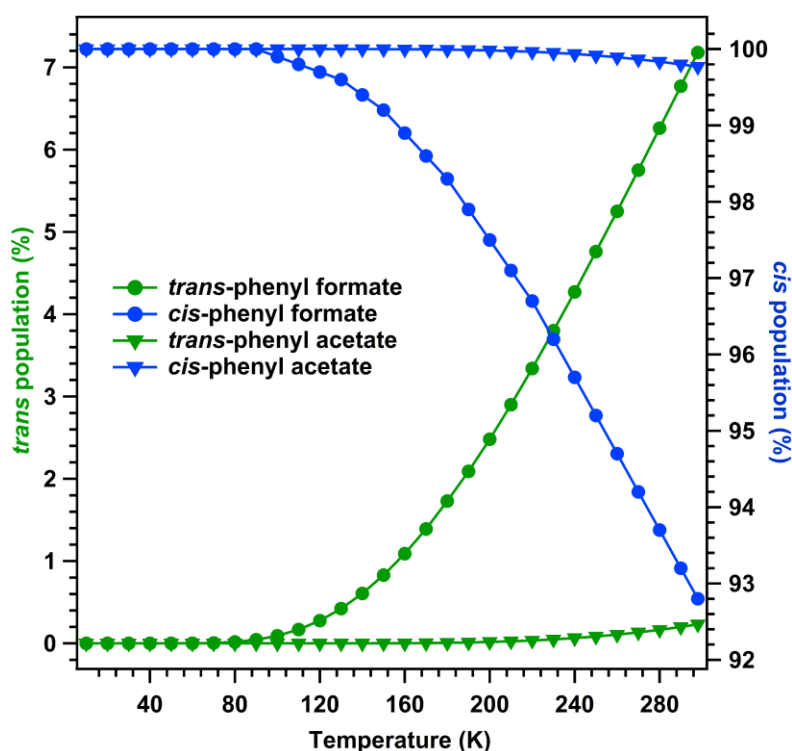


Figure 3.5. Boltzmann population distribution of the conformers of phenyl acetate and phenyl formate in the temperature range of 10-298 K calculated at the M05-2X/aug-cc-pVDZ level.

NBO analysis performed at the M05-2X/aug-cc-pVDZ level shows that the $E^{(2)}$ value of the $n \rightarrow \pi^*$ interaction between lone pair orbital on carbonyl oxygen and π^* orbital of the phenyl ring in *cis*-phenyl acetate is 5.15 kJ/mol (Figure 3.6). The *trans*-phenyl acetate does not have any $n \rightarrow \pi^*$ interaction. The $E^{(2)}$ value of the $n \rightarrow \pi^*$ interaction in *cis*-phenyl formate at the same level is 4.69 kJ/mol.⁹² The $E^{(2)}$ values of the $n \rightarrow \pi^*$ interaction in *cis* conformers of phenyl acetate and phenyl formate have been calculated at the different DFT levels (Table 3.4). Although the NBO energy of the *cis* conformer of phenyl acetate is slightly higher than phenyl formate at all the different DFT levels.

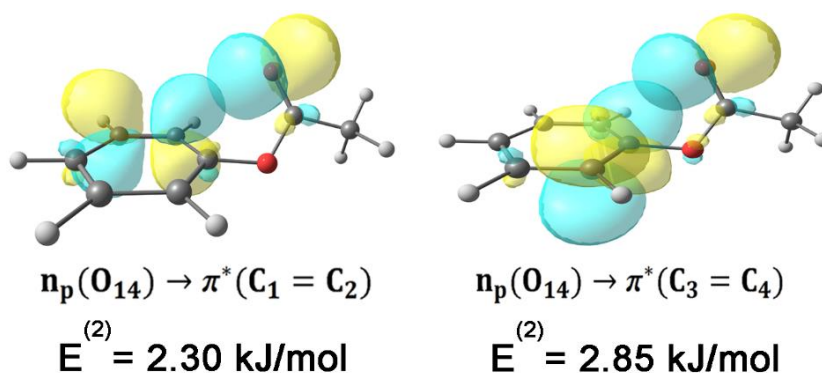


Figure 3.6. NBO orbital overlap in the *cis*-phenyl acetate with the $E^{(2)}$ values of $n \rightarrow \pi^*$ interaction calculated at the M05-2X/aug-cc-pVDZ level.

Table 3.4. $E^{(2)}$ values (kJ/mol) in *cis*-phenyl acetate and *cis*-phenyl formate calculated at different DFT levels

DFT levels	<i>cis</i> -phenyl acetate	<i>cis</i> -phenyl formate
M05-2X/aug-cc-pVDZ	5.15	4.69
ω B97X-D/aug-cc-pVDZ	4.81	4.31
M06-2X/aug-cc-pVDZ	4.60	4.14
M05-2X/6-311++G(d,p)	5.36	4.90
M05-2X/aug-cc-pVTZ	5.52	5.10

It should be pointed out that the significantly large energy difference (~ 8 kJ/mol) in the relative stability of the *cis* conformer than the *trans* conformer in the case of phenyl acetate compared to phenyl formate cannot be explained only in terms of slightly larger $n \rightarrow \pi^*$ interaction in the former one relative to the latter. The only difference in the *trans*-species of phenyl formate and phenyl acetate is the presence of the methyl group in the latter at the place of formyl hydrogen. Thus, there could be larger steric repulsion between the phenyl and methyl groups (C–H and C–C bond) in the *trans*-phenyl acetate than between the phenyl and formyl

hydrogen (C–H bond) in the *trans*-phenyl formate. Steric repulsion destabilization energy (steric) between the bonding orbitals is calculated by the natural steric analysis (NSA). NSA shows that the steric in *trans*-phenyl acetate is about 34.89 kJ/mol, while the same in *trans*-phenyl formate is about 25.31 kJ/mol. Higher steric in *trans*-phenyl acetate compared to *trans*-phenyl formate contributes significantly to its instability compared to its *cis* counterpart.

It has been observed from the experimental and theoretical IR spectra of phenyl acetate (Figure 3.4) that the carbonyl stretching frequency of the *cis* conformer is redshifted by 11 cm⁻¹ than the *trans* conformer. However, in the case of phenyl formate reported in the literature, the carbonyl stretching frequency of the *cis* conformer (1766 cm⁻¹) is redshifted by 31 cm⁻¹ than the *trans* conformer (1797 cm⁻¹).⁹² Apparently, it can be assumed that the significantly smaller amount of the carbonyl stretching frequency redshift in the *cis* conformer than the *trans* in the phenyl acetate with respect to phenyl formate is due to the methyl substitution. However, the overall redshift in the carbonyl stretching frequency of the *cis* conformer than the *trans* conformer of phenyl acetate has to be understood by detailed NBO analysis. Figure 3.7a shows various hyperconjugative interactions (R1, R2, and R3) and n→ π^* interaction (R4) in phenyl acetate.

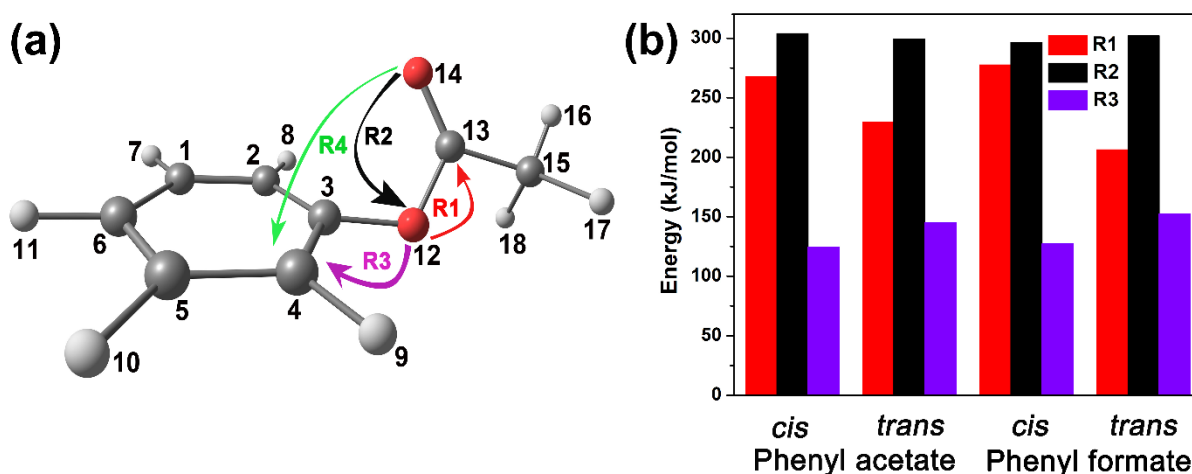


Figure 3.7. a) Representation of various hyperconjugative interactions, i.e., R1, R2, and R3, and R4 (n→ π^* interaction); and b) bar diagram showing the $E^{(2)}$ values of R1, R2, and R3 interactions calculated at the M05-2X/aug-cc-pVDZ level from NBO analysis.

Generally, these opposing hyperconjugative interactions affect the carbonyl stretching frequency of the ester carbonyl group.^{92, 183} R1 interaction involves the delocalization of electron density into the σ^* and π^* orbital of the carbonyl group, thus resulting in the redshift of the carbonyl stretching frequency. R2 interaction involves delocalizing the carbonyl oxygen lone pair electron density to the nearby σ^* orbital, resulting in the blueshift of carbonyl

stretching frequency. R3 interaction involves delocalizing the etheral oxygen lone pair electron density to nearby σ^* and π^* orbital except for the carbonyl group. The R2 interaction opposes the R1 interaction, resulting in the blueshift of carbonyl stretching frequency. Additionally, $n \rightarrow \pi^*$ interaction, which is present only in the *cis* conformer but not in the *trans* conformer of phenyl acetate or phenyl formate, can affect these hyperconjugative interactions and, hence, the carbonyl stretching frequency. Figure 3.7b shows a bar diagram of the $E^{(2)}$ values of the R1, R2, and R3 interactions for phenyl acetate or phenyl formate conformers. These $E^{(2)}$ values (R1, R2, R3, R4, and sterics) are provided in Table 3.5. A close inspection of Figure 3.7b shows that the R1 interaction is always higher in the *cis* conformer having $n \rightarrow \pi^*$ interaction compared to the *trans* conformer, which does not have any $n \rightarrow \pi^*$ interaction. On the other hand, the R2 interaction is almost similar in both conformers, while the R3 interaction is lower in the *cis* relative to the *trans* conformers. All these factors favor reducing the carbonyl stretching frequency in the *cis* conformer relative to that of the *trans* for both phenyl acetate and phenyl formate. However, the R1 interaction in the *cis* conformer compared to the *trans* conformer in the case of phenyl formate is much larger than that of phenyl acetate. Similarly, the R3 interaction in the *trans* conformer compared to the *cis* conformer of phenyl formate is larger than phenyl acetate. Thus, the redshift in the carbonyl stretching frequency of the *cis* conformer compared to that of the *trans* conformer of phenyl acetate (11 cm^{-1}) is smaller than that of phenyl formate (30 cm^{-1}).

Table 3.5. $E^{(2)}$ values (kJ/mol) for various types of interactions in the *cis* and *trans* conformers of phenyl acetate and phenyl formate calculated by NBO analysis at the M05-2X/aug-cc-pVDZ level

Interactions	Phenyl acetate		Phenyl formate	
	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>
R1	267.86	229.79	277.57	206.27
R2	303.93	299.41	296.48	302.13
R3	124.60	144.72	127.24	152.42
R4 ($n \rightarrow \pi^*$)	5.15	-	4.69	-
Sterics	-	34.89	-	25.31

In fact, different redshifts in the carbonyl stretching frequency of phenyl acetate and phenyl formate are due to the effect of methyl substitution on the hyperconjugation and $n \rightarrow \pi^*$ interaction. It has already been mentioned (Figure 3.6) that the $E^{(2)}$ value of $n \rightarrow \pi^*$ interaction

in the *cis*-phenyl acetate (5.15 kJ/mol) is only slightly higher than phenyl formate (4.69 kJ/mol). The increase in strength of $n \rightarrow \pi^*$ interaction in the *cis*-phenyl acetate compared to that of phenyl formate is supported by the geometrical parameters relevant to this interaction and the energy gap between the n and π^* orbitals ($\Delta E_{n-\pi^*}$) provided in Table 3.6. The EDG near the carbonyl group has been reported to increase the electron density over the donor oxygen and enhance the $n \rightarrow \pi^*$ interaction. In contrast, EWG decreases the electron density and thus dwindles the $n \rightarrow \pi^*$ interaction.^{45, 60} On the other hand, methyl substitution in phenyl acetate has a profound effect on the hyperconjugation interaction to reduce the redshift in the carbonyl stretching frequency of the *cis* conformer of phenyl acetate compared to that of the *trans* conformer.

Table 3.6. Geometrical parameters and $\Delta E_{n-\pi^*}$ (kJ/mol) of the *cis* conformer of phenyl acetate and phenyl formate in the S_0 state calculated at the M05-2X/aug-cc-pVDZ level

	<i>cis</i> -phenyl acetate	<i>cis</i> -phenyl formate
C=O (Å)	1.200	1.196
C=O...ring center (Å)	3.718	3.752
^a Θ	48.38 ⁰	-47.55 ⁰
$\angle C_3-O_{12}-C_{13}$	118.76 ⁰	118.74 ⁰
$\angle O_{12}-C_{13}-O_{14}$	123.76 ⁰	126.15 ⁰
^b $\angle C_3-O_{12}-C_{13}-O_{14}$	0.52 ⁰	-0.02 ⁰
^c $\angle C_4-C_3-O_{12}-C_{13}$	57.95 ⁰	-57.35 ⁰
^d $\Delta E_{n-\pi^*}$	1070.68	1081.97

^a Θ is the angle between the plane containing the carbonyl oxygen and the aromatic plane; ^b $\angle C_3-O_{12}-C_{13}-O_{14}$ is the O-C-O torsional angle; ^c $\angle C_4-C_3-O_{12}-C_{13}$ is the Ph-O torsional angle; ^d $\Delta E_{n-\pi^*}$ is the difference in the energy of lone pair orbital and π^* of the aromatic ring.

The contribution of $n \rightarrow \pi^*$ interaction on the reduction of the carbonyl stretching frequency in the *cis*-phenyl acetate compared to the *trans*-phenyl acetate is understood by the NBO deletion analysis provided in Table 3.7. NBO deletion analysis determines the occupancy of the lone pair orbital on the carbonyl oxygen after deleting a specific type of interaction. The lone pair electrons on the O_{14} atom of the carbonyl group of phenyl acetate get delocalized due to $n \rightarrow \pi^*$ interaction and R2 interaction. First, deletion of the R4, i.e., $n \rightarrow \pi^*$ interaction, increases the occupancy of the lone pair electron density (n_p) on the O_{14} atom of the carbonyl group and hence confirms the presence of $n \rightarrow \pi^*$ interaction. Second, the deletion of R2 and R4 interactions together with respect to the deletion of only R2 interaction increases the lone

pair occupancy of the O₁₄ atom. As the R2 interaction increases the carbonyl stretching frequency, the presence of the $n \rightarrow \pi^*$ interaction (R4) favors the reduction of the carbonyl stretching frequency by trimming the R2 interaction. The redshift in the carbonyl stretching frequency of the $n \rightarrow \pi^*$ donor carbonyl has been explained previously in Chapter 1 in phenyl formate and a model peptide (Cbz-Hyp-OMe) based on the effect of the $n \rightarrow \pi^*$ interaction on the neighboring hyperconjugative interactions which affect the carbonyl stretching frequency.^{92, 93}

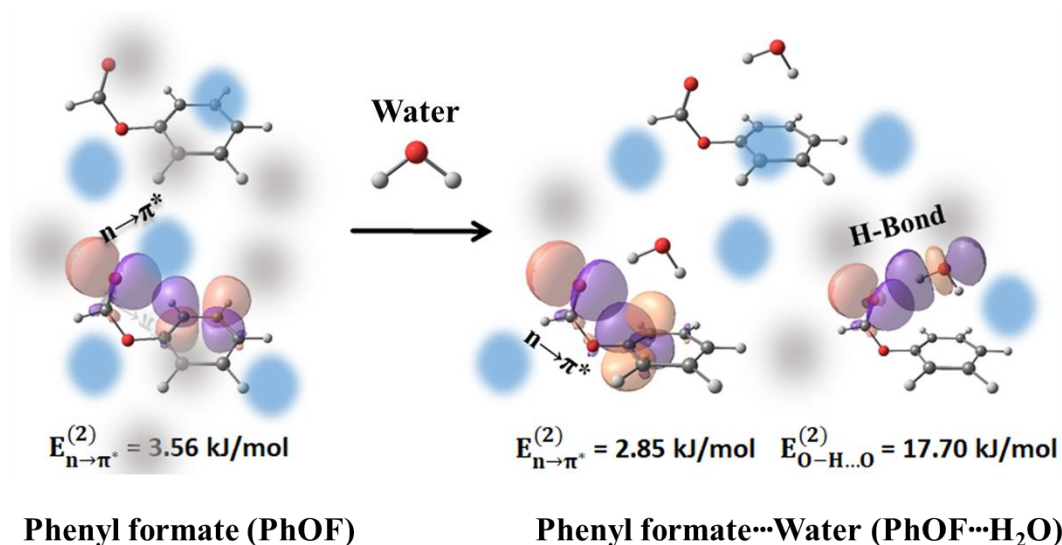
Table 3.7. Occupancy of the p -type lone pair of the carbonyl oxygen after deleting the specific type of interaction in the *cis* conformer of phenyl acetate calculated by NBO deletion analysis at the M05-2X/aug-cc-pVDZ level

S.No.	Interactions	Occupancy of O ₁₄ (n _p) lone pair
I	R1, R2, R3, R4 (Not Deleted)	1.850
II	R4 (Deleted)	1.851
III	R2, R4 (Deleted)	1.989
IV	R2 (Deleted)	1.987

3.4 Conclusion

We have shown the role of steric repulsion and $n \rightarrow \pi^*$ interaction in governing the conformational preference of phenyl acetate using gas-phase spectroscopic techniques and quantum chemistry calculations. The current spectroscopic study reports an exclusive observation of the *cis* conformer of phenyl acetate having an $n \rightarrow \pi^*$ interaction between the lone pair on the carbonyl oxygen and the π^* orbitals of the phenyl ring. In the case of an analogous ester, phenyl formate, observation of both the *cis* and *trans* conformers has been reported in the literature. Methyl substitution at the $n \rightarrow \pi^*$ donor (carbonyl group) significantly increases the steric repulsion in the *trans* conformer of phenyl acetate compared to that of phenyl formate and makes the former one too unstable to be observed in the experiment. We have observed the effect of methyl substitution in phenyl acetate on the strength of the $n \rightarrow \pi^*$ interaction, steric repulsion, and hyperconjugation. A smaller redshift in the carbonyl stretching frequency in the *cis* conformer with respect to the *trans* conformer in phenyl acetate compared to that in phenyl formate has been explained in terms of hyperconjugation as well as $n \rightarrow \pi^*$ interaction. We have shown that the steric effect renders complete selectivity towards the conformation having the $n \rightarrow \pi^*$ interaction. The present work may have a significant implication in designing drugs with defined conformational specificity.

Chapter 4: Effect of microhydration on $\text{C}=\text{O}\cdots\text{aromatic } n\rightarrow\pi^*$ interaction in phenyl formate



Adapted from: P. Panwaria, M. Juanes, K. K. Mishra, R. Saragi, K. Borish, I. Usabiaga, A. Camiruaga, J. A. Fernandez*, A. Lessari*, A. Das*, Microhydration of phenyl formate: Gas-phase laser spectroscopy, microwave spectroscopy, and quantum chemistry calculations. *ChemPhysChem*, **2022**, e202200330, 1-9.

4.1 Motivation of this work

In Chapter 3, we discussed that the strength of the $n \rightarrow \pi^*$ interaction can be tuned while we move to phenyl acetate from phenyl formate. Upon substitution of the methyl group at the place of the formyl hydrogen in phenyl formate, the methyl group pushes the electron density toward the carbonyl group due to the +I effect, increasing the strength of the $n \rightarrow \pi^*$ interaction due to an increase in the delocalization of the electron density from the carbonyl oxygen lone pair. Similarly, it can be assumed that if this lone pair electron density is reduced, it can decrease the strength of the $n \rightarrow \pi^*$ interaction. Instead of substituting the EWG at the $n \rightarrow \pi^*$ donor, we preferred reducing the electron density at the carbonyl oxygen by sharing its electron density through other intermolecular interactions. As we know that hydrogen bond is much stronger than the $n \rightarrow \pi^*$ interaction, we wanted to see the fate of the $n \rightarrow \pi^*$ interaction while the carbonyl group of phenyl formate is strongly hydrogen bonded in an intermolecular complex. Thus, we investigated the phenyl formate $\cdots$ water (phenyl formate $\cdots$ H₂O) complex and compared the results on this complex with respect to those on the phenyl formate monomer in terms of the non-covalent bonding interactions as well as the conformational preferences.

4.2 Introduction

A subtle interplay between various non-covalent interactions is the key to the specific structures and functions of biomolecules, such as proteins and nucleic acids.^{1, 2, 11, 12, 33, 184, 185} Water also plays an essential role in the stability and folding of biomolecules through hydrogen bonding and hydrophobic interactions.^{3, 186-191} Water molecules in the first hydration shell participate in direct hydrogen bonds with different binding sites of the receptors, stabilizing certain conformations.^{192, 193} Actually, the final or active shape of a biomolecule is often the result of the competition between intramolecular non-covalent interactions and intermolecular hydrogen bonds with the surrounding water molecules. The conformational preferences of flexible molecules change significantly in the presence of water molecules.^{2, 194, 195} For example, it has been reported from gas-phase experimental studies that the number of observed conformers of tryptamine, a metabolite of the essential amino acid tryptamine, is reduced from seven to one by adding a single water molecule.^{158, 196-200} Another example is the keto-enol tautomerization barrier in a small molecule such as 2-pyridone, which is significantly reduced in the presence of a single water molecule that bridges the two functional groups involved in the process.²⁰¹ It is also important to find the binding site the water molecule prefers when there are multiple hydrogen bonding sites in the solute molecule. Gas-phase spectroscopic studies of various model compounds with and without microhydration provide a molecular-level understanding

of the role of water in the structure, conformation, and physical processes of biomolecules and small molecular systems.^{158, 196-199, 202-204}

In this chapter, we have discussed our study on the 1:1 phenyl formate $\cdots$ H₂O complex using isolated jet-cooled electronic, vibrational, and rotational spectroscopy combined with quantum chemistry calculations. Previous spectroscopic studies in solution and gas-phase demonstrated that phenyl formate can exist as two conformers.^{92, 141} The most stable *cis* conformer has a weak $n\rightarrow\pi^*$ interaction between the carbonyl group and phenyl ring. In contrast, the higher energy *trans* conformer lacks $n\rightarrow\pi^*$ interaction since the carbonyl group is oriented away from the phenyl ring.⁹² Accordingly, the gas-phase electronic spectra indicate that the *trans* conformer is less populated.⁹² Nguyen and co-workers reported the microwave (MW) spectrum of the most stable *cis*-phenyl formate.²⁰⁵ Such a spectrum is complicated due to the perturbations caused by the large amplitude motion of the ester group relative to the phenyl ring. Following those previous works, we deal with the effect of a single water molecule solvation on the structure and relative stability of the two conformers of phenyl formate. Phenyl formate has three hydrogen bonding sites, i.e., the carbonyl oxygen, etheral oxygen, and π -cloud of the phenyl ring. Interestingly, all three binding sites can only act as hydrogen bond acceptors. The current chapter is quite intriguing as it explores the conformations of the hydrated monomer through joint microwave and UV/IR spectroscopic techniques.

4.3 Results and Discussion

We explored the conformational landscape of phenyl formate $\cdots$ H₂O by considering the complexation of a single water molecule at different interaction sites of both *cis* and *trans* conformers of the phenyl formate. Those conformers containing the *cis*-phenyl formate are labeled C1 and C2, while those based on the *trans*-phenyl formate are labeled T1 and T2. Figure 4.1 shows the optimized structures of low-energy conformers of the phenyl formate $\cdots$ H₂O at the B3LYP-D3(BJ)/def2-TZVP level. ZPE and BSSE corrected binding energies (ΔE_0), as well as relative electronic energies (E_{rel}) of the complexes calculated at 0 K, are provided in the figure. The structures and energetics of phenyl formate are also provided in Figure 4.1. The ΔE_0 and E_{rel} values of the low-energy conformers of the complex shown in Figure 4.1 have been calculated at different calculation levels (Table 4.1). C1 was identified as the global minimum, while the trend of energies of C2, T1, and T2 is consistent at most calculation levels. Thermally corrected ΔE_0 and E_{rel} values of the four low-energy conformers were also calculated in the 0-350 K range at the B3LYP-D3(BJ)/def2-TZVP level (Figures 4.2). ΔG calculations for the ΔE_0 show that C1 is the global minimum up to 130 K, and T1 starts to take

over C1 in terms of stability at higher temperatures (Figure 4.2a). On the other hand, ΔG calculations for the E_{rel} maintain the relative energy order of $C1 < C2 < T1 < T2$ throughout the temperature range of 0-350 K (Figure 4.2b).

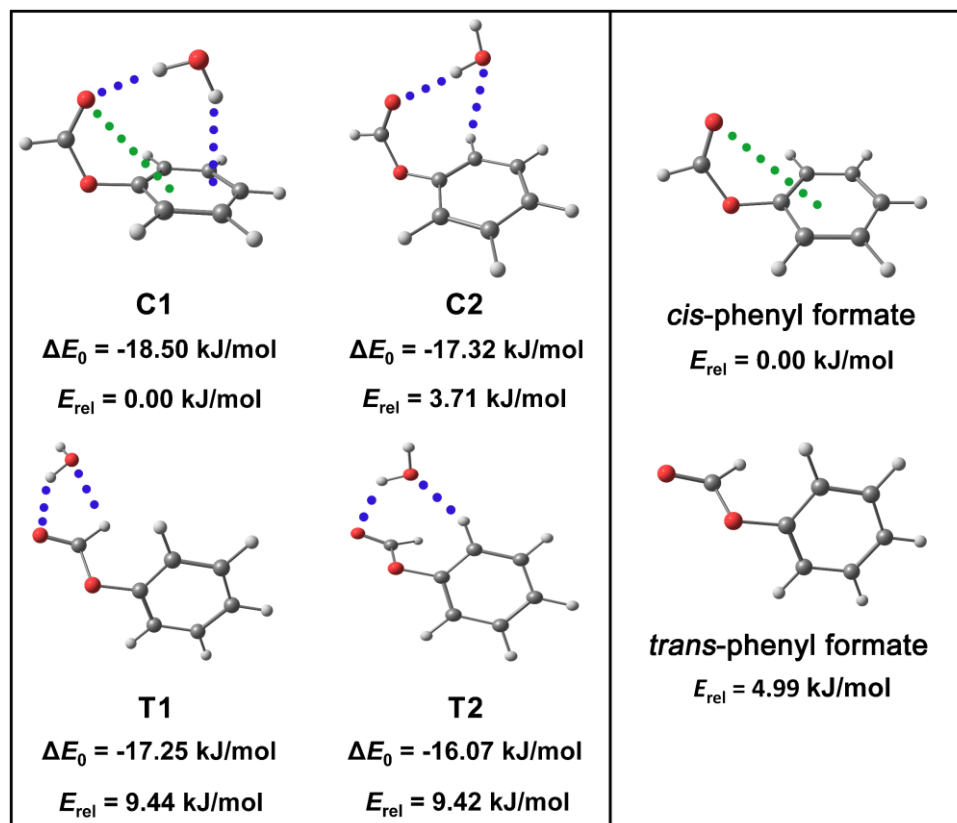


Figure 4.1. Optimized geometries of low-energy conformers of phenyl formate...H₂O and phenyl formate calculated at the B3LYP-D3(BJ)/def2-TZVP level. ZPE and BSSE corrected binding energies (ΔE_0), and ZPE corrected relative electronic energies (E_{rel}) of the conformers calculated at 0 K are provided in the figure.

Table 4.1. ZPE and BSSE corrected binding energies (ΔE_0 , kJ/mol) of the low-energy conformers of phenyl formate...H₂O calculated at the different calculation levels with relative electronic energies corrected with ZPE (E_{rel} , kJ/mol) in the parentheses

	C1	C2	T1	T2
B3LYP-D3(BJ)/def2-TZVP	-18.50 (0.00)	-17.32 (3.71)	-17.25 (9.44)	-16.07 (9.42)
ωB97X-D/def2-TZVP	-17.99 (0.00)	-15.79 (4.31)	-15.52 (9.69)	-14.37 (9.15)
B97-D3/aug-cc-pVTZ	-17.47 (0.00)	-15.01 (2.63)	-15.27 (6.93)	-14.19 (7.82)

B3LYP-D3(BJ)/ aug-cc-pVTZ	-18.57	-17.21	-17.31	-15.90
	(0.00)	(1.53)	(6.70)	(8.00)
B3LYP-D3(BJ)/6-311++G(d,p)	-19.73	-18.17	-18.07	-16.66
	(0.00)	(2.87)	(9.86)	(10.19)
MP2/6-311++G(d,p)	-11.81	-10.29	-10.95	-9.88
	(0.00)	(4.50)	(12.93)	(11.73)

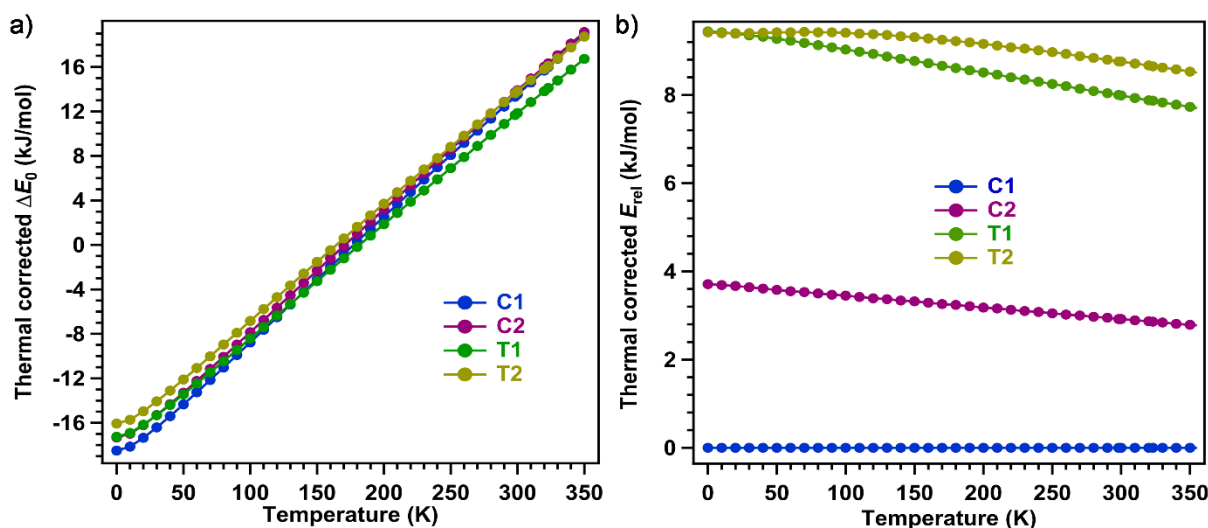
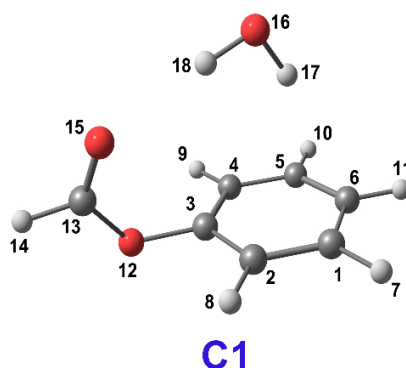


Figure 4.2. Plots of thermal corrected a) binding energies (ΔE_0 , kJ/mol); and b) relative electronic energies (E_{rel} , kJ/mol) of the low-energy conformers of phenyl formate...H₂O as a function of temperature (0-350 K) calculated at the B3LYP-D3(BJ)/def2-TZVP level.

A few selected S_0 state geometrical parameters of the low-energy conformers of phenyl formate and phenyl formate...H₂O are listed in Table 4.2. The most significant change is in the angle formed by the carbonyl and phenyl rings in the C1 and *cis*-phenyl formate (-91.1° compared to -59.0°). In the global minimum conformer C1, water bridges the carbonyl and phenyl ring, and its main stability comes from an O–H...O hydrogen bond. Secondary O–H... π and $n \rightarrow \pi^*$ interactions add additional stability to the dimer. In the case of both C2 and T2, the H₂O molecule forms an eight-membered cyclic hydrogen bond network with the C=O and one phenyl C–H group. However, the geometrical parameters, i.e., the strength of the O–H...O and C–H...O hydrogen bonds in these two structures, are different (Table 4.2). In the T1 structure, the H₂O molecule forms O–H...O and C–H...O hydrogen bonds with the C=O and formyl C–H group of phenyl formate, respectively.

Table 4.2. Geometrical parameters of low-energy conformers of phenyl formate and phenyl formate...H₂O calculated at the B3LYP-D3(BJ)/def2-TZVP level. The atom numbering

scheme has been provided above the table in the C1 conformer. $^a\Theta$ ($\angle C_4-C_3-O_{12}-C_{13}$) is the angle between the planes containing the carbonyl and phenyl groups of phenyl formate (Ph-O torsional angle or tilt angle); $^b\angle C_3-O_{12}-C_{13}-O_{15}$ is the O-C-O torsional angle



Parameters	Phenyl formate...H ₂ O				Phenyl formate	
	C1	C2	T1	T2	<i>cis</i>	<i>trans</i>
C=O (Å)	1.197	1.199	1.197	1.195	1.193	1.190
C ₁₃ -H ₁₄ (Å)	1.096	1.097	1.099	1.100	1.097	1.102
d _{C=O...ring center} (Å)	3.688	3.779	-	-	3.788	-
d _{H14...ring center} (Å)	-	-	3.463	3.437	-	3.439
$^a\Theta$ ($\angle C_4-C_3-O_{12}-C_{13}$)	-91.1°	-65.0°	-128.4°	-129.5°	-59.0°	-125.1°
$\angle C_3-O_{12}-C_{13}$	117.7°	119.7°	118.3°	117.8°	119.7°	118.2°
$\angle O_{12}-C_{13}-O_{15}$	126.3°	127.0°	121.6°	122.1°	126.8°	122.2°
$^b\angle C_3-O_{12}-C_{13}-O_{15}$	0.0°	0.7°	-174.8°	-169.6°	-0.4°	-174.9°
C=O...H ₁₆ -O ₁₈ (Å)	2.049	2.000	1.985	2.302	-	-
$\angle O_{15}\cdots H_{16}-O_{18}$	176.4°	158.8°	148.5°	135.3°	-	-
O ₁₆ -H ₁₇ (Å)	0.963	0.962	0.961	0.963	-	-
O ₁₆ -H ₁₈ (Å)	0.967	0.968	0.970	0.966	-	-
d _{O16-H17...π} (Å)	2.562	-	-	-	-	-
d _{C4-H9...O16} (Å)	-	2.530	-	2.504	-	-
$\angle C_4-H_9\cdots O_{16}$	-	118.3°	-	150.5°	-	-
d _{C13-H14...O16} (Å)	-	-	2.646	-	-	-
$\angle C_{13}-H_{14}\cdots O_{16}$	-	-	102.9°	-	-	-

It should be noted that the barrier for interconversion (Figure 4.3) of the higher energy conformer C2→C1 through the C=O...H-O intermolecular torsional coordinate is quite low ~175 cm⁻¹ (2.10 kJ/mol) at the B3LYP-D3(BJ)/aug-cc-pVTZ level. Similarly, T2 can interconvert into T1 through the same intermolecular torsional coordinate with a low barrier of

92 cm^{-1} (1.10 kJ/mol). Such low-energy barriers for the $\text{C2} \rightarrow \text{C1}$ and $\text{T2} \rightarrow \text{T1}$ interconversion point to the plausible conformational relaxation during the collisional cooling process and suggest a high probability of observing either C1 or T1 or both conformers in the experiments.

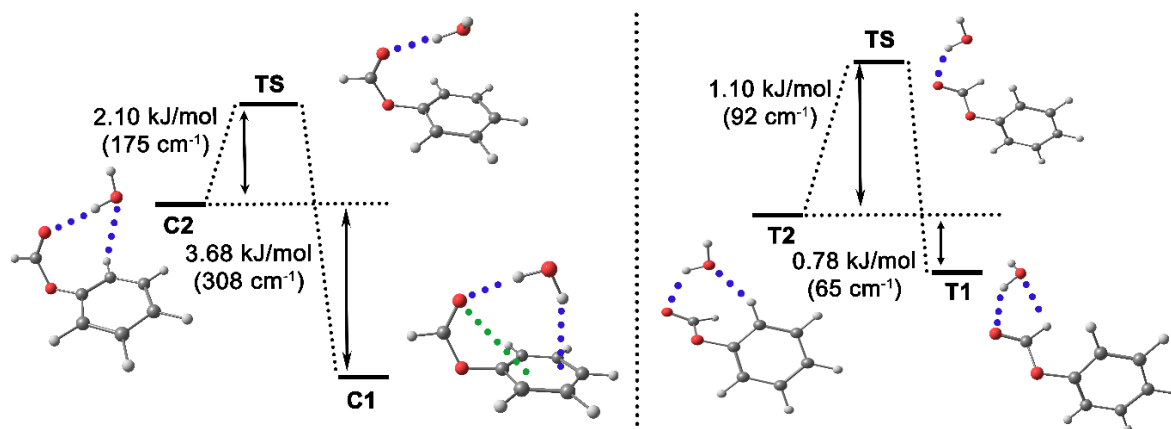


Figure 4.3. Energy barriers for the interconversion of $\text{C2} \rightarrow \text{C1}$ and $\text{T2} \rightarrow \text{T1}$ calculated at the B3LYP-D3(BJ)/aug-cc-pVTZ level.

Phenyl formate $\cdots\text{H}_2\text{O}$ complex was synthesized by the supersonic expansion of phenyl formate ($\geq 98\%$ purity, Sigma Aldrich) vapor (heated at ~ 330 K) seeded in a carrier gas of Ar or 30%He-70%Ne mixture (~ 3 bar) and bubbled through a small stainless steel sample holder filled with water (273 K) outside the vacuum chamber. The pulsed valve was heated at ~ 350 K to avoid condensation of phenyl formate vapor in the orifice of the valve. The TOF-MS of mixed vapor of phenyl formate and H_2O measured at 37494 cm^{-1} using 1C-R2PI spectroscopy is provided in Figure 4.4.

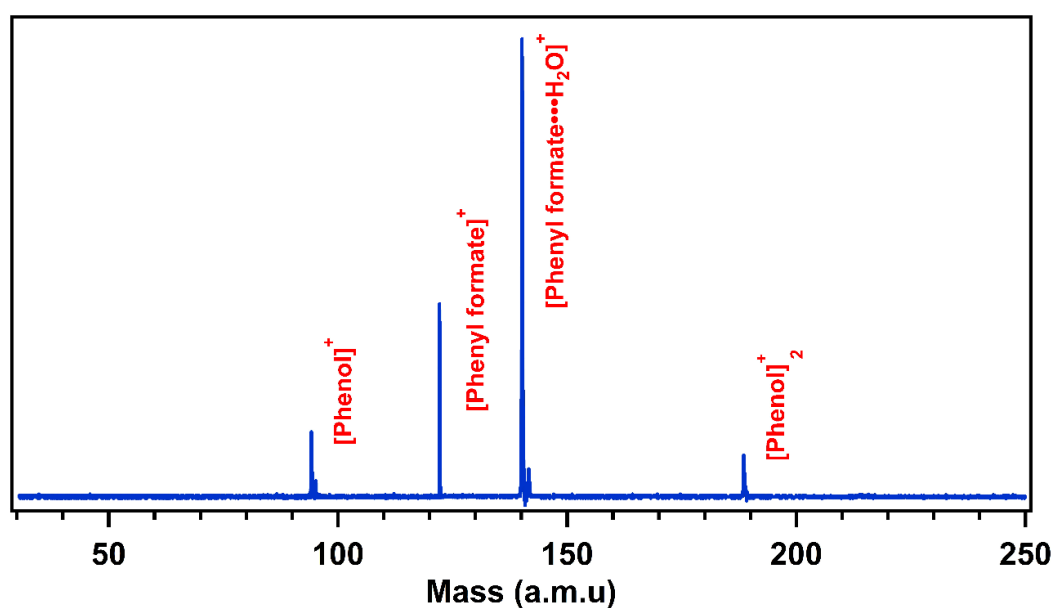


Figure 4.4. TOF-MS measured at 37494 cm^{-1} using 1C-R2PI spectroscopy.

Various experimental conditions such as H₂O vapor pressure, UV laser power, pulse valve opening time, and delay with respect to UV laser were set to maximize the signal of the 1:1 phenyl formate⋯H₂O. The mass-selected electronic spectrum of phenyl formate⋯H₂O complex has been measured using argon as the carrier gas employing 1C-R2PI spectroscopy (Figure 4.5a). The origin bands of the *cis* and *trans* conformers of the phenyl formate reported earlier appear at 37590 and 37487 cm⁻¹, respectively.⁹² Observation of two conformers of the complex, denoted as A and B in Figures 4.5b-c, is confirmed by UV-UV HB spectroscopy. Figure 4.5b-c shows conformation-specific electronic spectra of the complex obtained by probing the bands at 37494 and 37503 cm⁻¹, respectively, in the electronic spectrum.

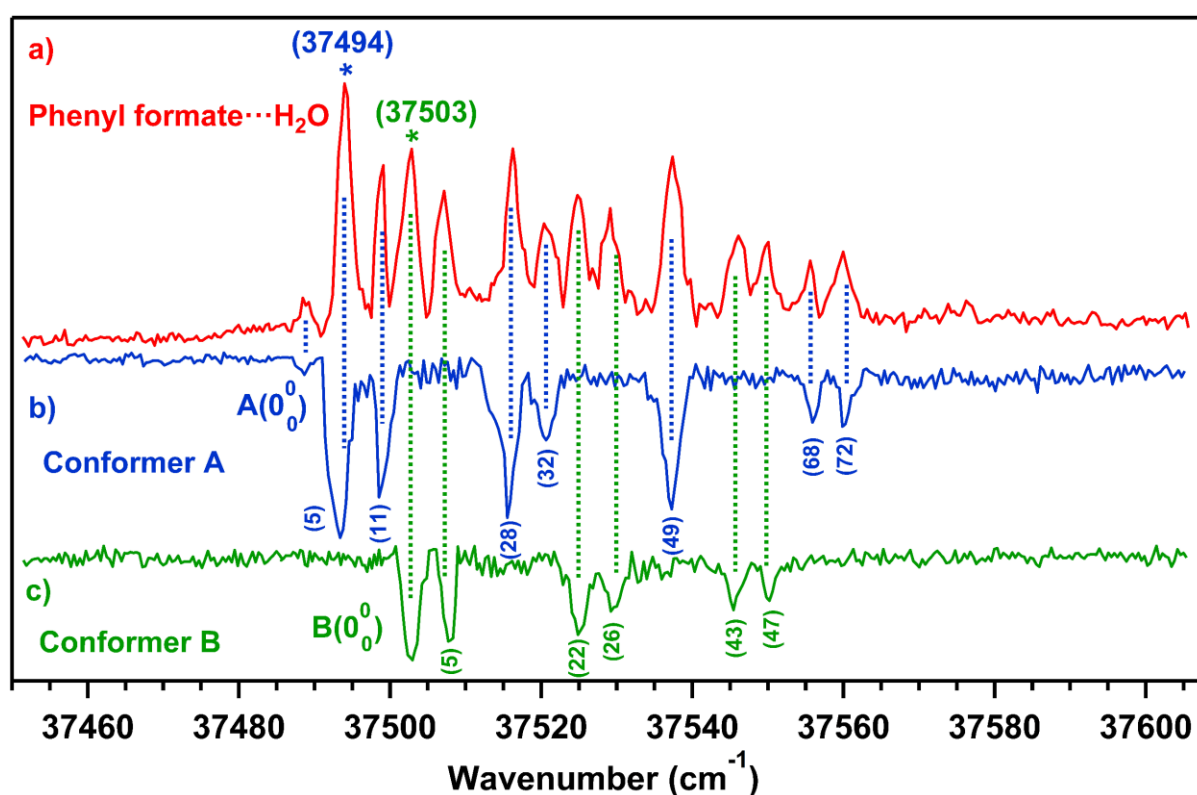


Figure 4.5. a) Mass-selected electronic spectrum of 1:1 phenyl formate⋯H₂O complex recorded using 1C-R2PI spectroscopy; and b-c) UV-UV hole-burning spectra of the conformers A and B of the phenyl formate⋯H₂O complex measured by probing the bands at 37494 and 37503 cm⁻¹ marked by blue and green asterisks, respectively, in the electronic spectrum. The number in the parenthesis below each band of the hole-burning spectra in parts b and c denotes the intermolecular vibrational frequency of the complex in cm⁻¹.

The electronic spectra of both the conformers A and B display several low-frequency vibronic bands, riding on the respective electronic origin band and exhibiting a strong Franck-Condon activity. However, the origin band of conformer A, appearing at 37489 cm⁻¹, presents

a very weak intensity compared to the rest of the vibronic bands. In contrast, the origin band of conformer B at 37503 cm^{-1} is the strongest transition in the spectrum. Interestingly, the electronic spectra of both the conformers are pretty similar. Both the conformers exhibit a 5 cm^{-1} intermolecular vibrational mode, which is further built on the progression of another mode of either 28 or 22 cm^{-1} . Another interesting feature appears from comparing the electronic spectra of the phenyl formate and phenyl formate $\cdots$ H $_2$ O.⁹² A long progression on the Ph–O torsional mode of 43 cm^{-1} dominates the electronic spectrum of the *cis*-phenyl formate, which is not prominent in the electronic spectra of the phenyl formate $\cdots$ H $_2$ O conformers.⁹² Conversely, the electronic spectra of the phenyl formate $\cdots$ H $_2$ O conformers mostly exhibit low-frequency intermolecular vibrations. Thus, the monohydration introduces rigidity in the flexible side-chain of the monomer due to the formation of hydrogen bonds. Hence, the resultant larger mass hinders the Ph–O torsional motion of the phenyl formate.

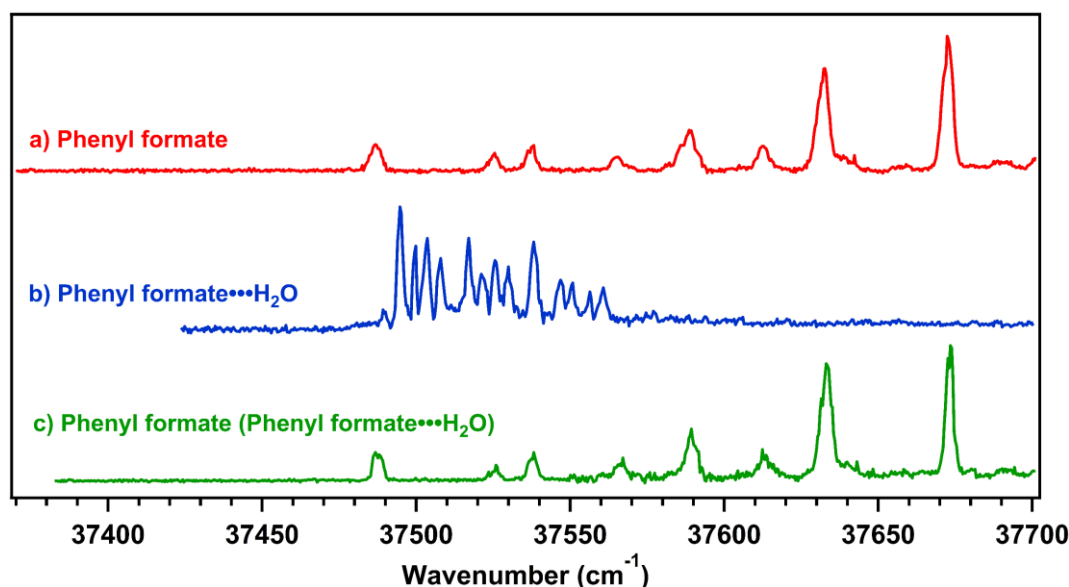


Figure 4.6. Comparison of the electronic spectra measured in the mass channels of a) phenyl formate monomer without the presence of water; b) phenyl formate $\cdots$ H $_2$ O complex; and c) phenyl formate monomer in the presence of the formation of phenyl formate $\cdots$ H $_2$ O complex in the experiment.

The electronic spectrum was also measured in the mass channel of the phenyl formate to check for any fragmentation of phenyl formate $\cdots$ H $_2$ O or higher complexes in the phenyl formate mass channel. Figure 4.6 shows a comparison of the electronic spectra measured in the phenyl formate mass channel without any flow of water vapor in the sample, phenyl formate $\cdots$ H $_2$ O mass channel, and phenyl formate mass channel with the flow of water vapor in the sample, i.e., formation of phenyl formate $\cdots$ H $_2$ O. The electronic spectra measured in the

phenyl formate mass channel with and without the flow of water vapor in the sample are identical, i.e., no fragmentation of higher complexes was observed in the monomer mass channel. The electronic spectrum of phenyl formate $\cdots$ H₂O was further measured using a mixture of 30%He-70%Ne carrier gas, and no additional bands were observed compared to the electronic spectra obtained with Ar carrier gas (Figure 4.7). In fact, the resolution of the electronic spectra obtained with Ar carrier gas is better than that obtained with the 30%He-70%Ne gas mixture. The electronic spectra presented in Figure 4.7 demonstrate that no additional conformation was missing in the experiment due to the use of Ar as a carrier gas.

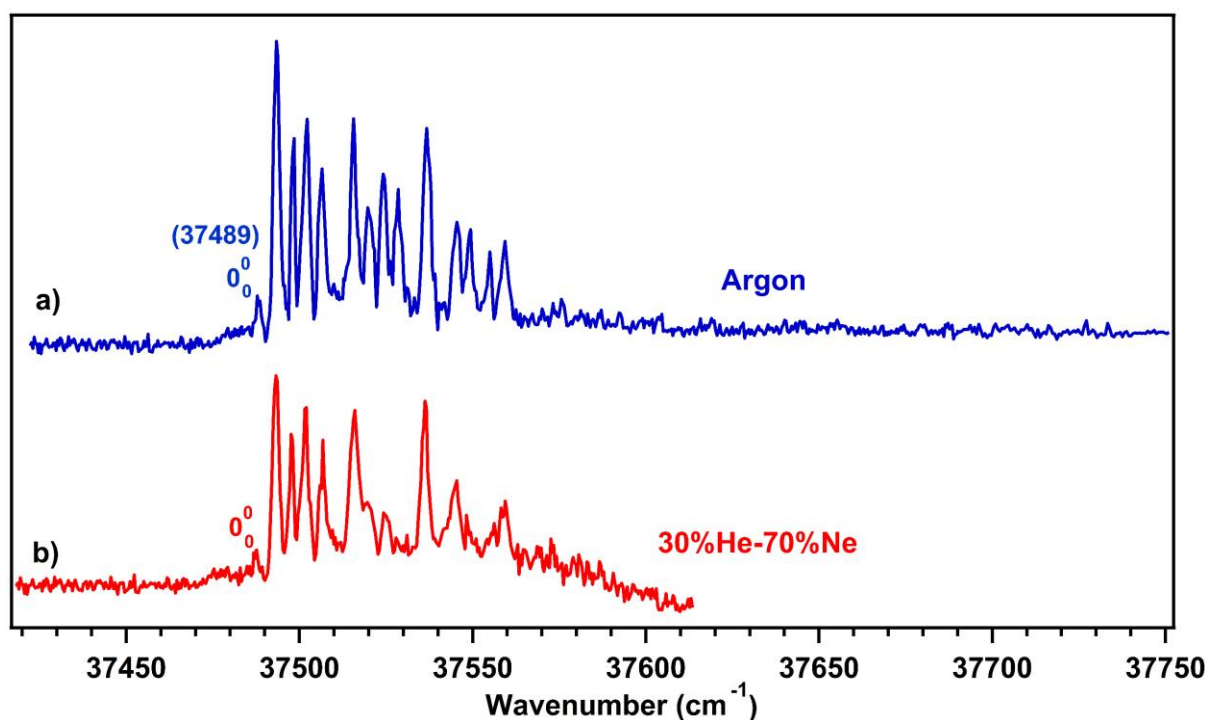


Figure 4.7. Comparison of the mass-selected electronic spectra of 1:1 phenyl formate $\cdots$ H₂O recorded using 1C-R2PI spectroscopy in a) Argon and b) 30% He-70% Ne carrier gases.

Figure 4.8e-f shows the RIDIR spectra of the conformers A and B of phenyl formate $\cdots$ H₂O in the carbonyl stretching region by probing the $A_0^0 + 5\text{ cm}^{-1}$ (37494 cm^{-1}) and B_0^0 (37503 cm^{-1}) bands marked by the blue and green asterisks in Figure 4.5a, respectively. The experimental IR spectra show the percentage depletion of the UV ion signal, which is approximately 35-40% for the monomer and complex IR spectra. The IR spectra of *cis* and *trans* conformers of phenyl formate and displaying the carbonyl stretching frequencies are provided in Figures 4.8a-c,⁹² for comparison. The theoretical IR spectra showing the carbonyl stretching frequency calculated at the B3LYP-D3(BJ)/def2-TZVP level for the phenyl formate $\cdots$ H₂O conformers are provided in Figures 4.8g-j. At the same time, the same for the

cis and *trans* conformers of phenyl formate are depicted in Figures 4.8b-d. The harmonic IR frequencies were scaled using a scaling factor obtained from the ratio of the experimental to the theoretical (harmonic) carbonyl stretching frequency of the *cis*-phenyl formate.⁹²

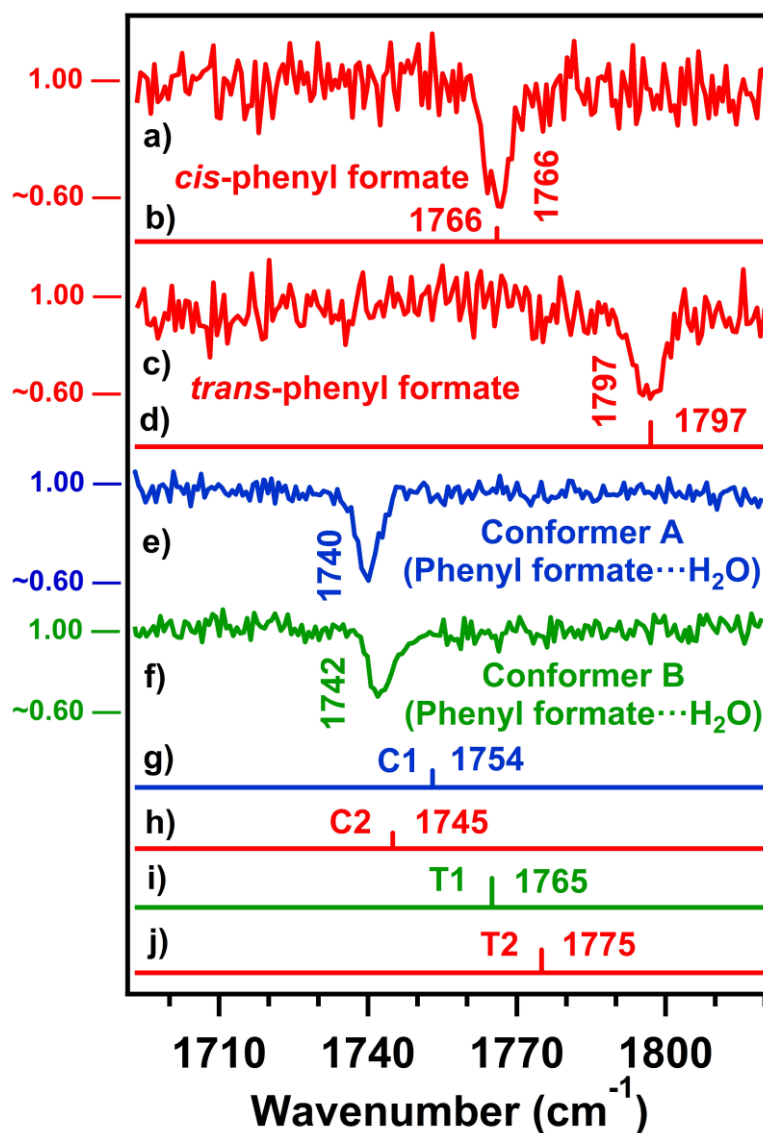


Figure 4.8. Experimental IR spectra of the *cis* and *trans* conformers of phenyl formate, as well as of phenyl formate...H₂O conformers measured in the carbonyl stretching region by RIDIR spectroscopy, are shown in panels a), c), e), and f), respectively. Panels b), d), g), h), i), and j) show the scaled IR spectra of the *cis* and *trans* conformers of phenyl formate, as well as phenyl formate...H₂O conformers, respectively, obtained at the B3LYP-D3(BJ)/def2-TZVP level. The harmonic carbonyl stretching frequencies of the phenyl formate...H₂O conformers are scaled with respect to the *cis*-phenyl formate.⁹²

Table 4.3. Scaled carbonyl stretching frequencies ($\nu_{\text{C=O}}$, cm⁻¹) of phenyl formate...H₂O conformers with respect to *cis*-phenyl formate obtained at different calculation levels

	C1	C2	T1	T2
B3LYP-D3(BJ)/def2-TZVP	1754	1745	1765	1775
ωB97X-D/def2-TZVP	1754	1746	1764	1777
B3LYP-D3(BJ)/aug-cc-pVTZ	1754	1745	1768	1776
B3LYP-D3(BJ)/6-311++G(d,p)	1754	1744	1766	1775
MP2/6-311++G(d,p)	1758	1753	1771	1781

Experimental carbonyl stretching frequencies of C1, T1, *cis*-phenyl formate,⁹² and *trans*-phenyl formate are 1740 cm⁻¹, 1742 cm⁻¹, 1766 cm⁻¹, and 1797 cm⁻¹, respectively. The scaling factors of 0.9757, 0.9546, 0.9795, 0.9773, and 0.9855 has been used at the B3LYP-D3(BJ)/def2-TZVP, ω B97X-D/def2-TZVP, B3LYP-D3(BJ)/aug-cc-pVTZ, B3LYP-D3(BJ)/6-311++G(d,p), and MP2/6-311++G(d,p) level by taking the ratio of experimental carbonyl stretching frequency and theoretical stretching frequency of *cis*-phenyl formate (1810, 1850, 1803, 1807, and 1792 cm⁻¹) calculated at the B3LYP-D3(BJ)/def2-TZVP, ω B97X-D/def2-TZVP, B3LYP-D3(BJ)/aug-cc-pVTZ, B3LYP-D3(BJ)/6-311++G(d,p), and MP2/6-311++G(d,p) level, respectively.

The carbonyl stretching frequency of the *cis*-phenyl formate is found to be redshifted with respect to that of the *trans*-phenyl formate by 31 cm⁻¹.⁹² The redshift in the carbonyl stretching frequency of *cis* conformers of phenyl formate and phenyl acetate with respect to their *trans* conformers has been explained in terms of n $\rightarrow$ π^* interaction in the *cis* conformer and subtle differences in hyperconjugation between *cis* and *trans* conformers.^{61, 92} The experimental carbonyl stretching frequencies of the phenyl formate $\cdots$ H₂O conformers are similar. A comparison between the experimental and theoretical IR spectra in the carbonyl stretching frequency region of phenyl formate $\cdots$ H₂O presented in Figures 4.8e-j suggests that the assignment of the observed conformers based on the carbonyl stretching frequency is not straightforward. It could be noted that the trend of the carbonyl stretching frequencies of the phenyl formate $\cdots$ H₂O conformers calculated at various DFT levels as well as MP2 level (Table 4.3) is similar to that obtained at the B3LYP-D3(BJ)/def2-TZVP level and presented in Figure 4.8. Very likely, the experimental determination of the IR spectra in the O–H stretching region would aid in assigning the experimentally observed conformers. Theoretical calculations predict that the intensity of the O–H stretching of different conformers of phenyl formate $\cdots$ H₂O is much lower than that of the carbonyl stretching. Table 4.4 shows the intensity of the carbonyl stretching of the phenyl formate monomer as well as both carbonyl and O–H stretching of different conformers of phenyl formate $\cdots$ H₂O calculated at the B3LYP-D3(BJ)/def2-TZVP level. Although the absolute intensity of the symmetric O–H stretching of the conformers of the complex is not very low, the signal for the O–H stretch is too perturbed to observe in the experiment due to some chemistry of phenyl formate and H₂O in the presence of heat.

Table 4.4. Intensity (km/mol) of the C=O stretching of phenyl formate as well as both C=O and O–H stretching of phenyl formate⋯H₂O conformers calculated at the B3LYP-D3(BJ)/def2-TZVP level

	C=O	Sym. O–H	Asymm. O–H
Water	-	4.46	43.94
<i>cis</i>-phenyl formate	282.51	-	-
<i>trans</i>-phenyl formate	493.85	-	-
C1	289.21	140.45	49.68
T1	505.40	234.24	87.49
C2	339.71	147.35	84.54
T2	495.24	23.12	69.08

Thus, the assignment of the two conformers of phenyl formate⋯H₂O observed in the electronic spectroscopy is tentatively done based on the shallow energy barrier (Figure 4.3) obtained for the interconversion between the two *cis* conformers and two *trans* conformers. Ruoff *et al.* have shown that collisional relaxation in a supersonic expansion is feasible if the barrier of interconversion is $\leq 350 \text{ cm}^{-1}$.¹⁸² Hence, there is a high probability of a very efficient relaxation of the C2 and T2 to C1 and T1, respectively, and the chances of the survival of the C2 and T2 in the experiment are significantly less. Similar low-energy barriers for the C2→C1 and T2→T1 interconversion were obtained from the calculations performed at the MP2 and different DFT levels (Table 4.5). Based on this calculation, the two conformers of phenyl formate⋯H₂O observed in the R2PI spectrum can be tentatively assigned as C1 and T1.

Table 4.5. Energy barrier (cm⁻¹) for interconversion of C2→C1 and T2→T1 calculated at the various calculation levels^a. The Energy barrier for interconversion is also provided in kJ/mol in parentheses

	C2→C1	T2→T1
B3LYP-D3(BJ)/def2-TZVP	196 (2.34)	17 (0.21)
B97-D3/aug-cc-pVTZ	260 (3.11)	23 (0.28)
B3LYP-D3(BJ)/aug-cc-pVTZ	175 (2.10)	92 (1.10)
B3LYP-D3(BJ)/6-311++G(d,p)	110 (1.32)	109 (1.31)
MP2/6-311++G(d,p)^b	77 (0.92)	56 (0.67)

^aQST2 (quadratic synchronous transit) approach was used to calculate the transition state for the interconversion of C2→C1 and T2→T1. The presence of one imaginary frequency

confirmed it as a transition state. Electronic energy without ZPE correction has been taken into account. ^bT2 conformer is lower in energy than T1 at the MP2/6-311++G(d,p) level; hence, the interconversion barrier is calculated for the interconversion of the T1 conformer to the T2.

Furthermore, broadband Fourier transform microwave spectroscopy has been employed to confirm the structure of phenyl formate⋯H₂O conformers observed in the supersonic expansion. Figure 4.9 shows the microwave spectrum of phenyl formate and phenyl formate⋯H₂O measured in the 2-8 GHz range. The microwave spectrum of phenyl formate was previously reported by Nguyen *et al.*²⁰⁵ Phenyl formate is a floppy molecule because of the large amplitude motion of the carboxylic substituent with respect to the phenyl ring. Consequently, the rotational spectrum is very complicated and requires a two-state torsion-rotation analysis with the inclusion of several Coriolis terms. The rotational spectrum of phenyl formate confirmed a conformational landscape dominated by a *cis* configuration characterized by four equivalent conformations with a *gauche* orientation of the carboxylic plane with respect to the phenyl ring. The *trans*-phenyl formate was not observed in the rotational spectrum. As the present work is focused on the monohydrated species, we did not expand the measurements on the phenyl formate. An enlarged microwave spectrum of phenyl formate⋯H₂O exhibiting typical rotational transitions (quantum numbers J, K_{-1}, K_{+1}) is shown in Figure 4.9. The negative traces in the figure correspond to simulations based on the experimental rotational parameters listed in Table 4.6. The transitions belonging to the conformers C1 and T1 appear in blue and green colors, respectively. The first set of rotational transitions was assigned to an asymmetric rotor commensurate to C1, with μ_b and μ_a -type selection rules and line intensities indicating $\mu_b > \mu_a$ (transitions marked in blue) following the theoretical prediction at the B3LYP-D3(BJ)/def2-TZVP level. Considering the tunneling doublings reported for the phenyl formate,²⁰⁵ similar vibration-rotation coupling effects were checked for phenyl formate⋯H₂O. However, only a few transitions showed apparent doublings, insufficient for a two-state analysis. The observed transitions could then be reproduced to experimental accuracy with a semi-rigid rotor Watson's Hamiltonian (S-reduction), including only quartic centrifugal distortion terms. Later, a few weaker transitions with only μ_a selection rules were also assigned in the spectrum to the second species denoted by T1 (marked in green). The T1 conformer was analyzed with a semi-rigid Hamiltonian. The number of transitions measured for the C1 species (96 transitions) is much larger than for the T1 species (24 lines). Thus, a spectral comparison between the two conformers in the enlarged section of the microwave spectrum is not straightforward. Unassigned transitions belonging to minor isotopic phenyl formate species, other phenyl formate complexes, and impurities remained in the spectrum. However, no other

rotational transitions could be attributed to other phenyl formate $\cdots$ H₂O conformers. No decomposition of phenyl formate was noticeable under the experimental conditions, as phenol lines were undetected. The fitted spectroscopic parameters of the C1 and T1 conformers of phenyl formate $\cdots$ H₂O are given in Table 4.6.

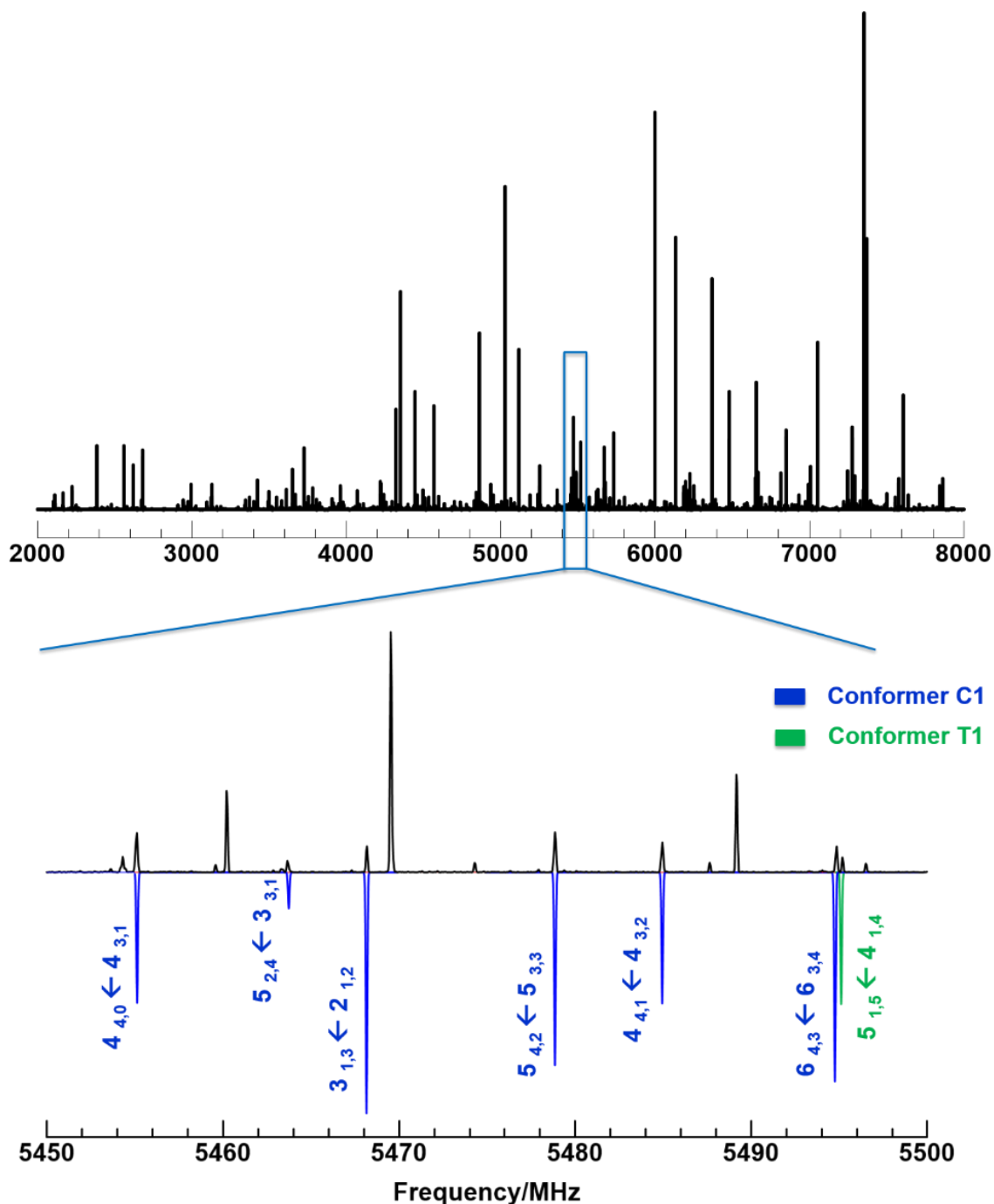


Figure 4.9. Microwave spectrum of phenyl formate $\cdots$ H₂O in the 2-8 GHz region and an enlarged 50 MHz section showing typical rotational transitions of the C1 and T1. The negative traces correspond to simulations based on the experimental parameters of Table 4.6. The unidentified transitions correspond to the monomer,²⁰⁵ other complexes, and impurities.

Table 4.6. Comparison of experimental rotational parameters of the two observed conformers with those of the C1 and T1 calculated at the B3LYP-D3(BJ)/def2-TZVP level

	Experimental	Theoretical C1	Experimental	Theoretical T1
$A^{[a]}$ / MHz	1756.1554 (14) ^[d]	1833.0 [4.2%] ^[f]	2632.10 (90)	2738.4 [3.9%]
B / MHz	1064.21608 (96)	1059.4 [-0.5%]	603.7285 (54)	597.8 [-1.0%]
C / MHz	865.17096 (96)	877.5 [1.4%]	532.4889 (46)	526.8 [-1.1%]
D_J / kHz	0.327 (19)	0.300	0.230 (35)	0.23
D_{JK} / kHz	1.781 (14)	2.020	-1.16 (58)	-0.46
D_K / kHz	-0.313 (38)	-1.190	[0.] ^[g]	8.80
d_1 / kHz	-0.0008 (18)	-0.0069	-0.066 (38)	-0.0646
d_2 / kHz	0.0759 (58)	0.1028	[0.]	-0.0205
μ_a / D	+ ^[e]	0.75	+	2.81
μ_b / D	++	4.06		0.50
μ_c / D		0.00		1.25
$N^{[b]}$	96		24	
$\sigma^{[c]}$ / kHz	17.7		24.2	

^[a]Rotational constants (A , B , C in MHz), Watson's S-reduction centrifugal distortion constants (D_J , D_{JK} , D_K , d_1 , d_2 in kHz) and electric dipole moment components in Debye (D). ^[b]Number of fitted transitions. ^[c]Microwave rms deviation of the fit (σ in kHz). ^[d]Standard errors in parentheses in units of the last digit. ^[e]Plus signs indicate qualitatively the intensity of the observed transitions. ^[f]Relative deviations of the predicted rotational constants (theory-experiment)/theory. ^[g]Centrifugal distortion constants in square brackets have been fixed to zero.

The structural assignment of the phenyl formate $\cdots$ H₂O conformers is based on the comparison of the experimental rotational parameters with those obtained from the B3LYP-D3(BJ)/def2-TZVP calculations (Table 4.6). It is pretty evident from the comparison that the two phenyl formate $\cdots$ H₂O conformers are C1 and T1. The conformational assignment is unambiguous, and the observed rotational constants have relatively small deviations with respect to the computational predictions (<1.4% for B and C , <4.2% for A). The deviation between the observed and calculated rotational constants for the intermolecular complexes such as dimer is generally larger than that for monomer species due to the presence of large amplitude vibrations associated with the relative displacements between the two moieties of the dimer. This large amplitude motion is largely anharmonic, so it is not easy to reproduce

this computationally. Furthermore, the rotational parameters of all four conformers of phenyl formate $\cdots$ H₂O calculated at the different calculation levels (Table 4.7) reinforce the assignment of the C1 and T1. The absence of the C2 and T2 in the expansion is very likely due to the conformational relaxation predicted by the theory. Observation of the C1 and T1 in the microwave experiment is quite persuasive and supports the tentative assignment proposed above for the two conformers detected in the electronic spectrum.

Table 4.7. Rotational parameters of phenyl formate $\cdots$ H₂O conformers calculated at the **1)** B3LYP-D3(BJ)/def2-TZVP; **2)** ω B97X-D/def2-TZVP; **3)** B97-D3/aug-cc-pVTZ; **4)** B3LYP-D3(BJ)/aug-cc-pVTZ; **5)** B3LYP-D3(BJ)/6-311++G(d,p); and **6)** MP2/6-311++G(d,p) levels

C1	(1)	(2)	(3)	(4)	(5)	(6)
<i>A</i> / MHz	1833.0	1843.7	1819.1	1802.0	1795.0	1782.6
<i>B</i> / MHz	1059.4	1063.2	1038.1	1060.4	1057.0	1059.6
<i>C</i> / MHz	877.5	881.4	863.9	870.9	868.4	872.6
<i>D_J</i> / kHz	0.30	0.25	0.27	0.34	0.42	0.19
<i>D_{JK}</i> / kHz	2.02	2.05	2.20	1.68	1.54	1.31
<i>D_K</i> / kHz	-1.19	-1.30	-0.76	-0.69	-0.74	-0.03
<i>d₁</i> / kHz	-0.0069	-0.0061	-0.0142	-0.0048	-0.0062	-0.0061
<i>d₂</i> / kHz	0.1028	0.0761	0.0601	0.1146	0.1556	0.0326
μ_a / D	0.75	0.72	0.72	0.85	0.89	0.56
μ_b / D	4.06	4.11	3.82	4.00	4.12	3.86
μ_c / D	0.00	0.00	0.32	0.00	0.00	0.33

C2	(1)	(2)	(3)	(4)	(5)	(6)
<i>A</i> / MHz	1758.7	1734.9	1664.4	1741.5	1759.7	1634.6
<i>B</i> / MHz	1019.9	1040.3	1025.5	1023.3	1015.9	1108.3
<i>C</i> / MHz	705.9	718.0	692.6	705.2	702.6	757.6
<i>D_J</i> / kHz	1.39	0.76	0.76	1.75	1.18	0.26
<i>D_{JK}</i> / kHz	-2.84	-0.22	-0.52	-2.42	-2.33	6.20
<i>D_K</i> / kHz	9.46	3.06	3.16	10.24	7.66	-5.26
<i>d₁</i> / kHz	-0.4828	-0.2318	-0.2686	-0.6137	-0.3928	-0.0372
<i>d₂</i> / kHz	-0.0782	-0.0614	-0.0590	-0.1219	-0.0685	-0.1746
μ_a / D	0.20	0.15	0.37	0.37	0.24	0.20

μ_b / D	1.80	1.91	1.63	1.69	1.64	1.51
μ_c / D	0.22	0.24	0.15	0.09	0.00	0.33

T1	(1)	(2)	(3)	(4)	(5)	(6)
<i>A</i> / MHz	2738.4	2730.0	2641.1	2791.1	2731.0	2561.3
<i>B</i> / MHz	597.8	600.5	590.2	587.3	595.7	618.4
<i>C</i> / MHz	526.8	530.5	516.3	520.6	526.3	540.1
<i>D_J</i> / kHz	0.23	0.21	0.24	0.27	0.25	0.22
<i>D_{JK}</i> / kHz	-0.46	-1.14	-1.56	-1.03	-0.77	-0.86
<i>D_K</i> / kHz	8.80	9.27	10.66	11.96	9.65	6.88
<i>d₁</i> / kHz	-0.0646	-0.0507	-0.0593	-0.0640	-0.0640	-0.0585
<i>d₂</i> / kHz	-0.0205	-0.0101	-0.0100	-0.0193	-0.0192	-0.0126
μ_a / D	2.81	2.93	2.59	2.95	2.63	2.14
μ_b / D	0.50	0.45	0.74	0.61	0.79	0.92
μ_c / D	1.25	1.41	0.95	0.81	0.93	1.27

T2	(1)	(2)	(3)	(4)	(5)	(6)
<i>A</i> / MHz	2434.1	2435.1	2352.7	2446.6	2416.8	2392.8
<i>B</i> / MHz	772.6	784.2	753.1	758.1	774.1	776.2
<i>C</i> / MHz	610.2	624.8	582.9	590.9	601.5	604.1
<i>D_J</i> / kHz	0.13	0.08	0.15	0.20	0.09	0.07
<i>D_{JK}</i> / kHz	2.32	0.87	0.51	0.74	0.54	0.57
<i>D_K</i> / kHz	0.19	1.78	1.93	2.15	2.07	2.24
<i>d₁</i> / kHz	0.0182	-0.0028	-0.0295	-0.0393	-0.0149	-0.0092
<i>d₂</i> / kHz	-0.0217	-0.0080	-0.0089	-0.0118	-0.0075	-0.0064
μ_a / D	2.72	2.80	2.01	1.99	2.01	1.76
μ_b / D	0.59	0.13	1.48	1.60	1.68	1.65
μ_c / D	0.29	0.15	0.02	0.34	0.14	0.03

We used NBO and NCI analyses to understand various non-covalent interactions in the phenyl formate...H₂O. Figure 4.10a shows NBO overlap and $E^{(2)}$ values (kJ/mol) for individual non-covalent interactions present in these conformers calculated at the B3LYP-D3(BJ)/def2-TZVP level.

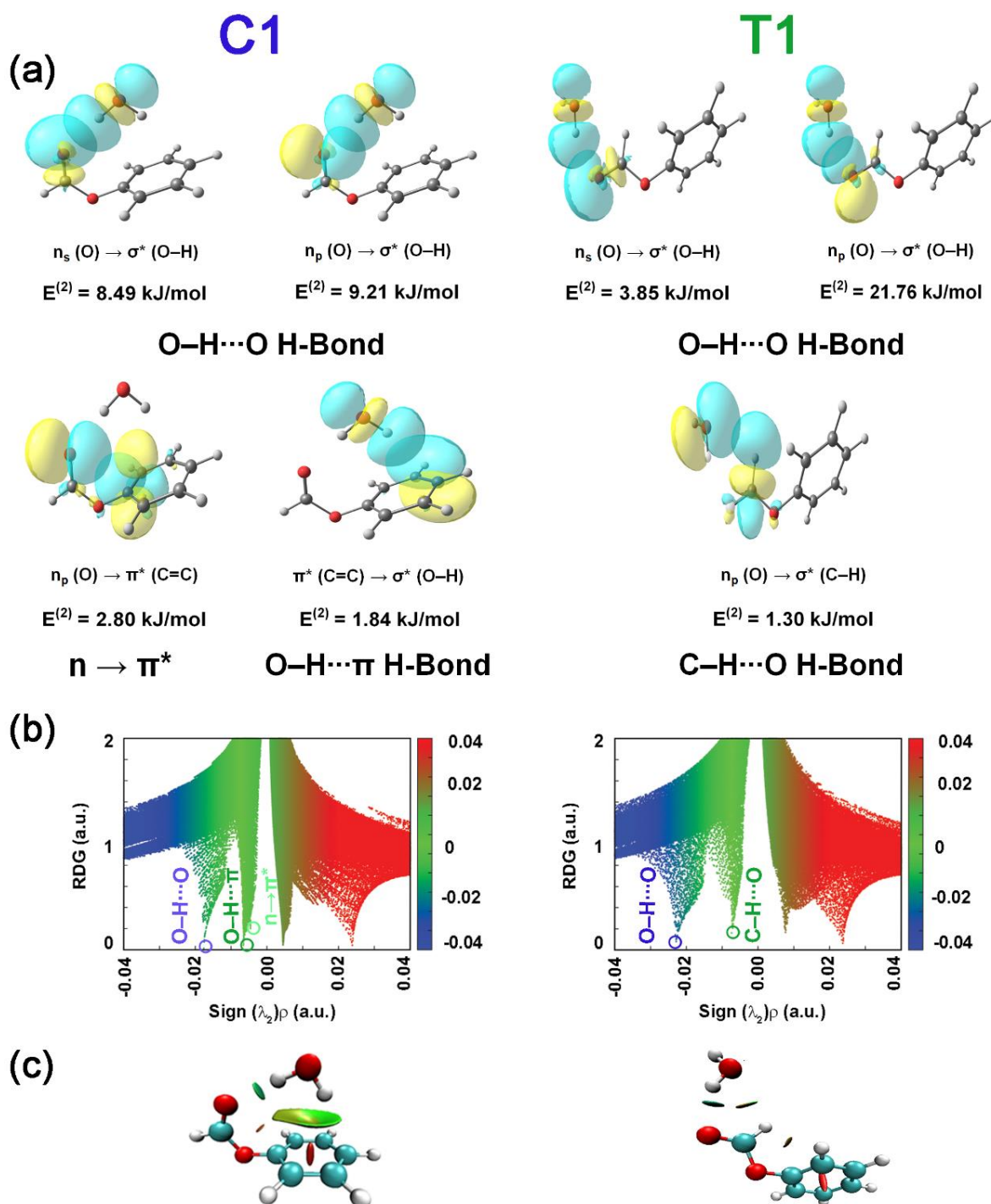


Figure 4.10. a) NBO overlap for various non-covalent interactions in the C1 and T1; b) NCI RDG (a.u.) plot versus $[\text{Sign}(\lambda_2)\rho, (\text{a.u.})]$ for the C1 and T1 with minima corresponding to various non-covalent interactions in the C1 and T1 are marked with circles of the same colors as the type of non-covalent interactions; c) NCI isosurface plots showing various non-covalent interactions in the C1 and T1. The gradient isosurface follows a blue-green-red color scheme over the range of $-0.04 < \text{Sign}(\lambda_2)\rho < 0.04$, where blue, green, and red colors denote very strong attraction, weak attraction, and strong repulsion, respectively. NBO and NCI calculations were performed on the optimized structures obtained from the B3LYP-D3(BJ)/def2-TZVP level.

In C1, H₂O forms a bridge between the carbonyl and phenyl ring of phenyl formate and the O–H···O hydrogen bond becomes the dominant interaction. Interestingly, the analysis shows overlap with both the *s*- and *p*-type lone pairs on the oxygen atom. It is noteworthy that the $E^{(2)}$ values for both the $n_s(\text{O}) \rightarrow \sigma^*(\text{O–H})$ and $n_p(\text{O}) \rightarrow \sigma^*(\text{O–H})$ interactions are very similar (~8–9 kJ/mol). The other O–H of water is involved in a weaker π -hydrogen bonding [$\pi(\text{C=C}) \rightarrow \sigma^*(\text{O–H})$] with an $E^{(2)}$ value of 1.84 kJ/mol. Insertion of a water molecule does not block the weak $n_p(\text{O}) \rightarrow \pi^*(\text{C=C})$ [$E^{(2)} = 2.80$ kJ/mol] interaction already present in the monomer, although with a slightly higher value of $E^{(2)}$ value of 3.56 kJ/mol (Figure 4.11).⁹² The reduction in the $n \rightarrow \pi^*$ interaction energy in the complex with respect to that in the monomer has been predicted by all the levels of calculation tried here (Table 4.8). Whereas, T1 is primarily stabilized by an O–H···O hydrogen bond where the n_p orbital, in comparison to the n_s orbital, of the carbonyl oxygen has a dominant contribution towards the delocalization into the $\sigma^*(\text{O–H})$ orbital (Figure 4.10a). The $E^{(2)}$ value for the secondary weak C–H···O hydrogen bond in T1 is 1.30 kJ/mol. Interestingly, the O–H···O hydrogen bond [$E^{(2)} = 25.61$ kJ/mol] in T1 is substantially stronger than in C1 [$E^{(2)} = 17.70$ kJ/mol]. It is because the H₂O molecule in T1 is free to optimize the strength of the O–H···O hydrogen bond, while in C1, it has to adjust its orientation in order to have both the O–H···O and O–H··· π hydrogen bonds.

Table 4.8. Comparison of the $E^{(2)}$ values (kJ/mol) for $n \rightarrow \pi^*$ interaction in C1 and *cis*-phenyl formate and hydrogen bond in C1 and T1 at the different calculation levels

	$n \rightarrow \pi^*$		H-Bond	
	C1	<i>cis</i> -phenyl formate	C1	T1
B3LYP-D3(BJ)/def2-TZVP	2.80	3.56	17.70	25.61
ωB97X-D/def2-TZVP	2.59	3.77	19.33	28.41
B3LYP-D3(BJ)/aug-cc-pVTZ	3.14	4.10	17.32	28.53
B3LYP-D3(BJ)/6-311++G(d,p)	3.64	3.97	18.33	25.48

NCI analysis further corroborates the non-covalent interactions revealed in the C1 and T1 by the NBO analysis. The NCI RDG and isosurface plots are shown in Figures 4.10b and c, respectively. The RDG minimum at a larger negative value of $\text{sign}(\lambda_2)\rho$ for the T1 (-0.023 a.u.) compared to the C1 (-0.018 a.u.) confirms that the O–H···O hydrogen bond is relatively stronger in T1 (Figure 4.10b). The NCI results also indicate the presence of additional relatively weaker non-covalent interactions, i.e., O–H··· π hydrogen bond and $n \rightarrow \pi^*$ interaction in the C1 and C–H···O interaction in the T1. A comparison of the RDG plots for the conformers of the

phenyl formate $\cdots$ H₂O and phenyl formate is provided in Figure 4.11. Further, a superposition of the RDG plots of the C1 and *cis*-phenyl formate has been displayed in Figure 4.12.

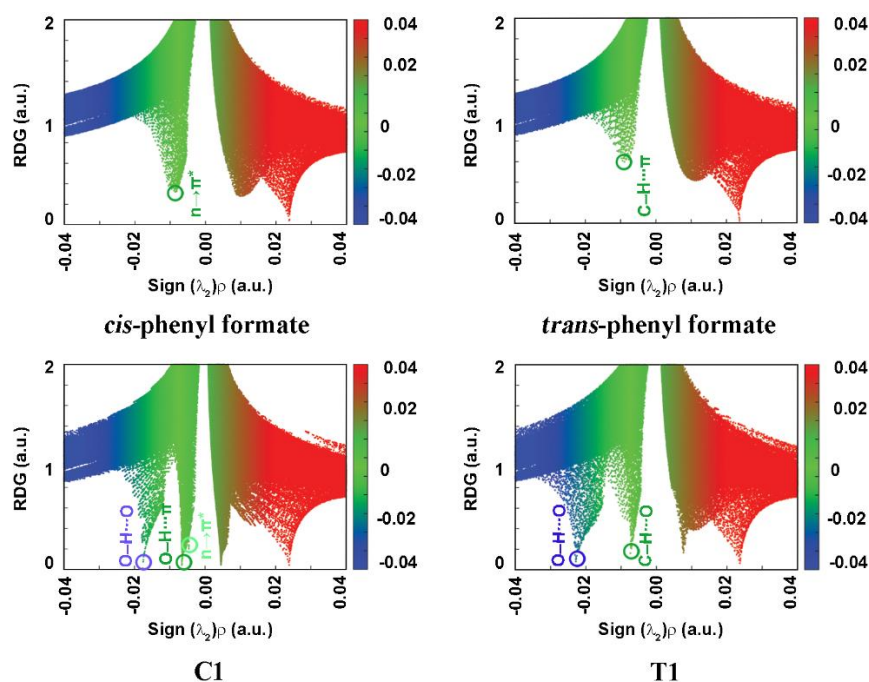


Figure 4.11. NCI RDG plot versus $[\text{Sign}(\lambda_2)\rho, (\text{a.u.})]$ for the conformers of the phenyl formate and phenyl formate $\cdots$ H₂O with minima corresponding to the various non-covalent interactions are marked with the same colors with the type of non-covalent interactions. Calculations were performed on the optimized structures obtained from the B3LYP-D3(BJ)/def2-TZVP level.

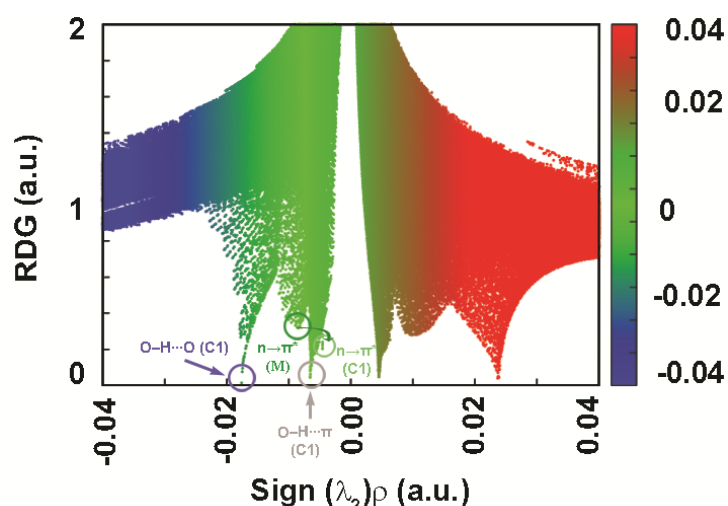


Figure 4.12. Overlap of NCI RDG plot versus $[\text{Sign}(\lambda_2)\rho, (\text{a.u.})]$ of the *cis*-phenyl formate and C1. Calculations were performed at the B3LYP-D3(BJ)/def2-TZVP level.

The minima corresponding to the O–H $\cdots$ O (blue), O–H $\cdots$ π (grey), and $n\rightarrow\pi^*$ (light green) of the C1 are marked with C1 in parentheses. In contrast, the minimum corresponding

to the $n \rightarrow \pi^*$ (dark green) of the *cis*-phenyl formate is marked with M in parentheses. It should be noted here that the minima for the C1 are less negative than the *cis*-phenyl formate, which confirms the weakening of $n \rightarrow \pi^*$ in C1 than *cis*-phenyl formate. The curved arrow (dark green) shows the movement of the minima from the *cis*-phenyl formate to C1, i.e., the more negative region to the less negative region. The NCI analysis reconfirms that the strength of $n \rightarrow \pi^*$ interaction in C1 is reduced compared to that in the phenyl formate monomer.

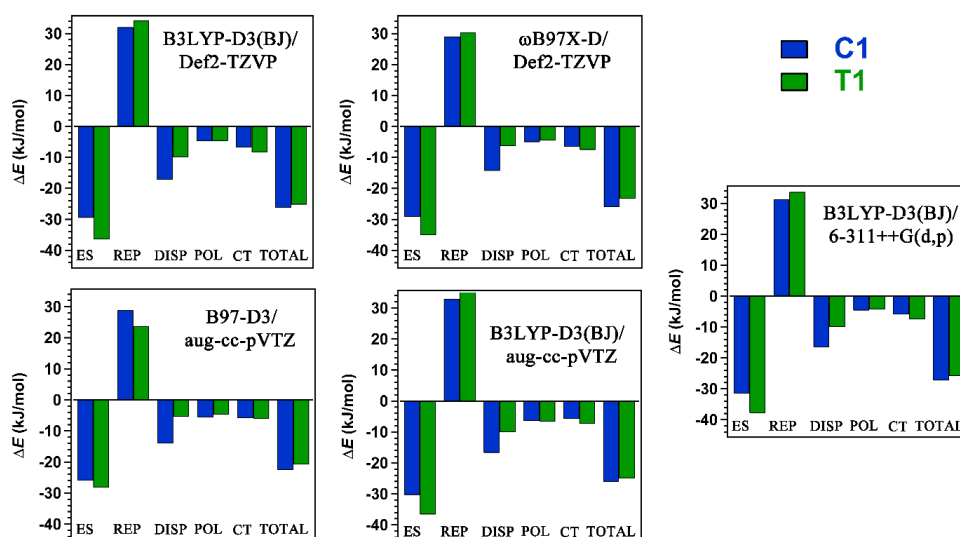


Figure 4.13. Decomposition of interaction energies (kJ/mol) of the C1 and T1 using ALMO-EDA at various calculation levels.

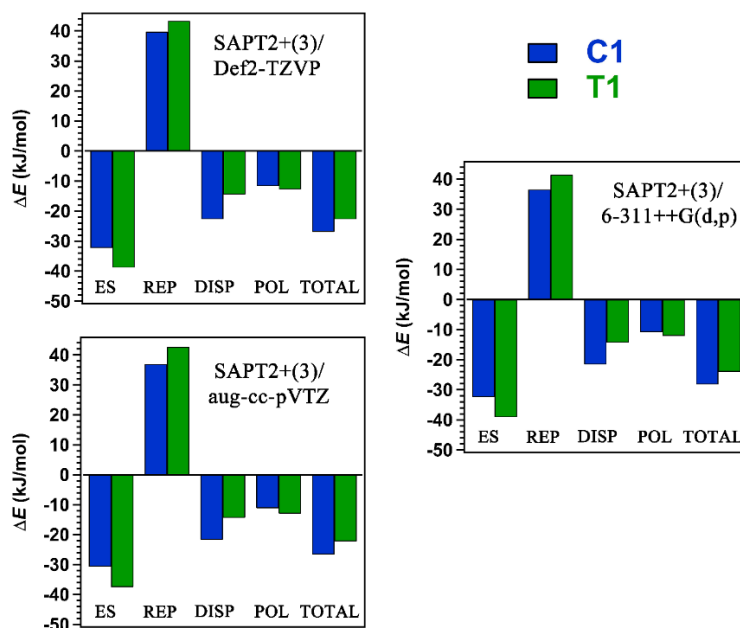


Figure 4.14. Decomposition of interaction energies (kJ/mol) of the C1 and T1 using the SAPT analysis at the SAPT/def2-TZVP, SAPT/aug-cc-pVTZ, and SAPT/6-311++G(d,p) levels on

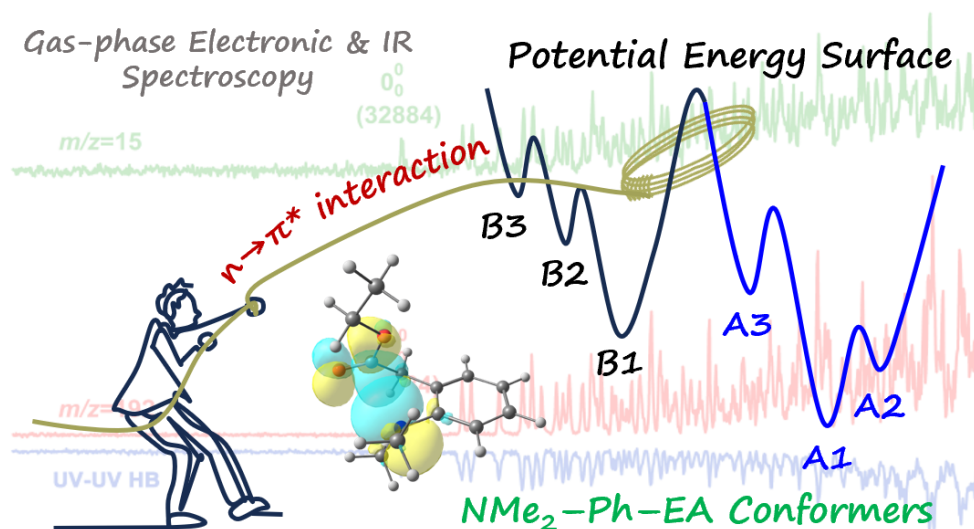
the optimized geometries calculated at the B3LYP-D3(BJ)/def2-TZVP, B3LYP-D3(BJ)/aug-cc-pVTZ, and B3LYP-D3(BJ)/6-311++G(d,p) levels, respectively.

EDA analysis of the C1 and T1 (Figures 4.13 and 4.14) performed at the different calculation levels using ALMO-EDA and SAPT2+3 methods reveal the components of the interaction energy contributing to the stability of the complex. Interestingly, the dispersion in C1 is significantly larger than in T1, while the electrostatic contribution in C1 is smaller than in T1. The larger dispersion in the C1 could be due to the O–H $\cdots\pi$ hydrogen bond, which is absent in T1. It has been demonstrated in the literature that dispersion forces play a significant role in the stabilization of the π -hydrogen bonding.^{206, 207}

4.4 Conclusion

In summary, we have studied the 1:1 complex of phenyl formate with H₂O as the first step in the solvation of phenyl formate using microwave, electronic, and IR spectroscopy in a supersonic jet. Experimental results have been interpreted in the light of quantum chemistry calculations. Two conformers of phenyl formate $\cdots$ H₂O were found in both microwave and mass-selected UV/IR spectroscopy experiments. In principle, the structures of the observed conformers C1 and T1 are analogous to those of the *cis*-phenyl formate and *trans*-phenyl formate conformers of the monomer, respectively. One of the conformers of the phenyl formate $\cdots$ H₂O designated as C1 is found to be stabilized primarily by an O–H $\cdots$ O=C hydrogen bond accompanied by a much weaker n $\rightarrow\pi^*$ interaction and O–H $\cdots\pi$ hydrogen bond. On the other hand, the structure of the other observed conformer of the phenyl formate $\cdots$ H₂O termed T1 is dominated by an O–H $\cdots$ O=C hydrogen bond, which is stronger than that in C1. The prediction of efficient relaxation of the higher energy conformers C2 and T2 from quantum chemistry calculations agrees with their absence in the expansion. In the case of the electronic spectroscopy experiment, the assignment of the observed conformers is mainly based on shallow isomerization barriers of the higher energy conformers C2 and T2. The presence of the very weak n $\rightarrow\pi^*$ interaction in the C1 conformer of phenyl formate $\cdots$ H₂O has been identified only through NBO and NCI analyses. The overall finding demonstrates that the conformational preferences of the monohydrated phenyl formate are similar to those of the phenyl formate monomer.

Chapter 5: Observation of $\text{N}\cdots\text{C}=\text{O}$ $\text{n}\rightarrow\pi^*$ interaction in the photofragmented product of ethyl 2-(2-(dimethylamino) phenyl) acetate



Adapted from: P. Panwaria* and A. Das*, $\text{N}\cdots\text{C}=\text{O}$ $\text{n}\rightarrow\pi^*$ Interaction: Gas-phase electronic and vibrational spectroscopy combined with quantum chemistry calculations. (Manuscript under review).

5.1 Motivation of this work

In the previous chapters, we have discussed the various ways for tuning the strength of $\text{C}=\text{O}\cdots\text{aromatic } n\rightarrow\pi^*$ interactions in phenyl acetate and phenyl formate $\cdots$ water complex, where carbonyl oxygen lone pair electron density delocalizes into the π^* orbital of the phenyl ring. We have explored this $\text{C}=\text{O}\cdots\text{aromatic } n\rightarrow\pi^*$ interaction using gas-phase electronic and vibrational spectroscopy with the help of quantum chemistry calculations. Hitherto, these spectroscopic methods have been used for studying the $\text{C}=\text{O}\cdots\text{C}=\text{O}$ and $\text{C}=\text{O}\cdots\text{aromatic } n\rightarrow\pi^*$ interactions. However, there is no report in the literature where gas-phase electronic and vibrational spectroscopy has been utilized to study the $\text{N}\cdots\text{C}=\text{O } n\rightarrow\pi^*$ interaction. Here, the lone pair orbital of the nitrogen atom delocalizes into the π^* orbital of the carbonyl group. To fill this gap in the literature and to understand the $\text{N}\cdots\text{C}=\text{O } n\rightarrow\pi^*$ interaction, we synthesized the ethyl 2-(2-(dimethylamino) phenyl) acetate ($\text{NMe}_2\text{-Ph-EA}$).

5.2 Introduction

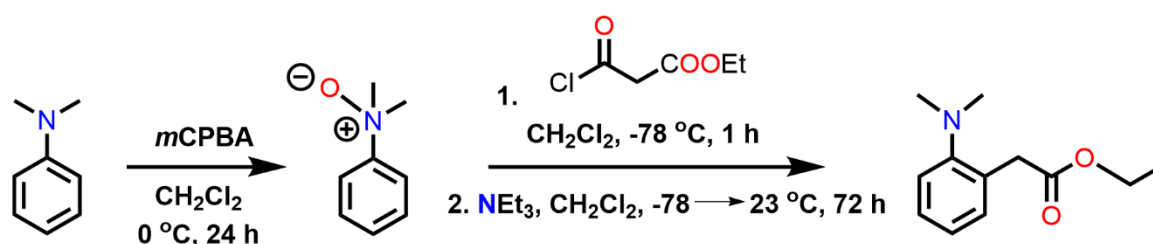
Mottus and co-workers first observed $\text{N}\cdots\text{C}=\text{O } n\rightarrow\pi^*$ interaction in protopine using UV-Vis and IR spectroscopy.⁷⁰ The $\text{N}\cdots\text{C}=\text{O } n\rightarrow\pi^*$ interaction was also observed further in the crystal structures of protopine, cryptopine, clivorine, 1-dimethylaminonaphthalene-8-ketones, and 2-(dimethylamino) biphenyl-2'-carboxaldehydes.^{86, 99, 100} Isolated gas-phase IR spectroscopy has been exploited to recognize the $\text{C}=\text{O}\cdots\text{C}=\text{O}$ and $\text{C}=\text{O}\cdots\text{aromatic } n\rightarrow\pi^*$ interaction by measuring the redshift in carbonyl stretching frequency in the conformers with respect to those lacking this interaction.^{10, 16, 47, 61, 62, 69, 92, 93, 125, 141, 208, 209} Heretofore, $\text{N}\cdots\text{C}=\text{O } n\rightarrow\pi^*$ interaction has not been studied using gas-phase IR spectroscopy and ^{13}C VT NMR spectroscopy. However, a handful of reports from Lopez and co-workers employing microwave spectroscopy¹³⁵⁻¹³⁷ demonstrated the role of intermolecular $\text{N}\cdots\text{C}=\text{O } n\rightarrow\pi^*$ interaction in stabilizing the complexes of pyridine with aldehydes and ketones along with the secondary $\text{C-H}\cdots\text{O}$ hydrogen bonding. Maciel and co-workers, as well as Rademacher and co-workers, have measured ^{13}C NMR spectra by probing the carbonyl carbon of a series of cyclic aminoketones having transannular $\text{N}\cdots\text{C}=\text{O } n\rightarrow\pi^*$ interaction.²¹⁰⁻²¹² Raines and co-workers showed the presence of $\text{C}=\text{O}\cdots\text{C}=\text{O } n\rightarrow\pi^*$ interaction by measuring the equilibrium constant for the interconversion of the *cis* and *trans* conformers of *N*-formyl-L-proline methyl ester through ^1H NMR spectroscopy.⁵⁶ Recently, Biswal and co-workers utilized ^{13}C NMR spectroscopy by probing the chemical shift of the nitrile carbon as a function of temperature as well as the concentration of pyridine-*N*-oxide to demonstrate the presence of $\text{O}\cdots\text{C}\equiv\text{N } n\rightarrow\pi^*$ interaction in the complex of pyridine-*N*-oxide $\cdots$ dimethyltetracyclopentane.²¹³

In this chapter, we have presented gas-phase IR as well as NMR spectroscopic evidence of $N\cdots C=O$ $n\rightarrow\pi^*$ interaction present in ethyl 2-(2-(dimethylamino) phenyl) acetate (NMe₂-Ph-EA). Herein, ¹³C NMR chemical shift of the carbonyl carbon of NMe₂-Ph-EA is compared with ethylphenyl acetate (Ph-EA), lacking the $n\rightarrow\pi^*$ donor. Furthermore, ¹³C VT NMR spectra of NMe₂-Ph-EA have been measured to probe the $N\cdots C=O$ $n\rightarrow\pi^*$ interaction. Additionally, ¹H NMR chemical shifts of the α -protons of the carbonyl group of NMe₂-Ph-EA are monitored as a function of temperature. ¹H NMR chemical shift of the α -protons of the carbonyl group of NMe₂-Ph-EA are also compared with those of Ph-EA at room temperature. Gas-phase electronic and vibrational spectra of NMe₂-Ph-EA are measured in the mass channels of $m/z=15$ and 192 photofragmented products. Detailed quantum chemistry calculations have been performed to establish the presence of the $n\rightarrow\pi^*$ interaction in NMe₂-Ph-EA. Structural assignments of some other photofragmented products are also performed using gas-phase spectroscopy. The present work demonstrates the importance of the $n\rightarrow\pi^*$ interaction in preferential stabilization of the low-energy conformations of flexible molecular systems.

5.3 Results and Discussion

5.3.1 Synthesis and characterization

Ethyl 2-(2-(dimethylamino) phenyl) acetate (NMe₂-Ph-EA) was synthesized in order to perform the aimed study of this chapter. It was synthesized using the two-step synthesis reported in the literature (Scheme 5.1).²¹⁴ All the chemicals were obtained from commercial sources and used without further purification.



Scheme 5.1. Synthetic scheme of ethyl 2-(2-(dimethylamino) phenyl) acetate (NMe₂-Ph-EA)

A clear solution of *meta*-chloroperbenzoic acid (*m*CPBA) (5 gm) in diethyl ether (100 ml) was washed three times with an aqueous solution of KH₂PO₄ (0.05 M) and NaOH (0.025 M). This solution was dried over MgSO₄ and filtered, and the solvent was evaporated to obtain pure *m*CPBA (3.25 gm) and utilized in the first step of the reaction as an oxygen source. A clear solution of *N, N*-dimethylaniline (500 mg) in HPLC grade CH₂Cl₂ (20 ml) was cooled and stirred in the round bottom flask (RB) at 0 °C. The equimolar *m*CPBA solution in CH₂Cl₂

(20 ml) was dissolved slowly in the RB at 0 °C. The solution was brought upto room temperature gradually after 15 minutes of addition of the reagent and stirred for 48 h under an inert atmosphere. The slurry of the reaction mixture (prepared in basic alumina) was loaded directly to the basic alumina column using 25% MeOH (in CH₂Cl₂) as eluent and purified using column chromatography. The solvent was evaporated to obtain the purified *N*, *N*-dimethylaniline-*N*-oxide (350 mg).

N, *N*-dimethylaniline-*N*-oxide (200 mg) dissolved in CH₂Cl₂ (30 ml) was cooled and stirred while maintaining the temperature at -78 °C. Ethyl malonyl chloride (0.2 ml) was added dropwise *via* a syringe to this solution and stirred for 1 h. Distilled NEt₃ (0.35 ml) was added to this solution and then brought upto room temperature gradually after 15 minutes of addition (NEt₃) and stirred for 72 h. The reaction mixture was purified using 2% EtOAc (in *n*-hexane) as eluent through column chromatography. The solvent was evaporated to obtain the purified NMe₂-Ph-EA (pale yellow liquid). HRMS spectrum shown in Figure 5.1 shows the successful formation of the compound. ¹H (Figure 5.2) and ¹³C NMR (Figure 5.3) spectra performed in the CDCl₃ solvent match well with the previously reported one.²¹⁴ Moreover, these spectra illustrate the purity of the synthesized NMe₂-Ph-EA.

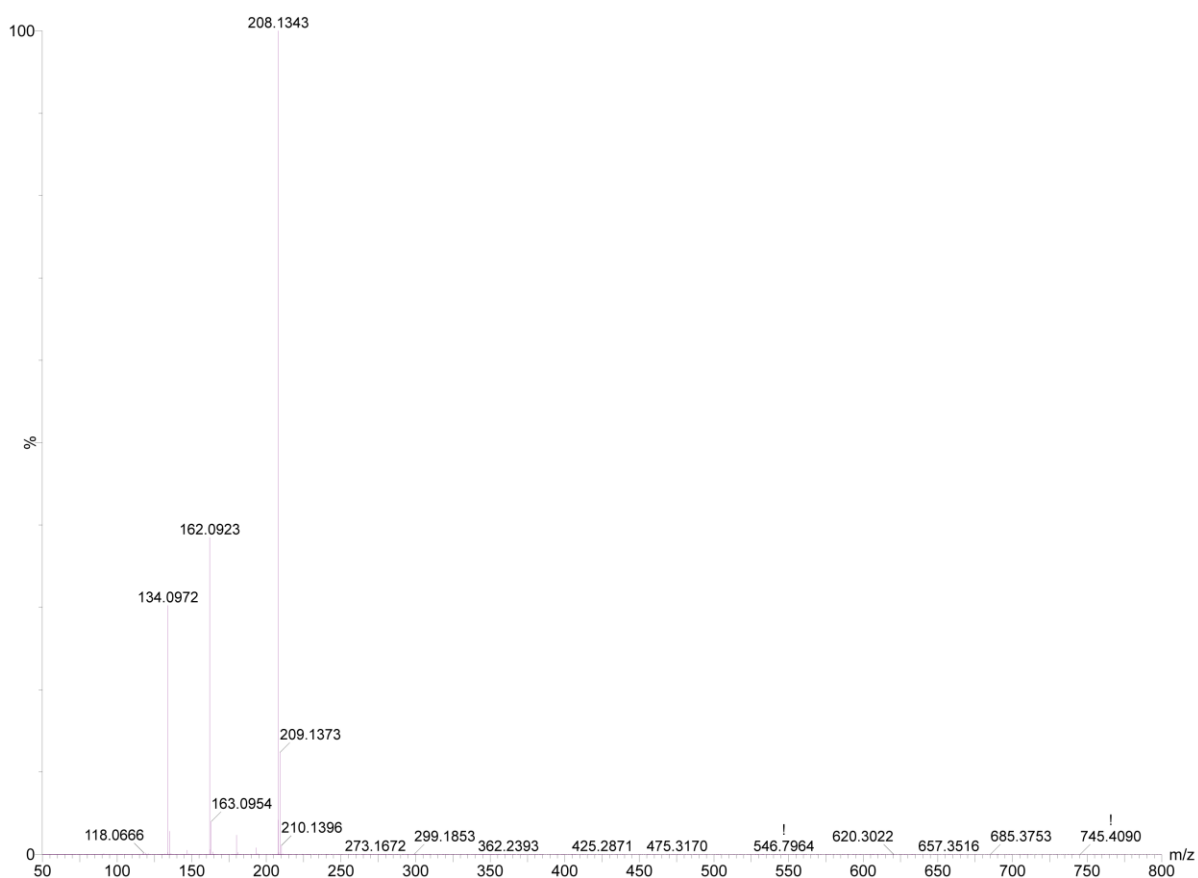
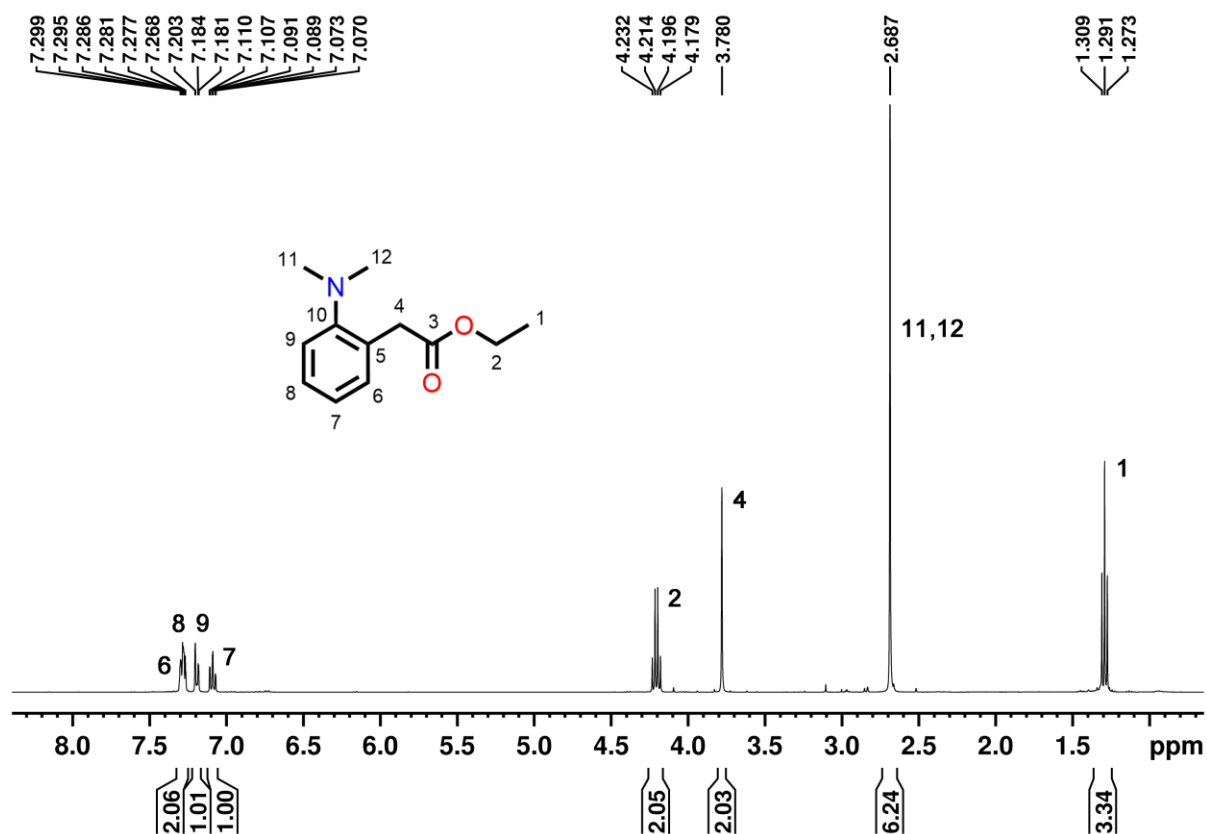
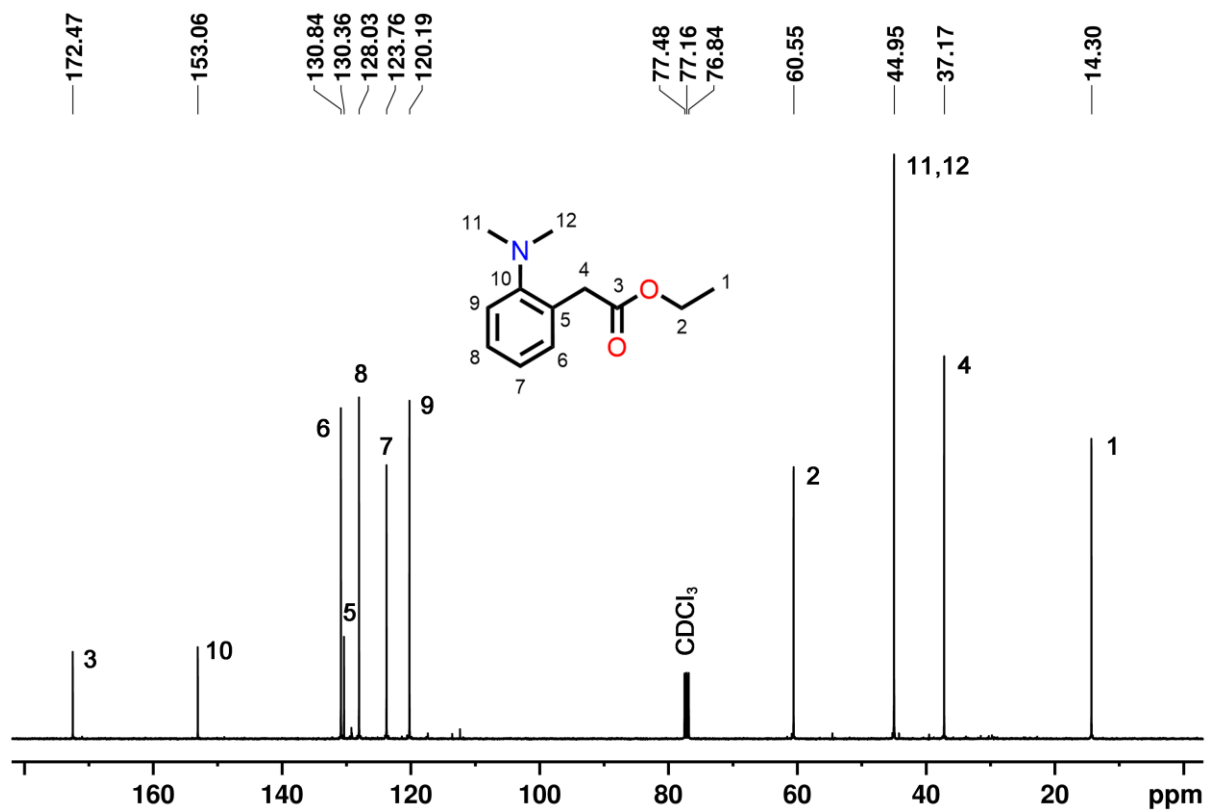


Figure 5.1. HRMS spectrum of NMe₂-Ph-EA.

Figure 5.2. ¹H NMR spectrum of NMe₂-Ph-EA.Figure 5.3. ¹³C NMR spectrum of NMe₂-Ph-EA.

5.3.2 NMR spectroscopic evidence of $\text{N}\cdots\text{C}=\text{O}$ $\text{n}\rightarrow\pi^*$ interaction

We have tried to seek the solution-phase evidence of the $\text{N}\cdots\text{C}=\text{O}$ $\text{n}\rightarrow\pi^*$ interaction in $\text{NMe}_2\text{-Ph-EA}$ by probing the chemical shift of the carbonyl carbon through ^{13}C NMR spectroscopy performed in CDCl_3 solvent. The ^{13}C chemical shift of the carbonyl carbon in $\text{NMe}_2\text{-Ph-EA}$ (172.48 ppm) was compared with that of Ph-EA (171.65 ppm) and found to be downfield than that of ethylphenyl acetate (Ph-EA) by 0.83 ppm, indicating the presence of the $\text{N}\cdots\text{C}=\text{O}$ $\text{n}\rightarrow\pi^*$ interaction. The presence of the $\text{N}\cdots\text{C}=\text{O}$ $\text{n}\rightarrow\pi^*$ interaction was further delineated by ^{13}C variable temperature (VT) NMR (Figure 5.4) spectroscopy performed in the 218–328 K temperature range. It was found that the chemical shift of the carbonyl carbon shows a gradual upfield shift of 0.62 ppm from 172.97 to 172.35 ppm with the increase in the temperature, proving the weakening of the $\text{n}\rightarrow\pi^*$ interaction. Thus, the deshielding of the carbonyl carbon in $\text{NMe}_2\text{-Ph-EA}$ with respect to Ph-EA and shielding of the carbonyl carbon with the increase in temperature proves the presence of the $\text{N}\cdots\text{C}=\text{O}$ $\text{n}\rightarrow\pi^*$ interaction in solution-phase.

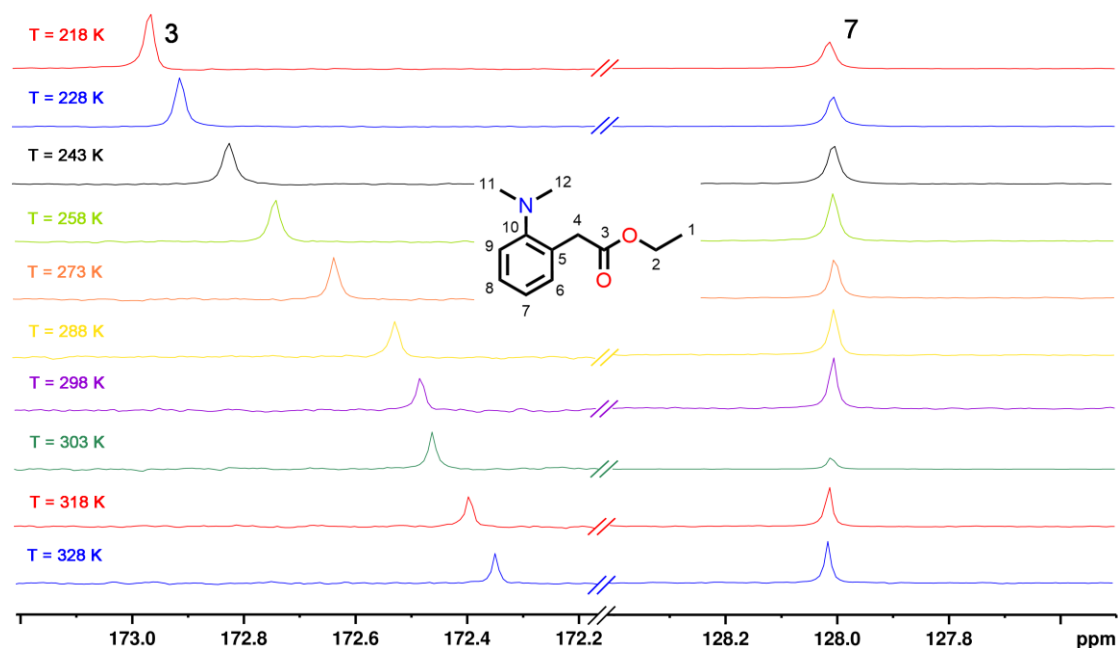


Figure 5.4. ^{13}C VT NMR spectrum of $\text{NMe}_2\text{-Ph-EA}$ showing gradual upfield shifting of the carbonyl carbon (3) with respect to the carbon atom at the *para* position of $-\text{NMe}_2$ group (7) upon the increase in temperature.

The signature of the $\text{N}\cdots\text{C}=\text{O}$ $\text{n}\rightarrow\pi^*$ interaction has also been obtained by monitoring the ^1H chemical shift of the $\alpha\text{-CH}_2$ protons in $\text{NMe}_2\text{-Ph-EA}$. The ^1H chemical shift of the $\alpha\text{-CH}_2$ protons for $\text{NMe}_2\text{-Ph-EA}$ was compared with the Ph-EA , respectively. The ^1H chemical shift of the $\alpha\text{-CH}_2$ protons in $\text{NMe}_2\text{-Ph-EA}$ (3.66 ppm) was downfield than that of the Ph-EA (3.54 ppm) by 0.12 ppm. It is expected that in the presence of the $\text{N}\cdots\text{C}=\text{O}$ $\text{n}\rightarrow\pi^*$ interaction,

delocalization of electron density from the σ orbital of the C–H bond into the σ^*/π^* orbital of the carbonyl will be enhanced, thus resulting in the deshielding of the α -protons. The presence of $\text{N}\cdots\text{C}=\text{O}$ $n\rightarrow\pi^*$ interaction was further delineated by the VT ^1H (Figure 5.5) NMR spectroscopy performed in CDCl_3 solvent in the 218–328 K temperature range. The chemical shift of the α - CH_2 protons of $\text{NMe}_2\text{-Ph-EA}$ shows the gradual upfield shift of 0.03 ppm from 3.68 to 3.65 ppm with the increase in the temperature. Thus, the deshielding of the ^1H chemical shift of $\text{NMe}_2\text{-Ph-EA}$ with respect to Ph-EA and shielding of these chemical shifts with the increase in the temperature proves the presence of the $\text{N}\cdots\text{C}=\text{O}$ $n\rightarrow\pi^*$ interaction in the solution-phase.

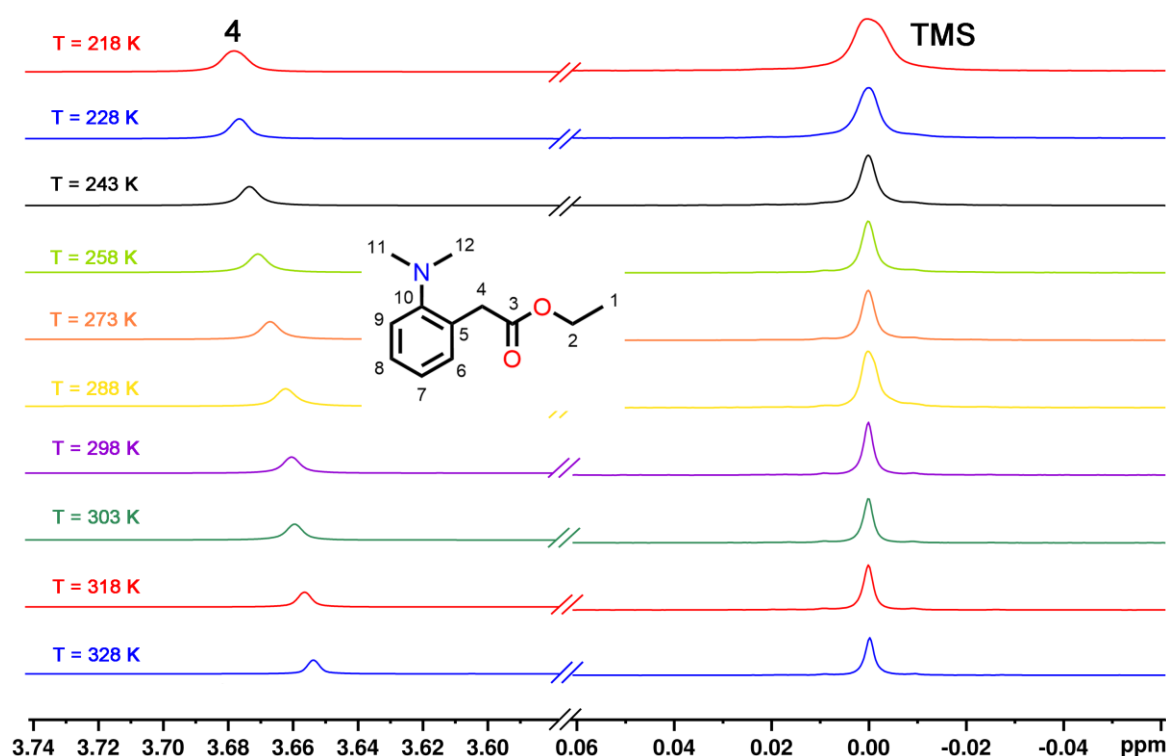


Figure 5.5. ^1H VT NMR spectrum of $\text{NMe}_2\text{-Ph-EA}$ showing the gradual upfield shifting of α - CH_2 protons (4) with respect to the TMS upon the increase in temperature.

5.3.3 Conformational landscape

After seeking the solution-phase spectroscopic evidence of the $\text{N}\cdots\text{C}=\text{O}$ $n\rightarrow\pi^*$ interaction from ^1H and ^{13}C VT NMR spectroscopy, we moved further to look for its gas-phase spectroscopic evidence. Before the start of the gas-phase experiments, the conformational landscape of $\text{NMe}_2\text{-Ph-EA}$ was obtained. The S_0 state optimized geometries of the six low-energy conformers of $\text{NMe}_2\text{-Ph-EA}$ having the $n\rightarrow\pi^*$ interaction with ZPE corrected relative energies (E_{rel} , kJ/mol) calculated at the B3LYP-D3/def2-TZVP level are provided in Figure 5.6. These conformers are classified into two rotameric groups, i.e., A (A1, A2, and A3) and B (B1, B2,

and B3), based on the orientation of the $-\text{COOCH}_2\text{CH}_3$ moiety with respect to the phenyl ring. These rotamers differ in the orientation of the methyl group of ester ($-\text{CH}_2-\text{CH}_3$). The global minimum A1 is lower in energy than A2 and A3 by 1.69 and 2.18 kJ/mol, respectively, whereas B1 is lower in energy than B2 and B3 by 0.36 and 1.83 kJ/mol, respectively. Further, A1 is lower in energy than B1 by 1.84 kJ/mol.

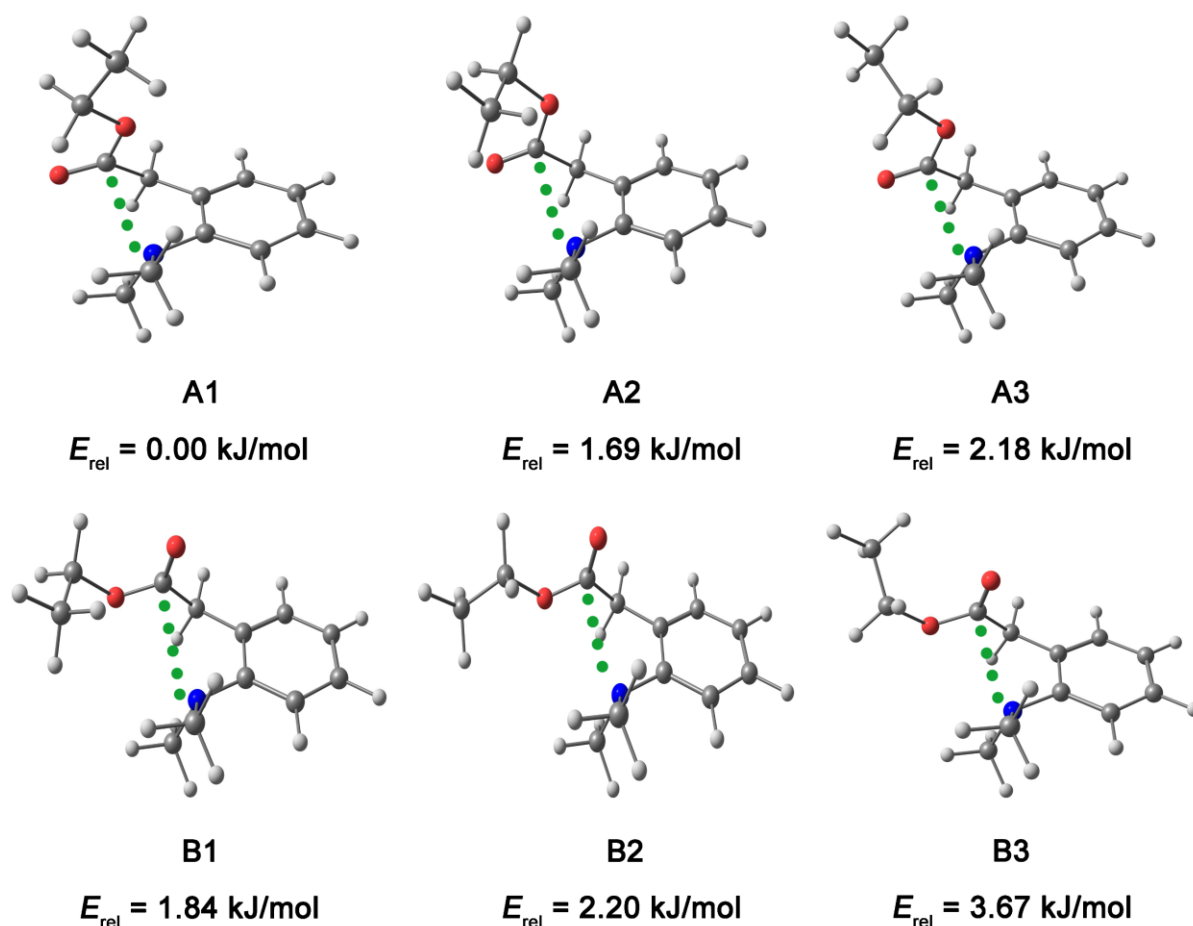


Figure 5.6. S_0 state optimized geometries of low-energy conformers of $\text{NMe}_2\text{-Ph-EA}$ with ZPE corrected relative energies (E_{rel} , kJ/mol) calculated at the B3LYP-D3/def2-TZVP level.

Thermal correction (0-400 K) to the relative energies is done to incorporate entropy contribution by calculating their relative change in Gibbs free energies (ΔG_{rel}) at the B3LYP-D3/def2-TZVP level, and it is found that A1 is the most stable conformer (Figure 5.7). The trend of ZPE corrected relative energies of these six low-energy conformers are consistent at different calculation levels (including DFT and MP2), and these energies at different calculation levels are provided in Table 5.1. It can be inferred that the A1 conformer is the global minimum at various calculation levels. Moreover, relative energies without ZPE correction are also provided in Table 5.1.

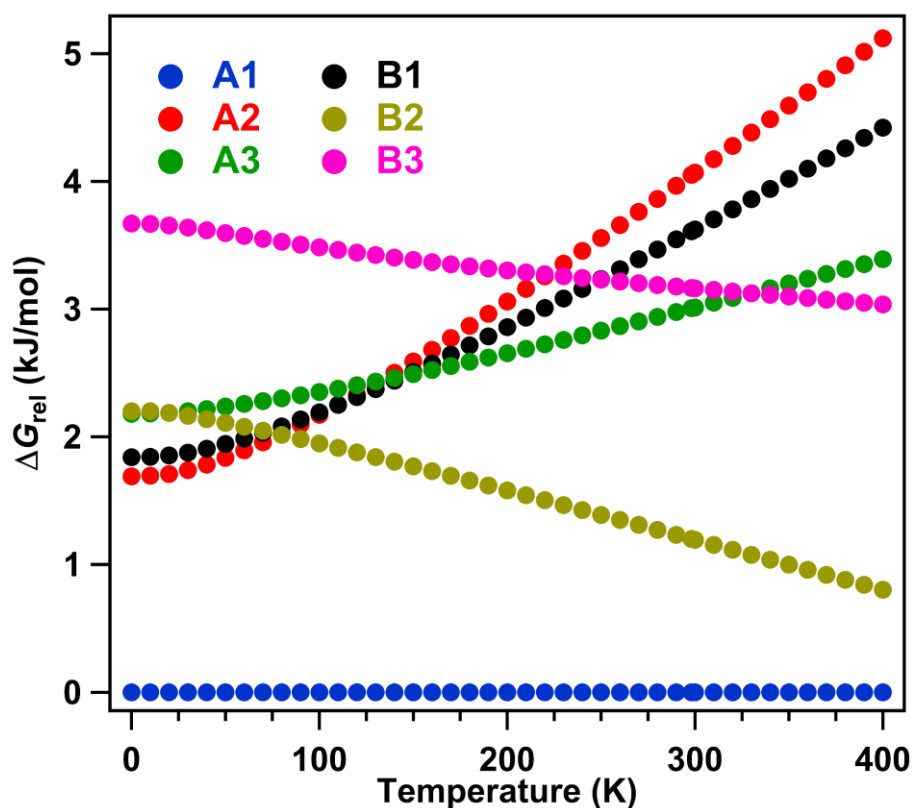


Figure 5.7. Plots of thermal corrected relative energy with ZPE correction (ΔG_{rel} , kJ/mol) of the various conformers as a function of temperature (0-400 K) calculated at the B3LYP-D3/def2-TZVP level.

Table 5.1. Zero-point energy (ZPE) corrected relative energies (E_{rel} , kJ/mol) of various conformers calculated at the **A)** B3LYP-D3/def2-TZVP; **B)** B3LYP-D3/aug-cc-pVTZ; **C)** B3LYP-D3/6-311++G(d,p); **D)** ω B97X-D/def2-TZVP; **E)** ω B97X-D/aug-cc-pVTZ; **F)** ω B97X-D/6-311++G(d,p); **G)** B97-D3/def2-TZVP; **H)** B97-D3/aug-cc-pVTZ; **I)** B97-D3/6-311++G(d,p); and **J)** MP2/6-311++G(d,p) levels. Relative energy without ZPE correction (E_{ele} , kJ/mol) of various conformers are provided in the parentheses

	A	B	C	D	E	F	G	H	I	J
A1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	(0.00)	(0.02)	(0.00)	(0.65)	(0.61)	(0.26)	(0.56)	(0.56)	(0.29)	(0.00)
A2	1.69	1.70	2.23	1.18	1.04	1.43	1.04	1.03	1.35	3.62
	(0.00)	(0.00)	(0.39)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(1.89)
A3	2.18	2.28	2.30	1.72	1.61	2.69	1.58	1.65	1.57	2.78
	(1.65)	(1.75)	(1.72)	(2.46)	(2.48)	(2.28)	(1.6)	(1.74)	(1.46)	(2.37)
B1	1.84	1.92	2.15	1.09	1.04	1.72	1.40	1.47	1.60	2.74
	(0.81)	(0.89)	(1.00)	(0.76)	(0.76)	(0.46)	(0.95)	(1.00)	(0.75)	(2.30)

B2	2.20	2.38	2.24	2.03	2.00	2.51	2.28	2.41	2.33	2.06
	(2.58)	(2.76)	(2.68)	(3.32)	(3.43)	(3.15)	(3.08)	(3.23)	(2.91)	(2.83)
B3	3.67	3.89	3.68	3.72	3.73	3.65	3.17	3.36	3.22	3.83
	(3.54)	(3.77)	(3.54)	(4.31)	(4.43)	(4.07)	(3.57)	(3.74)	(3.28)	(4.09)

There could be conformational relaxation within group A and B rotamers *via* low interconversion energy barriers during the collisions of the sample molecule with the carrier gas during supersonic expansion.¹⁸² The interconversion barriers of these rotamers calculated by scanning the $-(C=O)OC-C-$ dihedral angle at an interval of 5° using a relaxed potential energy scan (PES) are shown in Figure 5.8. The interconversion barriers for $A2 \rightarrow A1$, $A3 \rightarrow A1$, $B2 \rightarrow B1$, and $B3 \rightarrow B2$, which were found to be 301 (3.60), 256 (3.06), 206 (2.46), and 281 (3.37) cm^{-1} , respectively (also provided in kJ/mol in parentheses) calculated at the B3LYP-D3/def2-TZVP level, bespeak the relaxation of the conformers belonging to groups A and B to the respective minima A1 and B1. Thus, either the A1 or B1 conformers could be present in the experiment. The interconversion barriers for $A2 \rightarrow A1$, $A3 \rightarrow A1$, $B2 \rightarrow B1$, and $B3 \rightarrow B2$ were also calculated from the transition state search and were found to be 306 (3.66), 257 (3.07), 206 (2.46), 284 (3.39) cm^{-1} , respectively (also provided in kJ/mol in parentheses), which is similar to the relaxed PES.

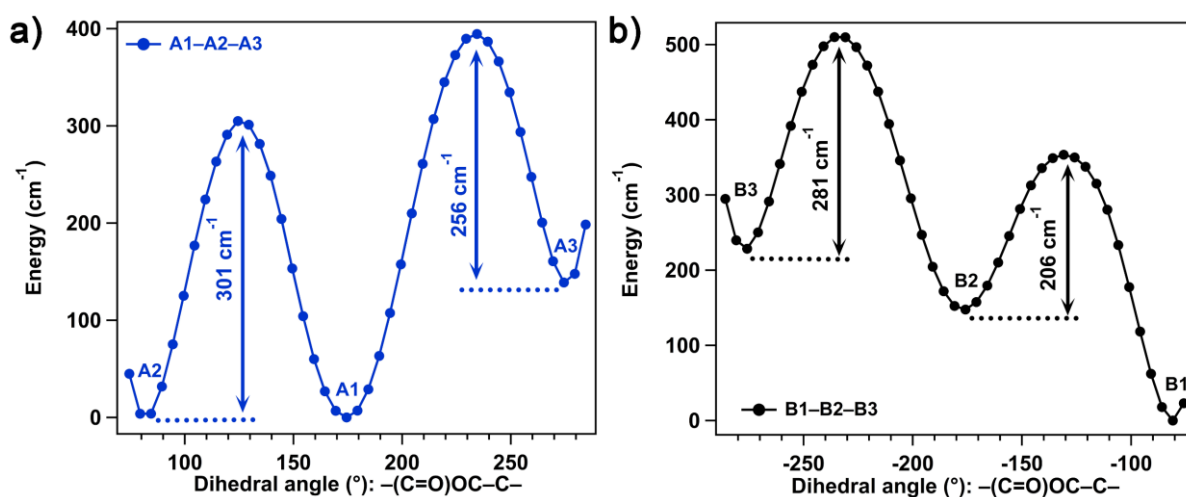


Figure 5.8. Relaxed PES of the $-(C=O)OC-C-$ dihedral angle (rotation of the methyl group) for group a) A (blue trace) and b) B (black trace) conformers calculated at the B3LYP-D3/def2-TZVP level.

Interestingly, the higher energy conformers of $\text{NMe}_2\text{-Ph-EA}$ lack the $n \rightarrow \pi^*$ interaction. S_0 state optimized geometries of these high-energy conformers are provided in Figure 5.9.

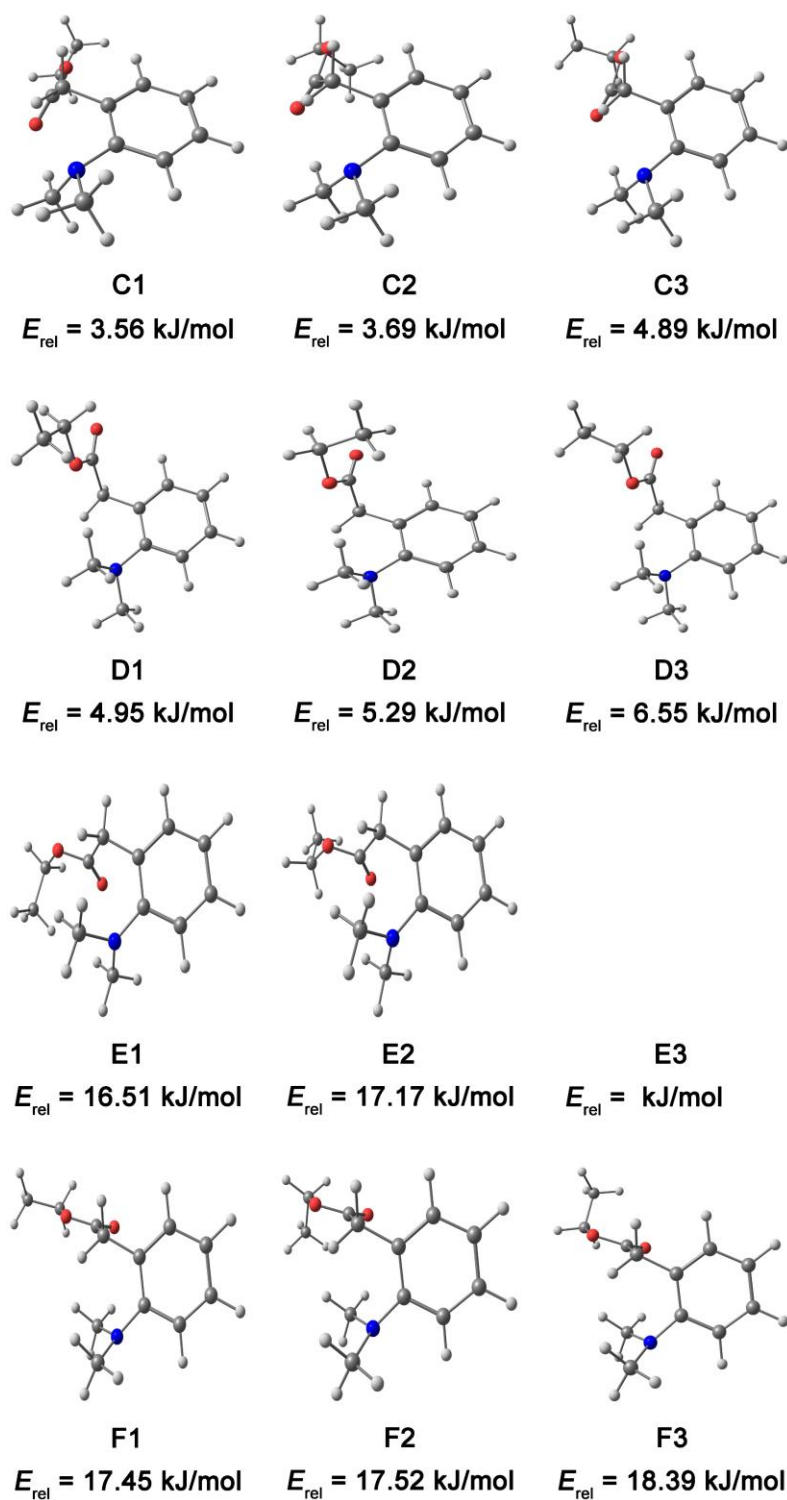


Figure 5.9. Optimized geometries of higher-energy conformers of NMe₂–Ph–EA lacking n→π* interaction with ZPE corrected relative energies (E_{rel} , kJ/mol) calculated at the B3LYP-D3/def2-TZVP level.

5.3.4 TOF-MS of NMe₂–Ph–EA

NMe₂–Ph–EA is a derivative of a well-known compound *N*, *N*-dimethylaniline (NMe₂–Ph) with ethyl acetate (EA) at its *ortho* position, separated by sp³ hybridized –CH₂– group from the

phenyl ring. The electronic spectrum of NMe₂-Ph-EA is expected to appear near the electronic spectral region of NMe₂-Ph having the origin band (0_0^0) at 32896 cm⁻¹ (304 nm)²¹⁵ as both share the same chromophore (NMe₂-Ph). However, no NMe₂-Ph-EA mass signal was observed in TOF-MS recorded using the one-color non-resonant two-photon ionization technique in the 29850-34000 cm⁻¹ region (294.1-335 nm), as shown in Figures 5.10 and 5.11.

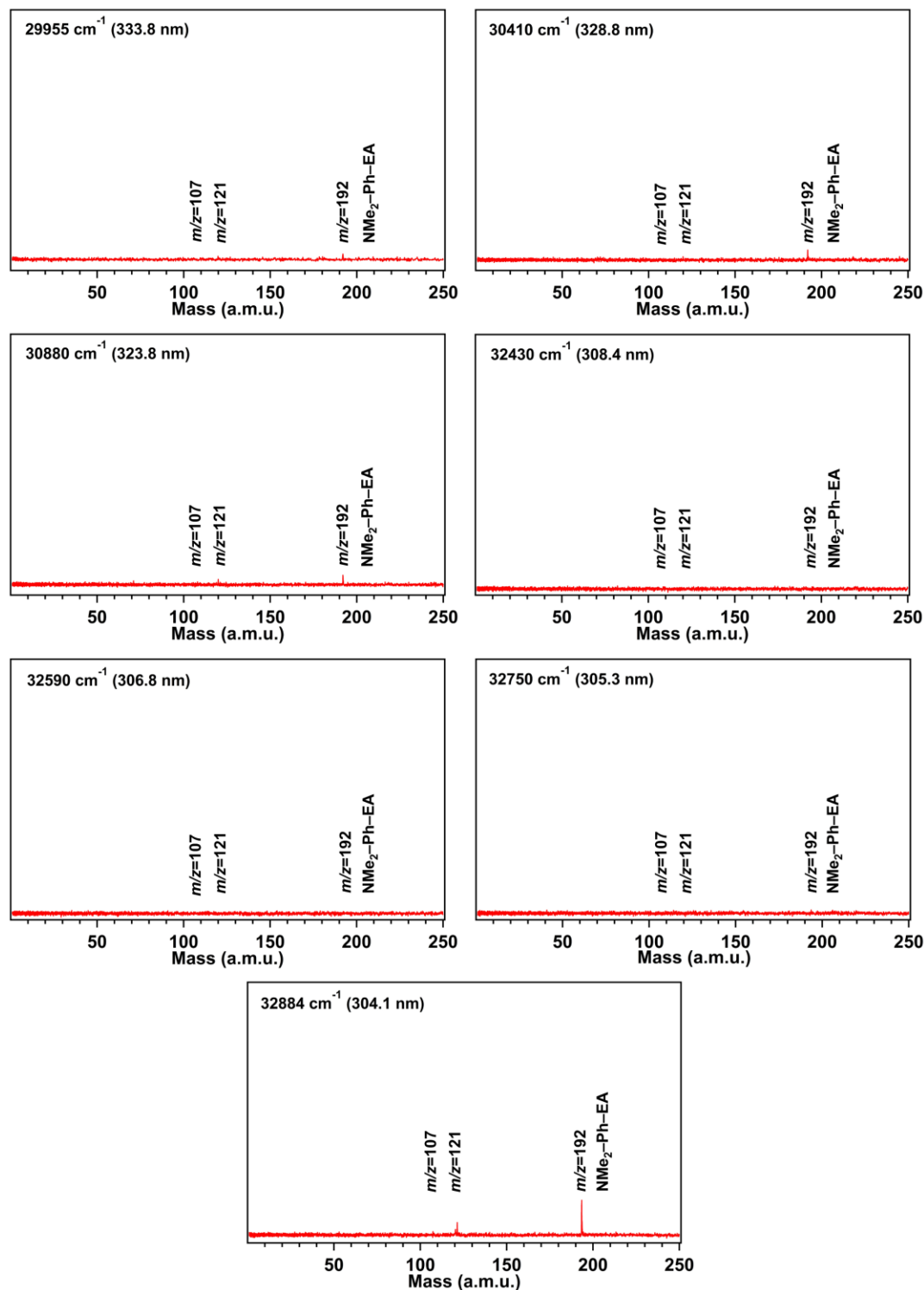


Figure 5.10. TOF-MS of NMe₂-Ph-EA recorded in the 29850-33000 cm⁻¹ region.

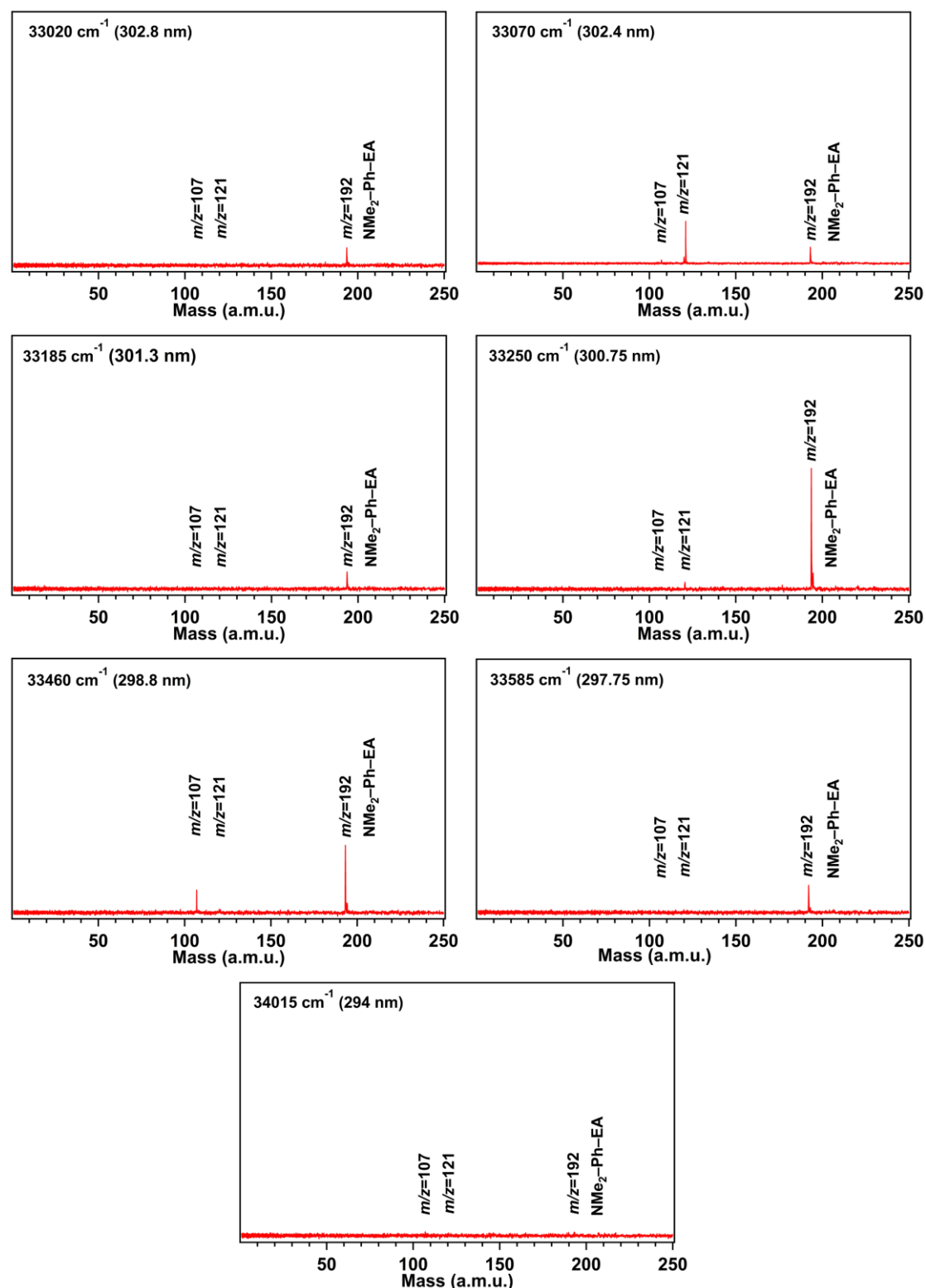


Figure 5.11. TOF-MS of NMe₂-Ph-EA recorded in the 33000-34050 cm⁻¹ region.

NMe₂-Ph-EA mass signal started appearing (Figure 5.12) with a laser frequency of >34100 cm⁻¹ (293.3 nm). The maximum NMe₂-Ph-EA mass signal was observed at 35400 cm⁻¹ (282.5 nm), which was very far away from the electronic spectral region (32896 cm⁻¹) of the chromophore.

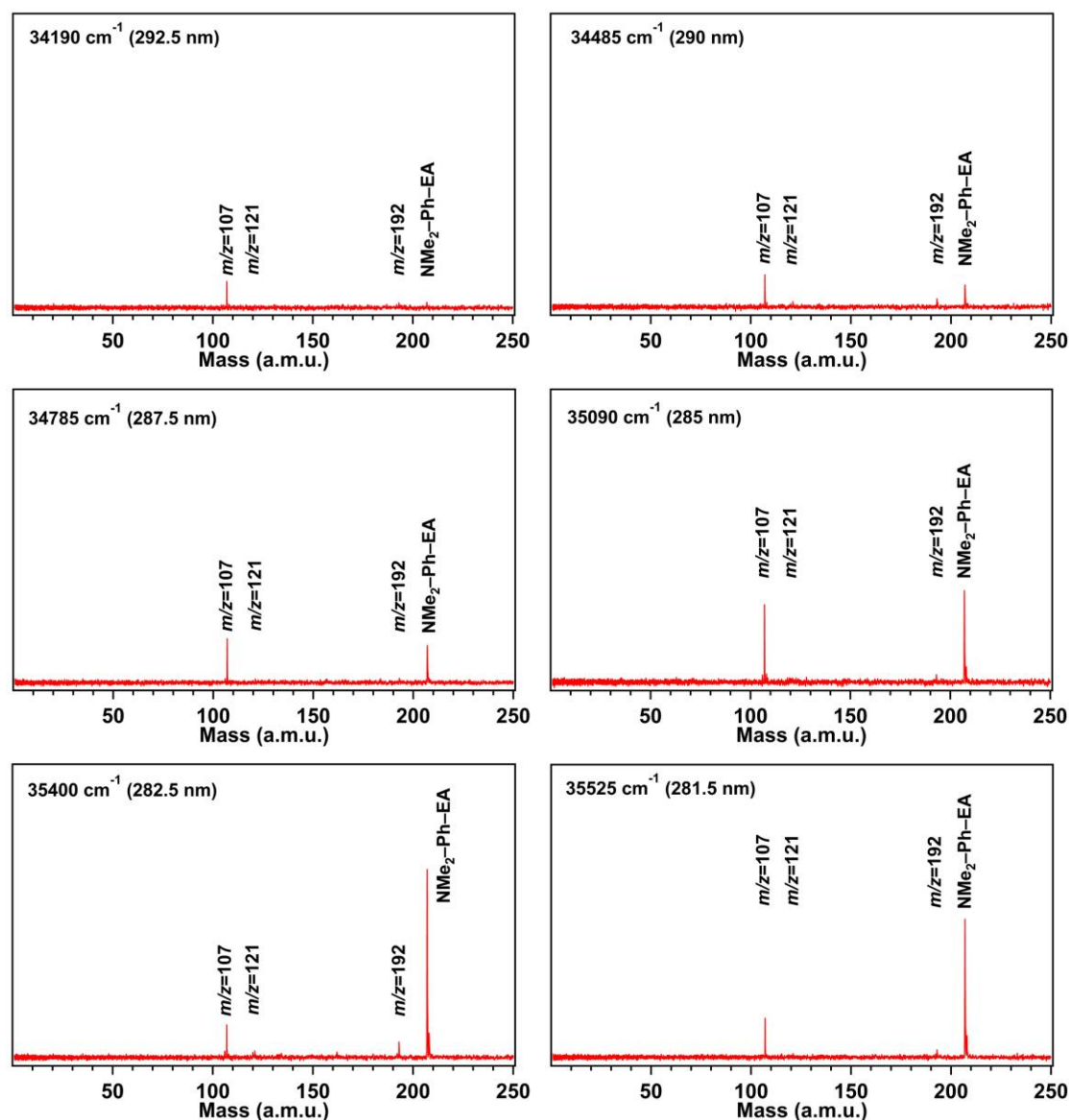


Figure 5.12. TOF-MS of NMe₂-Ph-EA recorded in the 34150-35550 cm⁻¹ region.

Apart from NMe₂-Ph-EA mass signal in these TOF-MS shown in Figures 5.10-5.12, several other mass signals corresponding to the photofragmented products with lower m/z than NMe₂-Ph-EA are observed. The mass signals below $m/z=207$ are indeed the photofragments of NMe₂-Ph-EA because this synthesized molecule is free from any impurities/side-products, as confirmed by the ¹H and ¹³C NMR spectra provided in Figures 5.2 and 5.3. The possibilities of fragmentation from the -NMe₂ group and the -EA side-chain of NMe₂-Ph-EA cannot be ruled out. Initially, we attempted to measure the electronic spectrum in NMe₂-Ph-EA mass channel by scanning the laser in the 29850-35900 cm⁻¹ (278.6-335 nm) region using 1C-R2PI spectroscopy. However, no electronic band was observed for NMe₂-Ph-EA by scanning this extended wavelength range. There are reports in the literature on measuring the electronic spectrum of several isolated molecular systems in the mass channels of their fragmented

products, such as amphetamine, ephedrine, pseudoephedrine, and 1,2,3,4-tetrahydro-3-isoquinolinemethanol.²¹⁶⁻²²⁰ Thus, similar attempts are made here to record the electronic spectrum of NMe₂-Ph-EA in the mass channels of the photofragmented products. It can be noticed in Figures 5.10-5.12 that $m/z=107$, 121, and 192 are the dominant fragments of NMe₂-Ph-EA. Thus, efforts are made to trace the electronic spectrum of NMe₂-Ph-EA in the mass channels of these three major fragments (107, 121, and 192).

5.3.5 Electronic spectroscopy at $m/z=107$ fragment mass channel

The electronic spectrum at the $m/z=107$ fragment mass channel recorded in the 33200-34600 cm⁻¹ (289-301.2 nm) region is shown in Figure 5.13. It can be mentioned here that the electronic spectrum measured in the mass channel of any photofragmented product by the R2PI technique will represent the electronic spectrum of NMe₂-Ph-EA if the fragmentation occurs in the ionic state. On the other hand, if the fragmentation occurs in the excited state of NMe₂-Ph-EA, then the electronic spectrum obtained in the fragment mass channel would be identical to the electronic spectrum of the photofragmented product. It is found that the electronic spectrum recorded in the $m/z=107$ fragment mass channel is exactly similar to the reported electronic spectrum of *N*-methylaniline.²¹⁵ Hence, the $m/z=107$ photoproduct is fragmented from the excited state of NMe₂-Ph-EA following some dissociative pathway and gets further ionized through S₀→S₁ electronic excitation.

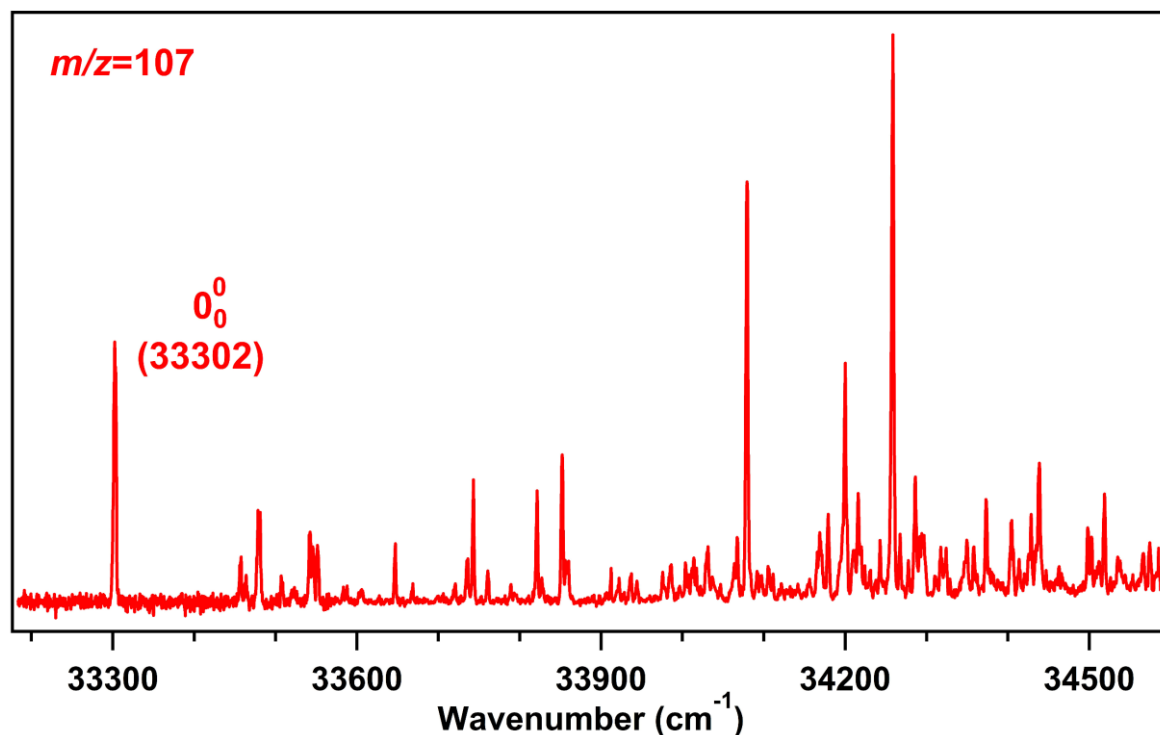


Figure 5.13. Mass-selected 1C-R2PI spectrum of $m/z=107$ fragment mass channel.

Further, the IR stretching frequency of the N–H group (as it is not reported to the best of our knowledge) by probing an electronic band at the $m/z=107$ fragment mass channel was determined using RIDIR and IRIG spectroscopy (Figure 5.14), and the observed N–H stretching frequency was 3471 cm^{-1} . Moreover, the RIDIR and IRIG spectra (Figure 5.14) of pure *N*-methylaniline were also recorded and found to be identical to those obtained at the $m/z=107$ fragment mass channel.

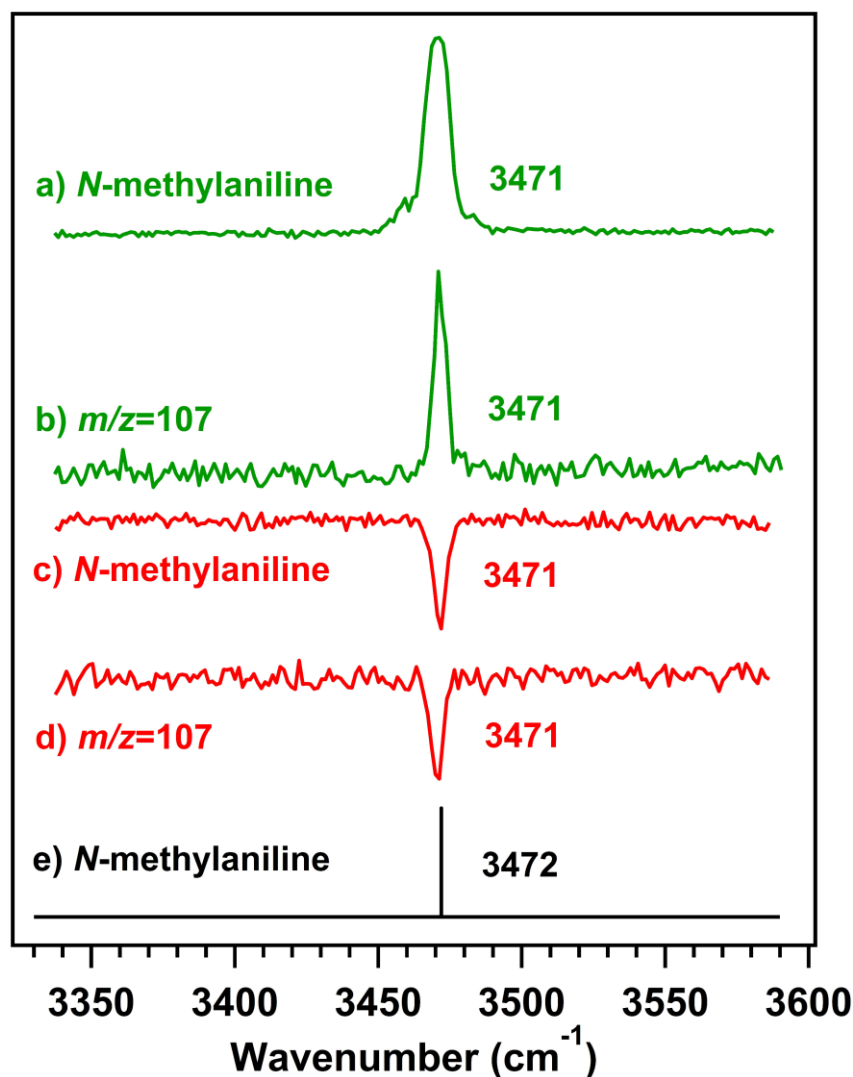


Figure 5.14. Experimentally recorded IRIG spectra (green traces) of a) *N*-methylaniline; b) $m/z=107$ fragment mass channel; RIDIR spectra (red traces) of c) *N*-methyl aniline; d) $m/z=107$ fragment mass channel; and e) Theoretical scaled IR spectrum of *N*-methylaniline calculated at the B3LYP-D3/def2-TZVP level. The harmonic stretching frequency is scaled with respect to the symmetric N–H stretching frequency of aniline (scaling factor=0.9623).²²¹

The vibronic bands ($<200\text{ cm}^{-1}$) of the electronic spectrum measured in this mass channel have been tentatively assigned based on the S_1 state vibrational frequencies of *N*-

methylaniline calculated at the CIS/6-311++G(d,p) level. It can be noticed from the detailed assignment of these bands provided in Table 5.2 that these bands are due to the methyl rotation and out-of-plane bending of the methyl group. As the structure of the $m/z=107$ fragment corresponds to *N*-methylaniline, and the electronic spectrum obtained in this mass channel belongs to the fragment but not NMe₂–Ph–EA. Further, efforts were made to record the electronic spectrum at the $m/z=121$ fragment mass channel, which is 15 mass unit (CH₃) higher than the $m/z=107$ fragment.

Table 5.2. Observed and calculated S_1 state vibrational frequencies (cm⁻¹) of experimentally observed conformer of the NHMe–Ph with the assignment of vibrational modes upto 200 cm⁻¹ of the electronic spectrum and their description. S_1 state frequencies are calculated at the CIS/6-311++G(d,p) level

Observed	Calculated	Assignment	Description of modes
0		0 ₀ ⁰	
155	126	45 ₀ ¹	Methyl rotation
162	137	44 ₀ ¹	Out-of-plane bending of methyl group
179			

5.3.6 Electronic spectroscopy at $m/z=121$ fragment mass channel

The electronic spectrum at the $m/z=121$ fragment mass channel is recorded in the 33050–33700 cm⁻¹ (296.7–302.6 nm) region (Figure 5.15). The electronic spectrum at the $m/z=121$ fragment mass channel is found to be identical to the reported electronic spectrum of NMe₂–Ph.²²² Thus, it is concluded that the $m/z=121$ photoproduct also fragments from the excited state of NMe₂–Ph–EA following some dissociative pathway, and its structure corresponds to the NMe₂–Ph. Hence, similar to the $m/z=107$ fragment mass channel, the electronic spectrum in the $m/z=121$ fragment mass channel does not correspond to the electronic spectrum of NMe₂–Ph–EA. The vibronic bands (<200 cm⁻¹) of the electronic spectrum measured in this mass channel have been tentatively assigned based on the S_1 state vibrational frequencies of NMe₂–Ph calculated at the CIS/6-311++G(d,p) level. It can be noticed from the detailed assignment of these bands provided in Table 5.3 that bands upto 122 cm⁻¹ are due to the fundamental and overtones of the asymmetric methyl rotation of the –NMe₂ group. However, other modes are also involved, such as out-of-plane bending of the –NMe₂ group, symmetric methyl rotation, and phenyl twisting. It shows that the close vibronic progression observed in the electronic spectrum of NMe₂–Ph compared to the *N*-methylaniline was due to coupled methyl rotation.

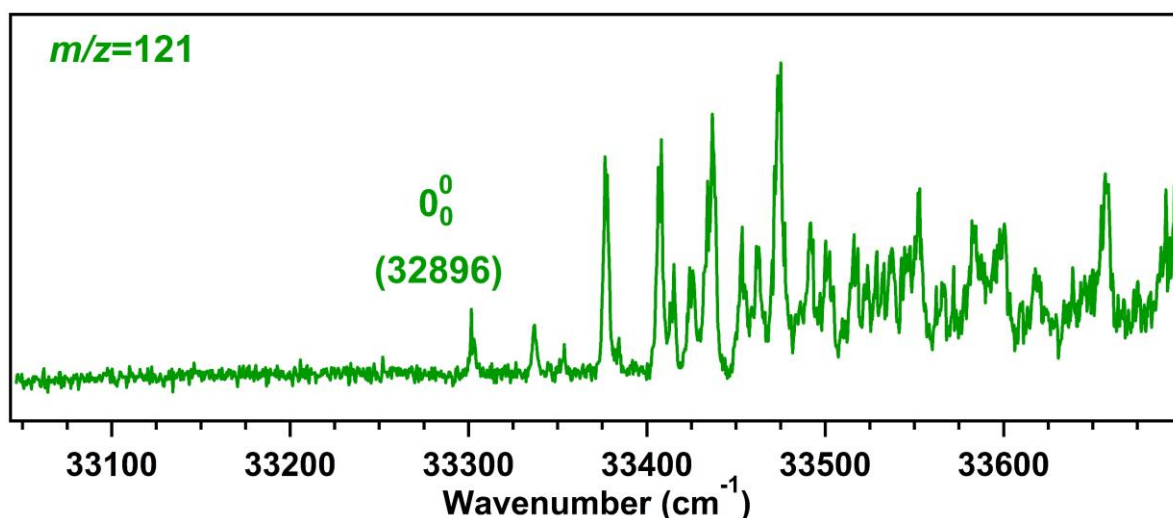


Figure 5.15. Mass-selected 1C-R2PI spectrum of $m/z=121$ fragment mass channel.

Table 5.3. Observed and calculated S_1 state vibrational frequencies (cm^{-1}) of experimentally observed conformer of the $\text{NMe}_2\text{-Ph}$ with the assignment of vibrational modes upto 200 cm^{-1} of the electronic spectrum and their description. S_1 state frequencies are calculated at the CIS/6-311++G(d,p) level

Observed	Calculated	Assignment	Description of modes
0		0_0^0	
35	31	54_0^1	Asymmetric methyl rotation
75		54_0^2	
106		54_0^3	
122		54_0^4	
135	128	53_0^1	Out of plane bending along $\text{C}(\text{sp}^2)\text{-N}$ bond
152		54_0^5	
161		$54_0^1 53_0^1$	
173	167	52_0^1	Symmetric methyl rotation
190	180	51_0^1	Asymmetric methyl rotation + phenyl twisting
199		$54_0^1 52_0^1$	

5.3.7 Electronic spectroscopy at $m/z=192$ fragment mass channel

The electronic spectrum measured at the $m/z=192$ fragment mass channel has closely spaced vibronic bands in the $32600\text{-}33290\text{ cm}^{-1}$ ($306.7\text{-}300.4\text{ nm}$) region (Figure 5.16b). As discussed in the previous section, the $m/z=107$ and 121 fragment mass channels have fragmented from

the excited state; it could be possible that the $m/z=192$ fragment mass channel also fragments from the excited state. We remained curious to know its origin, whether it is fragmenting in the excited or ionic state of $\text{NMe}_2\text{-Ph-EA}$. The $m/z=192$ fragment mass channel is the closest analogue of $\text{NMe}_2\text{-Ph-EA}$ as this fragment is only 15 mass (methyl) unit less than $\text{NMe}_2\text{-Ph-EA}$. Thus, it is quite intriguing to search for the $m/z=15$ fragment in the mass spectrum, which can be the counterpart of the 192 fragment. We also searched for the counterpart $m/z=15$ fragment (methyl) in the mass spectrum to know whether it is fragmenting from an excited or ionic state. Interestingly, the methyl fragment lacking any UV chromophore will not be observed in the TOF-MS unless this fragment is produced only in the ionic state.

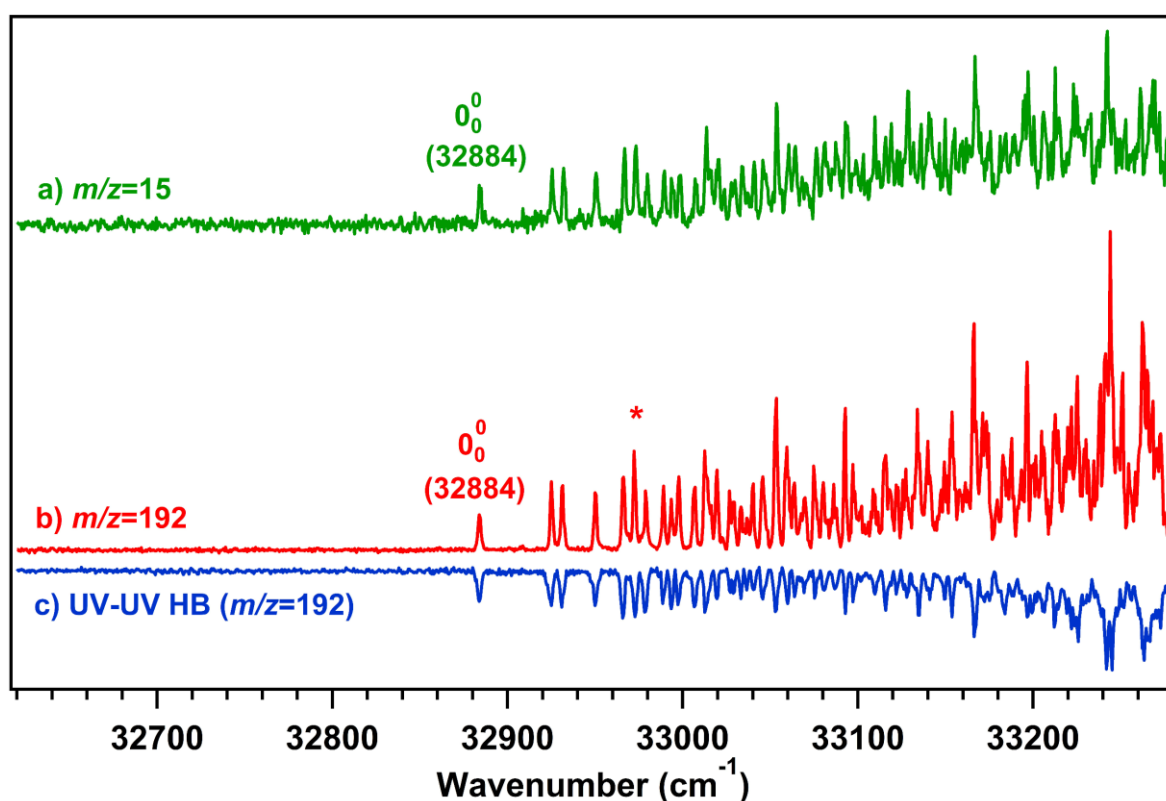


Figure 5.16. Mass-selected 1C-R2PI spectra of $\text{NMe}_2\text{-Ph-EA}$ recorded in the a) $m/z=15$ fragment mass channel; b) $m/z=192$ fragment mass channel; c) UV-UV HB spectrum of $\text{NMe}_2\text{-Ph-EA}$ recorded in the $m/z=192$ fragment mass channel by probing the band at 32972 cm^{-1} marked by a red-colored asterisk in Figure 5.15b.

We could observe the $m/z=15$ fragment mass channel in TOF-MS recorded at 32972 cm^{-1} (Figure 5.17) by tuning the delay between the pulse valve opening and the firing of the UV laser. It can be noticed that the mass signal intensities of the other photofragmented products observed in Figures 5.10-5.12 are very minimal. It is expected due to different time delays for optimizing the $m/z=192$ and $m/z=15$ fragment mass channels. It should be noted here

that the appearance of the methyl group in the mass spectrum alone cannot conclude that the $m/z=192$ fragment is fragmenting from the ionic state as this methyl fragment can also originate from the other photofragmented products, as can be observed in the TOF-MS shown in Figures 5.10-5.12. Thus, efforts were made to record the electronic spectrum in the $m/z=15$ fragment to comment on the mode of the fragmentation of the $m/z=192$ fragment. Interestingly, the electronic spectrum measured in the $m/z=15$ fragment mass channel (Figure 5.16a) is identical to that obtained in the $m/z=192$ fragment mass channel (Figure 5.16b). Hence, the $m/z=15$ and 192 fragments are fragmenting from the ionic state of $\text{NMe}_2\text{-Ph-EA}$. Thus, the electronic spectra measured in these fragmented mass channels ($m/z=15$ and 192 fragments) correspond to the electronic spectrum of $\text{NMe}_2\text{-Ph-EA}$ arising due to its $S_0 \rightarrow S_1$ excitation.

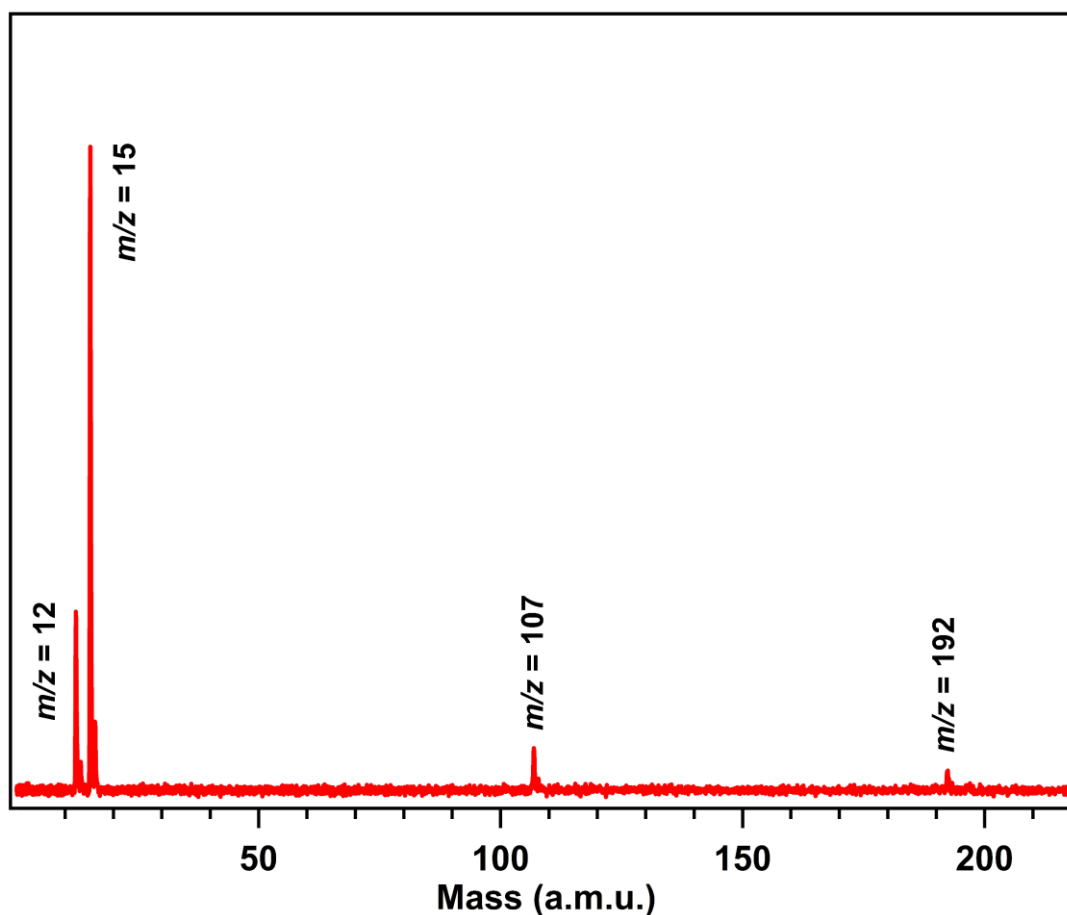


Figure 5.17. TOF-MS of $\text{NMe}_2\text{-Ph-EA}$ recorded at 32972 cm^{-1} depicting the ion signal of $m/z=15$ (methyl) along with other fragments using 1C-R2PI spectroscopy.

Further, UV-UV HB spectroscopy is performed by fixing the probe laser at 32972 cm^{-1} (marked by a red asterisk in Figure 5.16b), as its electronic spectrum could originate from multiple conformers of $\text{NMe}_2\text{-Ph-EA}$. As discussed in Section 5.3.2, the energy barrier of interconversion of groups A and B conformers suggests the possibility of observing either A1

or/and B1 conformer in the experiment. However, the UV-UV HB spectrum (Figure 5.16c) shows depletion in the ion signal for all the vibronic bands and confirms the presence of a single conformer of NMe₂-Ph-EA in the experiment. The electronic spectrum of NMe₂-Ph-EA is also recorded in the 30%He-70%Ne gas mixture as a buffer gas, anticipating the possibility of conformational relaxation due to heavy carrier gas (Ar). However, the electronic spectrum obtained using 30%He-70%Ne gas mixture (Figure 5.18) does not show an appearance of any new band and repudiates the conformational relaxation.

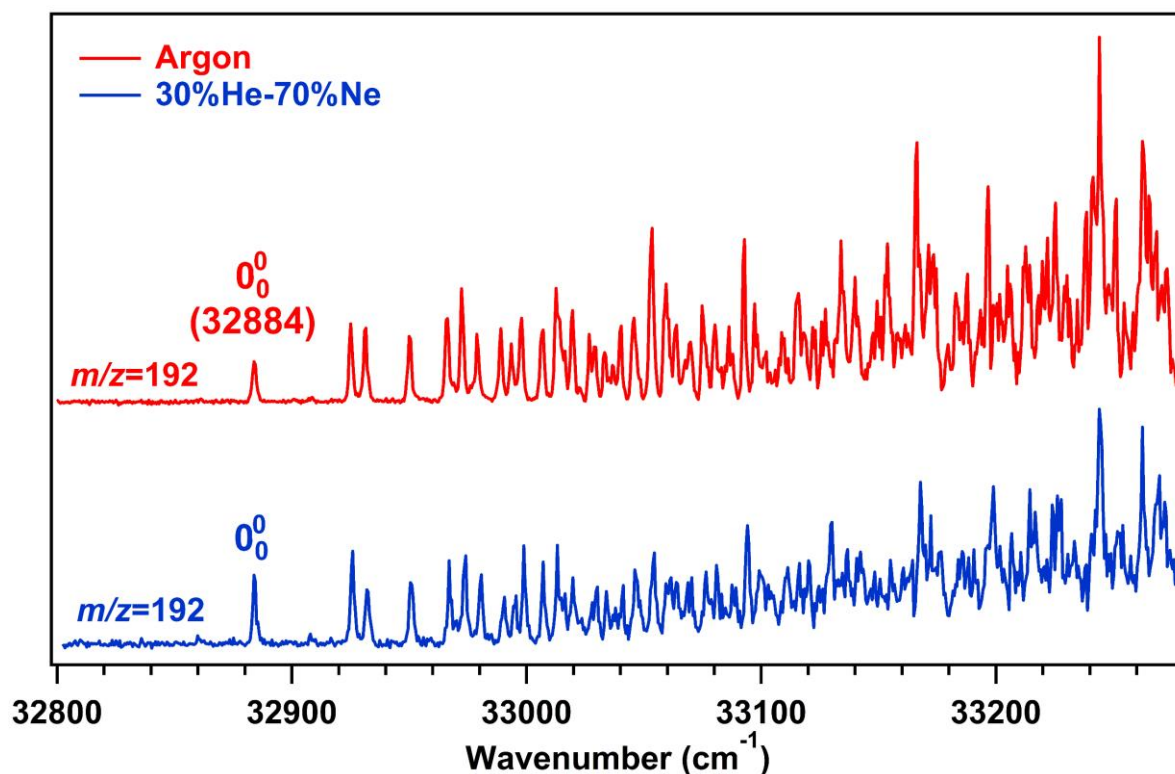


Figure 5.18. Comparison of the mass-selected electronic spectra of $m/z=192$ fragment mass channel recorded using 1C-R2PI spectroscopy in Argon (red trace) and 30% He-70% Ne (blue trace) carrier gases.

5.3.8 Conformational assignment of the experimentally observed conformer of NMe₂-Ph-EA

The structure of the experimentally observed conformer of NMe₂-Ph-EA is assigned by measuring its IR spectrum and comparing it with the theoretical IR spectra of its possible low-energy conformers. RIDIR spectroscopy for the $m/z=192$ fragment mass channel was performed in the carbonyl stretching region by probing the electronic band at 32972 cm⁻¹ of the $m/z=192$ fragment. Figure 5.19a shows the RIDIR spectrum with an IR peak at 1753 cm⁻¹. The harmonic carbonyl stretching frequencies are scaled using a factor of 0.9829 obtained by

the ratio of experimental (1787 cm^{-1}) to calculated (1818 cm^{-1}) $\nu_{\text{C=O}}$ of *cis*-phenyl acetate.⁶¹ It can be noticed from Figure 5.19b-g that the carbonyl stretching frequencies of group A and B rotamers are very close to each other. It is expected due to their similar structures differing in the methyl group orientation.

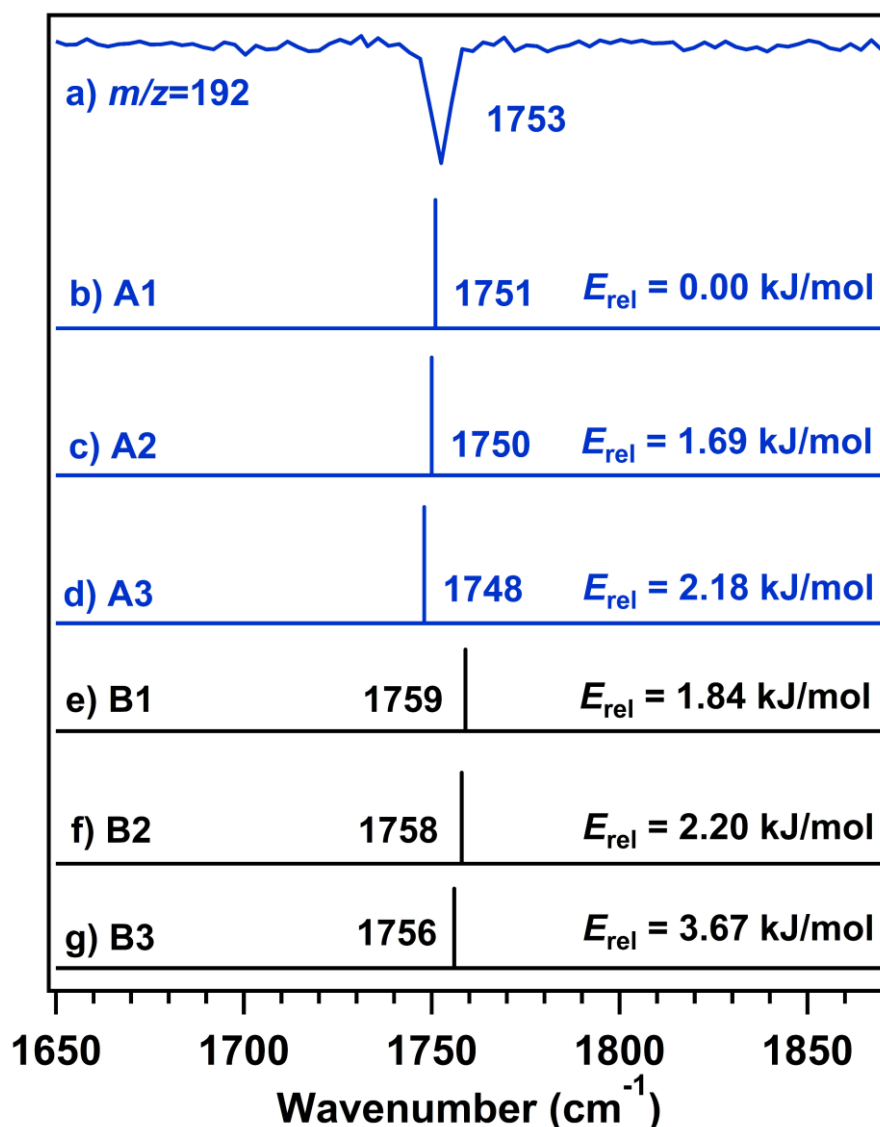


Figure 5.19. a) RIDIR spectrum in the $m/z=192$ fragment mass channel; b-g) Theoretical scaled IR spectra of group A and B conformers. Harmonic stretching frequencies are scaled with respect to the *cis*-phenyl acetate (scaling factor = 0.9829).⁶¹

Based on the low interconversion energy barrier for the rotamers of groups A and B, the possibility of observing the A1 and B1 conformers in the experiment is suggested. It can be noticed from Figures 5.19d and 5.19g that there is a difference of 8 cm^{-1} in the carbonyl stretching frequency of A1 and B1. The scaled carbonyl stretching frequencies of all the low-energy conformers of groups A and B are provided in Table 5.4, and the trend of these carbonyl

stretching frequencies obtained at different calculation levels is mostly consistent. The carbonyl stretching frequency of the experimentally observed conformer is in close agreement with the A1 conformer and is found to be the global minimum at various calculation levels. Thus, the experimentally observed conformer could be tentatively assigned to the A1 conformer. However, based on their close carbonyl stretching frequency, either the A1 or B1 conformer could be present in the experiment.

Table 5.4. Theoretical scaled carbonyl stretching frequency ($\nu_{C=O}$, cm^{-1}) of various low-energy conformers calculated at the **A)** B3LYP-D3/def2-TZVP; **B)** B3LYP-D3/aug-cc-pVTZ; **C)** B3LYP-D3/6-311++G(d,p); **D)** ω B97X-D/def2-TZVP; **E)** ω B97X-D/aug-cc-pVTZ; **F)** ω B97X-D/6-311++G(d,p); **G)** B97-D3/ def2-TZVP; **H)** B97-D3/aug-cc-pVTZ; **I)** B97-D3/6-311++G(d,p); and **J)** MP2/6-311++G(d,p) levels

	A	B	C	D	E	F	G	H	I	J
A1	1751	1750	1748	1752	1752	1750	1747	1747	1744	1757
A2	1750	1750	1747	1750	1751	1749	1747	1746	1744	1757
A3	1748	1748	1746	1749	1750	1748	1745	1745	1743	1757
B1	1759	1759	1758	1760	1760	1758	1758	1758	1755	1765
B2	1758	1758	1756	1759	1760	1756	1758	1757	1754	1762
B3	1756	1756	1754	1757	1758	1754	1756	1756	1754	1761

Experimental carbonyl stretching frequencies of A1 and *cis*-phenyl acetate are 1753 and 1787 cm^{-1} , respectively. A scaling factor of 0.9829, 0.9862, 0.9824, 0.9602, 0.9633, 0.9587, 1.0102, 1.0142, 1.0102, and 0.9829 have been used at the levels **A**, **B**, **C**, **D**, **E**, **F**, **G**, **H**, **I**, and **J** by taking the experimental and theoretical carbonyl stretching frequencies (1818, 1812, 1819, 1861, 1855, 1864, 1769, 1762, 1769, and 1818 cm^{-1}) ratio of *cis*-phenyl acetate calculated at the levels **A**, **B**, **C**, **D**, **E**, **F**, **G**, **H**, **I**, and **J**, respectively.

The vibronic bands present in the electronic spectrum of the observed conformer of $\text{NMe}_2\text{-Ph-EA}$ have been tentatively assigned by the excited state vibrational frequencies of the A1 conformer (Table 5.5) calculated at the CIS/6-311++G(d,p) level. It can be noticed from the detailed assignment of these bands provided in Table 5.5 that bands upto 100 cm^{-1} are mostly due to the bending and twisting of the -EA group, and later on, the contribution from the rotation of the methyl group, along with the bending of the -NMe_2 group also starts appearing. Thus, congestion of the vibronic bands in the electronic spectrum of $\text{NMe}_2\text{-Ph-EA}$ could be due to the involvement of the -EA and -NMe_2 groups. It was very much expected, as the vibronic congestion in $\text{NMe}_2\text{-Ph}$ was observed in comparison to NHMe-Ph due to the coupled methyl rotation, as seen in Tables 5.2 and 5.3.

Table 5.5. Observed and calculated S_1 state vibrational frequencies (cm^{-1}) of experimentally observed A1 conformer of $\text{NMe}_2\text{-Ph-EA}$ with the assignment of vibrational modes upto 200 cm^{-1} of the electronic spectrum and their description. S_1 state frequencies are calculated at the CIS/6-311++G(d,p) level

Observed	Calculated	Assignment	Description of modes
0		0_0^0	
41	29	90_0^1	Out-of-plane bending of $-\text{COOEt}$ group + Twisting of $\text{NMe}_2\text{-Ph}$
48	34	89_0^1	In-plane bending of $-\text{COOEt}$ group + Twisting of $\text{NMe}_2\text{-Ph}$
66	55	88_0^1	Twisting of $-\text{COOEt}$ group + Bending of $\text{NMe}_2\text{-Ph}$
82	82	$90_0^2/87_0^1$	Out-of-plane bending of $-\text{NMe}_2$ group
88	86	$86_0^1/90_0^1/89_0^1$	Twisting of $-\text{COOEt}$ group + Rotation of $-\text{NMe}_2$ group
95		89_0^2	
105	108	85_0^1	Rotation of $-\text{NMe}_2$ group
110		$90_0^1/88_0^1$	
114		$89_0^1/88_0^1$	
123		$90_0^3/90_0^1/87_0^1$	
129		$88_0^2/90_0^2/89_0^1/90_0^1/86_0^1$	
136	136	84_0^1	Rotation of $-\text{COOEt}$ group + Out-of- plane bending of $-\text{NMe}_2$ group
143		89_0^3	
146		$90_0^1/85_0^1$	
149		$90_0^2/88_0^1$	
153		$88_0^1/86_0^1$	
157	158	83_0^1	Rotation of methyl group of $-\text{NMe}_2$ + In- plane bending of $-\text{CH}_2\text{COOEt}$ group
162		87_0^2	
170		$87_0^1/86_0^1$	
176		86_0^2	
180		$90_0^2/89_0^2$	

186		$89_0^{286_0^1}$	
191		$90_0^{388_0^1}$	
196		88_0^3	

Also, the S_1 state vibrational frequency of Ph–EA (Table 5.6) also shows that the low-frequency vibrations are due to the –EA group. A comparison of the geometrical parameters (Table 5.7) and optimized geometries (Figure 5.20) of various conformers in the ground and excited states shows a significant change along the $C_5-C_6-N_{11}-C_{12/16}$ and $C_1-C_{20}-C_{23}-O_{24/25}$ dihedral angles.

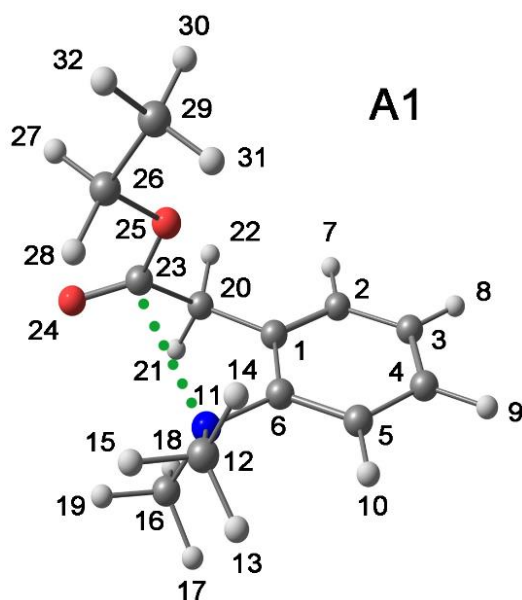
Table 5.6. Calculated S_1 state vibrational frequencies (cm^{-1}) of Ph–EA with the assignment of vibrational modes upto 200 cm^{-1} and their description. S_1 state frequencies are calculated at the CIS/6-311++G(d,p) level

Calculated	Description of modes
22	Twisting of phenyl ring + In-plane bending of –CH ₂ COOEt group
25	Out of plane bending of –COOEt group + Twisting of phenyl ring
70	Out of plane bending of –COOEt group
82	Twisting of –COOEt group
137	Out of plane bending of phenyl ring + Twisting of –COOEt group
174	Twisting of phenyl ring + Bending of –OEt group

Table 5.7. Geometrical parameters in the S_0 and S_1 of various low-energy conformers calculated at the B3LYP-D3/def2-TZVP and TD-B3LYP-D3/def2-TZVP level. The scheme of atom numbering is shown in A1 below the table

S_0	A1	A2	A3	B1	B2	B3
$d_{N\cdots C=O} (\text{\AA})$	2.752	2.851	2.758	2.838	2.766	2.776
$\angle N-C-O (^{\circ})$	102.4	100.8	101.9	98.9	99.9	98.6
$\angle C_5-C_6-N_{11}-C_{12} (^{\circ})$	31.4	26.3	31.7	34.1	36.3	37.6
$\angle C_5-C_6-N_{11}-C_{16} (^{\circ})$	-105.0	-109.0	-104.8	-100.0	-98.8	-97.5
$\angle C_1-C_{20}-C_{23}-O_{24} (^{\circ})$	-135.4	-133.5	-134.9	44.9	49.3	46.3
$\angle C_1-C_{20}-C_{23}-O_{25} (^{\circ})$	48.7	51.1	49.3	-139.2	-134.4	-137.4
$\angle C_{23}-O_{25}-C_{26}-C_{29} (^{\circ})$	174.5	81.9	-84.2	-80.8	-176.8	83.1

S ₁	A1	A2	A3	B1	B2	B3
^d N...C=O (Å)	3.564	3.558	3.565	3.210	3.795	3.770
∠N-C-O (°)	73.1	72.6	72.7	64.6	153.5	151.2
∠C ₅ -C ₆ -N ₁₁ -C ₁₂ (°)	84.1	84.3	84.0	67.0	83.7	82.6
∠C ₅ -C ₆ -N ₁₁ -C ₁₆ (°)	-96.7	-96.2	-96.8	-112.0	-94.9	-96.2
∠C ₁ -C ₂₀ -C ₂₃ -O ₂₄ (°)	-82.4	-82.6	-81.4	-82.1	88.0	85.1
∠C ₁ -C ₂₀ -C ₂₃ -O ₂₅ (°)	83.9	83.7	84.6	96.4	-81.1	-83.2
∠C ₂₃ -O ₂₅ -C ₂₆ -C ₂₉ (°)	174.8	76.4	-83.0	-83.8	-175.7	82.9



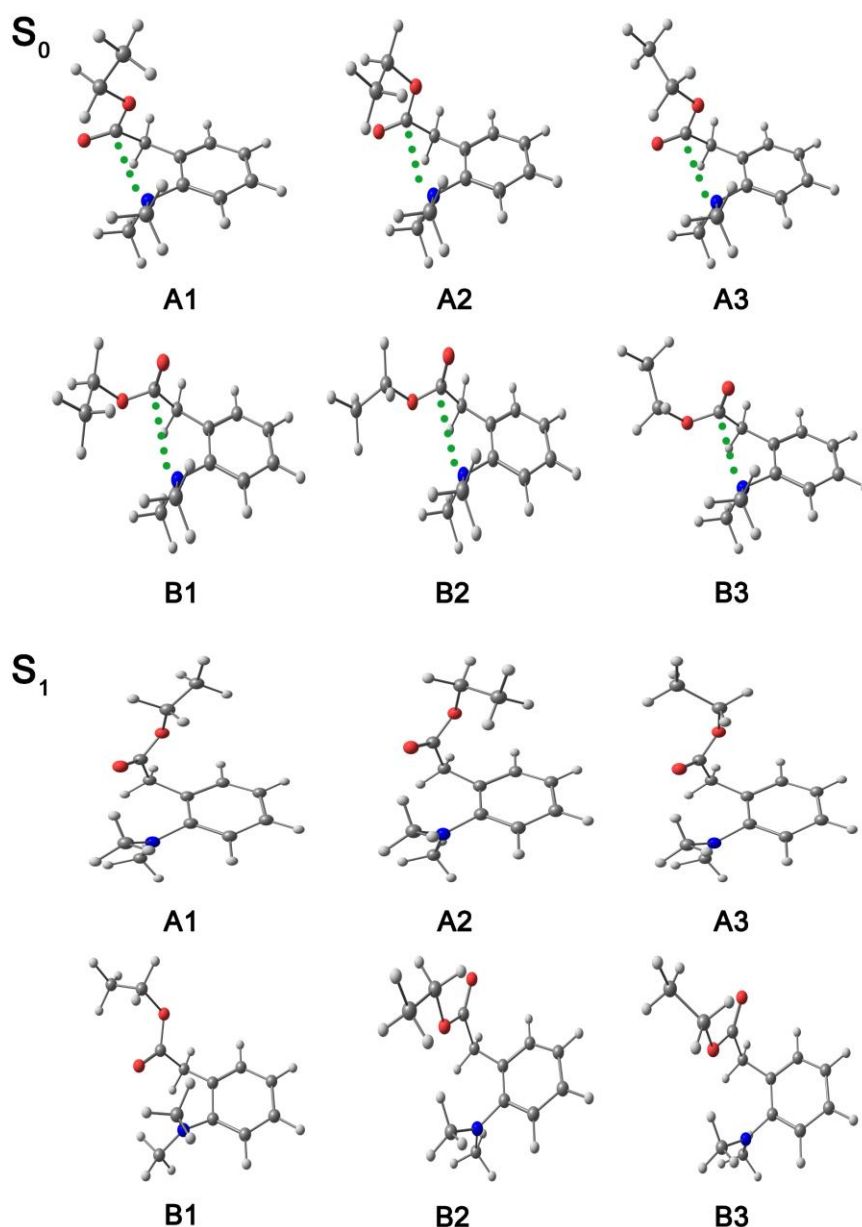


Figure 5.20. Comparison of optimized geometries of various low-energy conformers in the ground state (S_0) and excited state (S_1) states calculated at the B3LYP-D3/def2-TZVP and TD-B3LYP-D3/def2-TZVP level, respectively.

5.3.9 $n \rightarrow \pi^*$ interaction

A close look at the low-energy conformers of $\text{NMe}_2\text{-Ph-EA}$ and their geometrical parameters (Table 5.7), such as the Bürgi-Dunitz trajectory, reveals that these conformers are stabilized by an $n \rightarrow \pi^*$ interaction. However, the geometrical parameters for A2 and B1 significantly deviate from the Bürgi-Dunitz trajectory in their respective group, indicating the weak $n \rightarrow \pi^*$ interaction in them. NBO analysis was performed to calculate the $E^{(2)}$ values, which offers qualitative information on the $n \rightarrow \pi^*$ interaction. Figure 5.21 shows the orbital overlap for $n \rightarrow \pi^*$ interaction with the $E^{(2)}$ values calculated at the B3LYP-D3/def2-TZVP level.

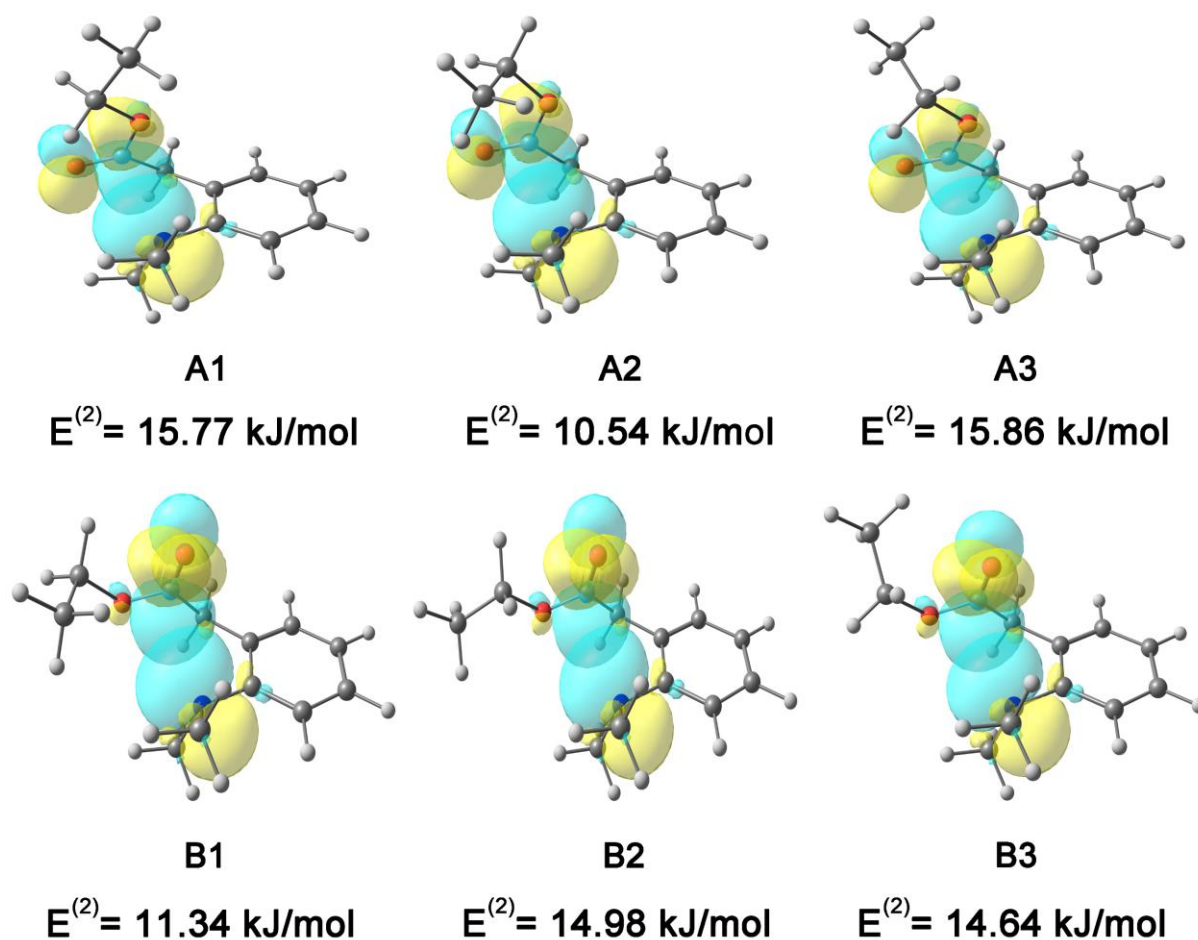


Figure 5.21. NBO orbital overlap with the $E^{(2)}$ values of $\text{N}\cdots\text{C}=\text{O}$ $\text{n}\rightarrow\pi^*$ interaction present in the various low-energy conformers calculated at the B3LYP-D3/def2-TZVP level.

The $\text{n}\rightarrow\pi^*$ interaction is relatively stronger in A1 [$E^{(2)} = 15.77$ kJ/mol] than B1 [$E^{(2)} = 11.34$ kJ/mol]. It should be noted that $E^{(2)}$ values are almost similar in A1 and A3 [$E^{(2)} = 15.86$ kJ/mol], and in B2 [$E^{(2)} = 14.98$ kJ/mol] and B3 [$E^{(2)} = 14.64$ kJ/mol], whereas $E^{(2)}$ values are least in A2 [$E^{(2)} = 10.54$ kJ/mol] and B1 in their respective groups, which was also suggested by their geometrical parameters. It can be noticed from the optimized geometries (Figure 5.6) of A2 and B1 conformers that the methyl group of the ester is oriented towards the $-\text{NMe}_2$ group, pointing to the steric repulsion between them. Natural steric analysis (NSA) confirms that steric repulsion exists between the σ orbitals of the C–H bonds of $-\text{NMe}_2$ and methyl group of the ester in A2 (3.72 kJ/mol) and B1 (3.26 kJ/mol), which was absent in other conformers, explaining the weak strength of the $\text{n}\rightarrow\pi^*$ interaction in them. The difference in occupancies of the lone pair and π^* orbitals after the deletion of the $\text{n}\rightarrow\pi^*$ interaction using NBO deletion analysis confirms the presence of the $\text{n}\rightarrow\pi^*$ interaction (Table S12). These differences in occupancies are the least for A2 and B1 in their respective groups, indicating the weak $\text{n}\rightarrow\pi^*$ interaction in these conformers. The difference in occupancies of the lone pair and π^* orbitals

were calculated with respect to unoptimized NMe₂-Ph and unoptimized ethylphenyl acetate (Ph-EA) after manually deleting the $n \rightarrow \pi^*$ acceptor and $n \rightarrow \pi^*$ donor groups, respectively (Table 5.8). It further confirms that the change in occupancies of these orbitals arises due to $n \rightarrow \pi^*$ interaction. The difference in the Wiberg bond index (WBI) values (depicting the bond order) of the carbonyl group with respect to unoptimized Ph-EA suggests the weakening of the carbonyl bond due to the $n \rightarrow \pi^*$ interaction (Table 5.8).

Table 5.8. Comparison of the difference in occupancies of lone pair orbital of the nitrogen atom and π^* orbital after deleting $n \rightarrow \pi^*$ interaction, and after deleting (NBO analysis after manual deletion) $n \rightarrow \pi^*$ acceptor (NMe₂-Ph) and $n \rightarrow \pi^*$ donor (Ph-EA) group with the difference in WBI values of carbonyl bond in the various low-energy conformers at the B3LYP-D3/def2-TZVP level

	NMe ₂ -Ph-EA		NMe ₂ -Ph	Ph-EA	
	$\Delta LP_{N,d}$	$\Delta \pi^*_{C=O,d}$	ΔLP_N	$\Delta \pi^*$	ΔWBI
A1	0.01225	0.01117	0.01126	0.00755	0.0158
A2	0.00881	0.00838	0.00860	0.00559	0.0129
A3	0.01250	0.01142	0.01189	0.00777	0.0160
B1	0.01043	0.00922	0.00922	0.00412	0.0117
B2	0.01267	0.01110	0.01120	0.00585	0.0144
B3	0.01290	0.01124	0.01167	0.00612	0.0152

QTAIM analysis was performed to get further insights into the $n \rightarrow \pi^*$ interaction. Various AIM parameters at the BCP, signifying the strength of the $n \rightarrow \pi^*$ interaction, are provided along with the molecular graphs in Figure 5.22. Interestingly, the BCP depicting the presence of the $N \cdots C=O$ $n \rightarrow \pi^*$ interaction is not observed in the molecular graphs of the A2 and B1. It does not lead to the absence of the $n \rightarrow \pi^*$ interaction in them,¹¹⁹ but states that the $n \rightarrow \pi^*$ interaction is weak in these conformers. Similar results supporting weak $n \rightarrow \pi^*$ interaction in A2 and B1 from each rotameric group were obtained from the various geometrical parameters and the NBO analysis [lower $E^{(2)}$ values]. NCI index analysis further corroborates the results obtained from the NBO and QTAIM analyses. NCI isosurface corresponding to the $n \rightarrow \pi^*$ interaction encircled by black color between the nitrogen atom and the carbonyl carbon can be observed in Figure 5.23.

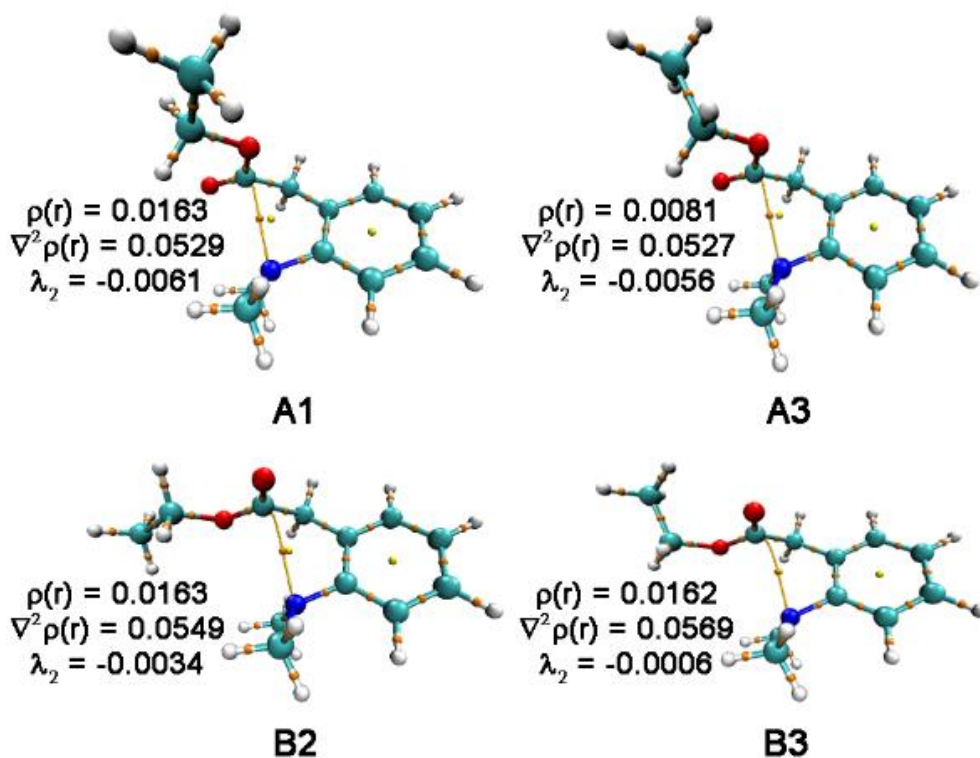


Figure 5.22. Molecular graphs of A1, A3, B2, and B3 conformers with AIM parameters at the BCP of N...C=O $n \rightarrow \pi^*$ interaction.

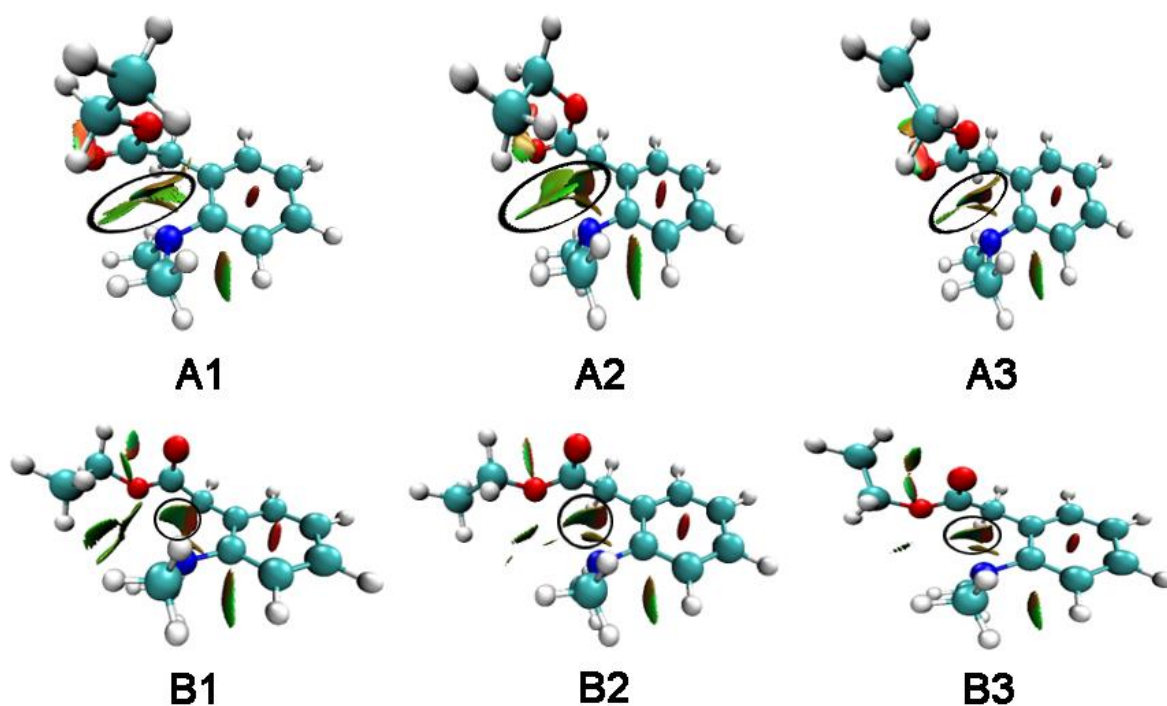


Figure 5.23. NCI isosurface plots of the various low-energy conformers showing isosurface for the $n \rightarrow \pi^*$ interaction encircled by black color. The gradient isosurface follows a blue-green-red color scheme over the range of $-0.04 < \text{Sign}(\lambda_2)\rho(r) < 0.04$, where blue, green, and red colors denote strong attraction, weak attraction, and strong repulsion, respectively.

Moreover, RDG minima corresponding to the $n \rightarrow \pi^*$ interaction marked by the black color circle can be observed in the NCI RDG plot versus $\text{Sign}(\lambda_2)\rho(r)$ (Figure 5.24). RDG minima for A1/A3 and B2/B3 have the same negative value of $\text{Sign}(\lambda_2)\rho(r)$, stating the similar strength of $n \rightarrow \pi^*$ interaction in these conformers. However, the RDG minima for A2 and B1 have the least negative $\text{Sign}(\lambda_2)\rho(r)$ values in their respective groups, showing that $n \rightarrow \pi^*$ interaction is weak in the former than the latter.

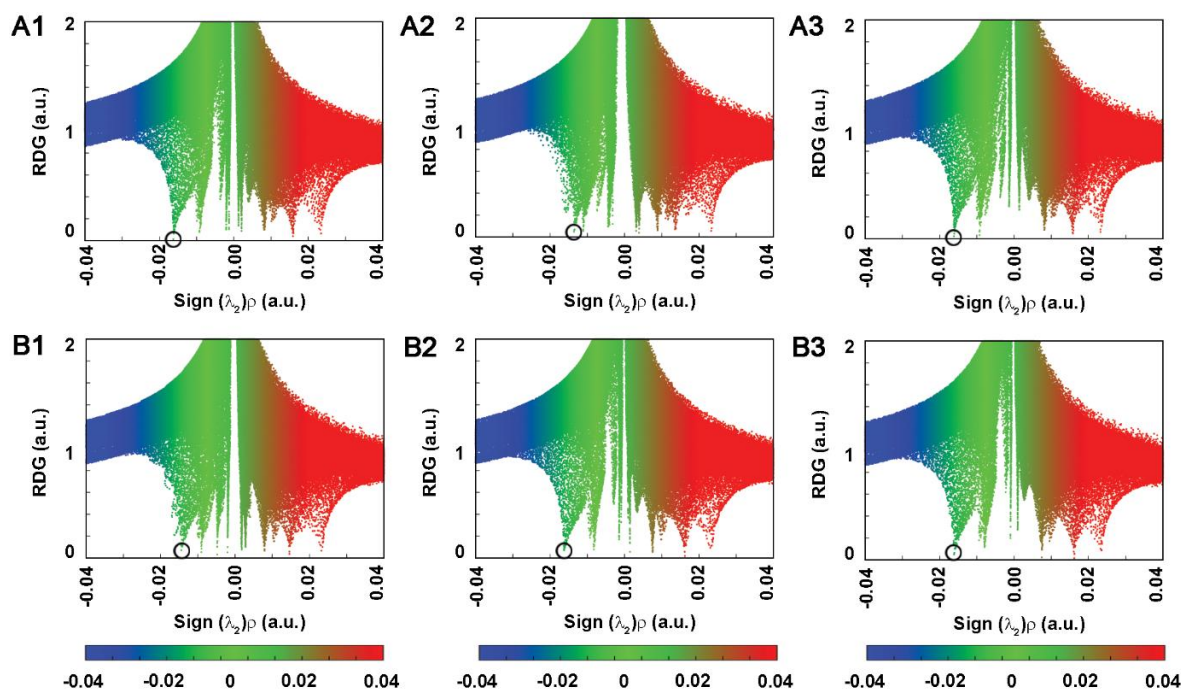


Figure 5.24. NCI plot of RDG (a.u.) versus $[\text{Sign}(\lambda_2)\rho(r), (\text{a.u.})]$ for the various low-energy conformers. RDG minima corresponding to $\text{N} \cdots \text{C}=\text{O}$ $n \rightarrow \pi^*$ interaction are marked with black circles.

Furthermore, RDG plots were superimposed on each other for A1/A2, B1/B2, and A1/B1 to show the relative strength of $n \rightarrow \pi^*$ interaction in these conformers (Figure 5.25).

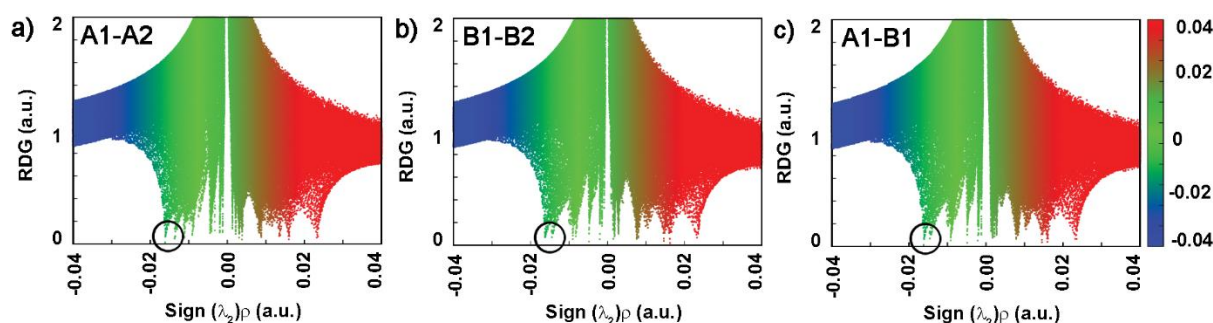


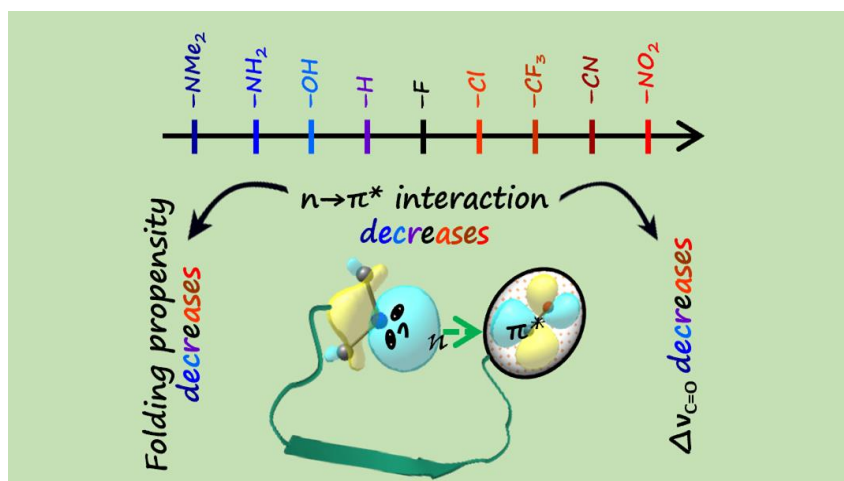
Figure 5.25. Overlap of NCI plot of reduced density gradient (RDG, a.u.) versus $\text{Sign}(\lambda_2)\rho(r)$ of a) A1 and A2; b) B1 and B2; c) A1 and B1 conformers, calculated at the B3LYP-D3/def2-

TZVP level. RDG minima corresponding to $N\cdots C=O$ $n\rightarrow\pi^*$ interaction are marked with black circles. RDG minima are left in A1, B2, and A1 in Figure 5.25a, b, and c, respectively.

5.4 Conclusions

We have studied the $N\cdots C=O$ $n\rightarrow\pi^*$ interaction in ethyl 2-(2-(dimethylamino) phenyl) acetate (NMe_2 -Ph-EA) using jet-cooled electronic and vibrational spectroscopy combined with quantum chemistry calculations. The electronic spectrum of NMe_2 -Ph-EA has been recorded in the mass channels of $m/z=15$ and 192 photofragments. It was proved that these fragmented species are dissociating from the ionic state of NMe_2 -Ph-EA. The presence of a single conformer of NMe_2 -Ph-EA in the experiment has been confirmed from UV-UV hole burning spectroscopy. We have provided gas-phase IR spectroscopic evidence of the $N\cdots C=O$ $n\rightarrow\pi^*$ interaction in the observed conformer of NMe_2 -Ph-EA with the help of theoretical calculations. Detailed computational analyses such as NBO, QTAIM, and NCI further establish the presence of the $n\rightarrow\pi^*$ interaction in the observed conformer. Quantum calculations have proved the presence of the $n\rightarrow\pi^*$ interaction in all the six low-energy conformers of NMe_2 -Ph-EA. Structural assignments of other photofragmented products $m/z=107$ and 121 have also been performed, and it has been found that these are fragmenting from the excited state of NMe_2 -Ph-EA. This report on governing conformational preferences due to the $n\rightarrow\pi^*$ interaction may be helpful in efficient drug designing and molecular recognition based on this non-covalent interaction.

Chapter 6: Intramolecular Modulation of $N\cdots C=O$ $n\rightarrow\pi^*$ Interaction in 3-[2-(dimethylamino) phenyl] propanal and its Role in the Folding of Flexible Side-Chain



Adapted from: **P. Panwaria** and A. Das*, Effect of substituents on the intramolecular $n\rightarrow\pi^*$ interaction in 3-[2-(Dimethylamino) phenyl] propanal: A computational study. *J. Phys. Chem. A* **2023**, 127, 3339-3346.

6.1 Motivation of this work

In Chapter 5, we have provided the first gas-phase electronic and vibrational spectroscopic evidence of the $\text{N}\cdots\text{C}=\text{O}$ $\text{n}\rightarrow\pi^*$ interaction in ethyl 2-(2-(dimethylamino) phenyl) acetate ($\text{NMe}_2\text{-Ph-EA}$). In $\text{NMe}_2\text{-Ph-EA}$, the lone pair orbital of the nitrogen atom delocalizes into the π^* orbital of the carbonyl group. We have also provided NMR spectroscopic evidence of the $\text{N}\cdots\text{C}=\text{O}$ $\text{n}\rightarrow\pi^*$ interaction. We continued further exploring how the $\text{N}\cdots\text{C}=\text{O}$ $\text{n}\rightarrow\pi^*$ interaction can be modulated. Interestingly, all gas-phase IR reports on the $\text{n}\rightarrow\pi^*$ interaction involved the measurement of the carbonyl stretching frequency, which was a part of the ester group and, hence, involved the effect of the hyperconjugation from the etheral oxygen to the carbonyl group. This hyperconjugation perturbs the role of the $\text{n}\rightarrow\pi^*$ interaction in carbonyl stretching frequency. Therefore, the effect of sole $\text{n}\rightarrow\pi^*$ interaction on the carbonyl stretching frequency is unclear. We tried to seek these answers in this chapter by studying molecular models of *para*-substituted 3-[2-(dimethylamino) phenyl] propanal using a computational approach.

6.2 Introduction

IR spectroscopy has been extensively used to determine the strength of hydrogen bonds. The redshift observed in the vibrational frequency of functional groups present in a molecular system generally determines the strength of the hydrogen bond.^{9, 10, 16, 177, 208, 223-225} Similar efforts to determine the strength of the $\text{n}\rightarrow\pi^*$ interactions have been put forward by our group by measuring the redshift in the carbonyl stretching frequency using gas-phase IR spectroscopy.^{61, 92, 93, 209} As discussed in Chapter 1, our group has shown the presence of $\text{C}=\text{O}\cdots\text{aromatic}$ $\text{n}\rightarrow\pi^*$ interaction in phenyl formate by measuring the redshift in the carbonyl stretching frequency of the *cis* conformer having the $\text{n}\rightarrow\pi^*$ interaction with respect to the *trans* conformer lacking the interaction.⁹² Our group have also demonstrated the $\text{C}=\text{O}\cdots\text{C}=\text{O}$ $\text{n}\rightarrow\pi^*$ interaction in a capped 4*R*-hydroxyproline.⁹³ Here, the redshift in the carbonyl stretching frequencies of both the amide ($\text{n}\rightarrow\pi^*$ donor) and ester ($\text{n}\rightarrow\pi^*$ acceptor) was observed in the experiment.⁹³ However, the redshift in the carbonyl stretching frequency observed as an indicator for the presence of the $\text{n}\rightarrow\pi^*$ interaction in the molecular systems studied so far is greatly influenced by the hyperconjugation interaction through neighboring heteroatoms.

Herein, we have performed a detailed quantum chemical analysis of the $\text{n}\rightarrow\pi^*$ interaction between the lone pair electrons on the nitrogen atom of the $-\text{NMe}_2$ group and the π^* orbital of the carbonyl group in 3-[2-(dimethylamino) phenyl] propanal (DMAPhP) where

the carbonyl group is free from hyperconjugation from neighboring heteroatoms. This molecular system is designed in such a way that the carbonyl group is separated by two sp^3 hybridized $-CH_2-$ groups from the aromatic ring. Hence, the phenyl ring has no perturbation in the $n \rightarrow \pi^*$ interaction. Additionally, the present work demonstrates another potential of $n \rightarrow \pi^*$ interaction in folding the flexible side-chain (propanal) of DMAPhP to provide conformational selectivity. Here, the $N \cdots C=O$ $n \rightarrow \pi^*$ interaction selectively stabilizes the global conformer of DMAPhP. The folding of the structures by the $n \rightarrow \pi^*$ interaction is similar to the hydrogen bonding interaction in the backbone of the polypeptide chain, which has a profound role in folding the secondary structures of proteins.^{184, 185, 226-228} Furthermore, we have explored modulation of the strength of the $n \rightarrow \pi^*$ interaction by varying substitutions ($R = -NMe_2, -NH_2, -OH, -H, -F, -Cl, -CF_3, -CN$, and $-NO_2$) from EDGs to EWGs at the *para* position of the $n \rightarrow \pi^*$ donor in DMAPhP.

6.3 Results and Discussion

The optimized geometries of four low-energy conformers (P1, P2, N1, and N2) within the energy limit of 7.00 kJ/mol of various *para*-substituted 3-[2-(dimethylamino) phenyl] propanal (*p*-R-DMAPhP) shown in Figure 6.1 are studied to investigate the effect of the electronic substitution (EDG to EWG) at the *para* position of *N, N'*-dimethylamino group ($-NMe_2$, $n \rightarrow \pi^*$ donor) on the intramolecular $n \rightarrow \pi^*$ interaction. The nomenclature of these conformers is done based on the presence and absence of the $n \rightarrow \pi^*$ interaction. Generally, the EDGs at the *para* position of the $-NMe_2$ group push the electron density towards the nitrogen atom and strengthen the $n \rightarrow \pi^*$ interaction, which decreases upon moving to the EWGs. Hammett constants are utilized to compare the strength of the $n \rightarrow \pi^*$ interaction for various *para* substitutions in DMAPhP.⁵⁹ The Hammett constants are widely used in organic chemistry to determine chemical reaction rates and mechanisms. Hammett constant is derived from the dissociation constant of benzoic acid, and it generally represents the electronic effect of various EDGs and EWGs on aromatic systems.²²⁹ This parameter is empirically used for the quantitative structure-activity relationship of aromatic compounds. Hammett constants of negative values correspond to the EDGs, positive for the EWGs, and zero for the hydrogen substitution. Interestingly, the global minimum conformer P1 is found to be stabilized by $n \rightarrow \pi^*$ interaction, while two other conformers, N1 and N2, lacking any $n \rightarrow \pi^*$ interaction, are higher in energy from the global minimum conformer (Figure 6.1). Another higher energy conformer, P2, having $n \rightarrow \pi^*$ interaction, is less stable from the

global minimum. A consistent trend in the energetics of the conformers is found at various DFT and MP2 levels (Table 6.1).

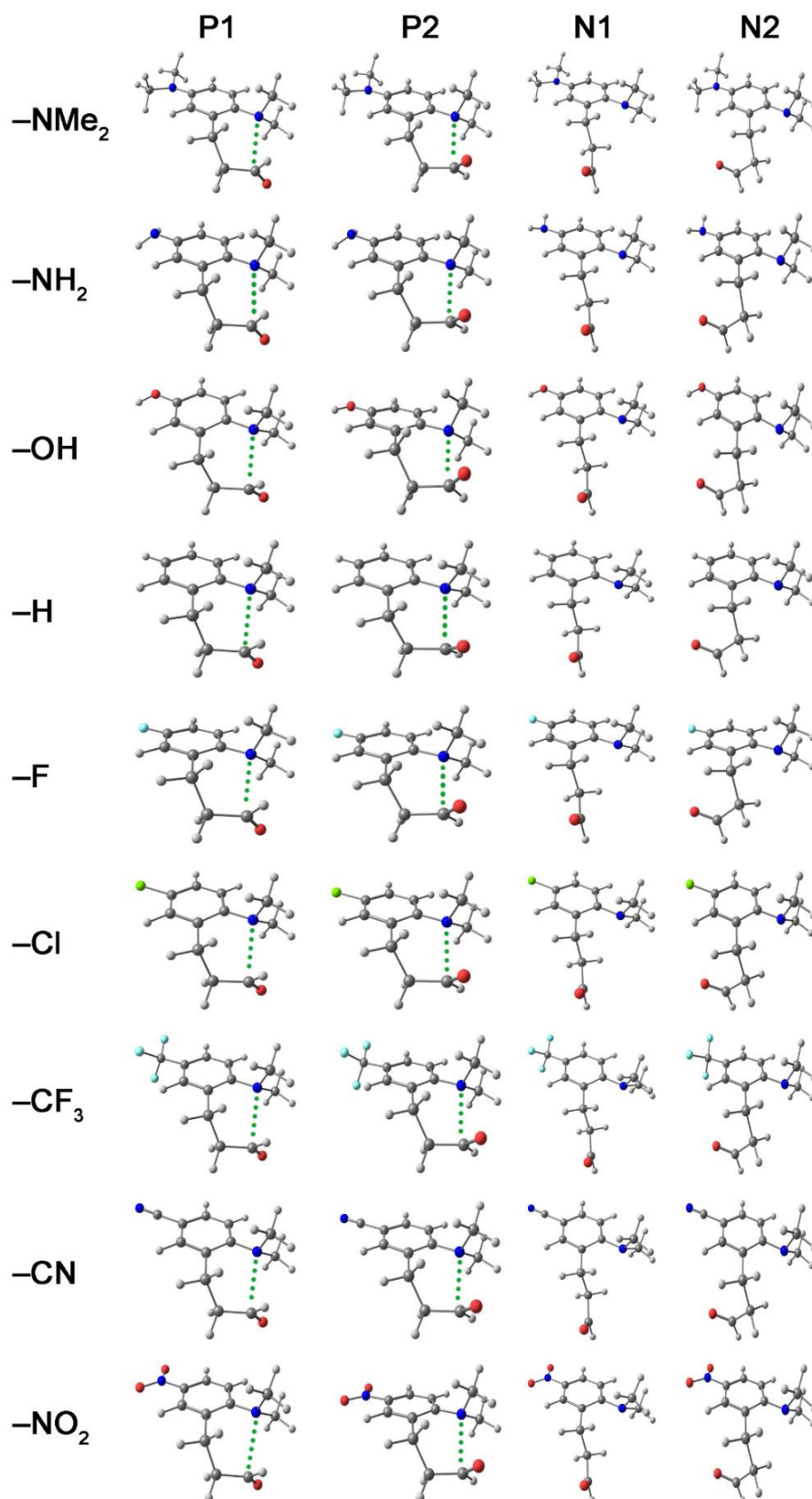


Figure 6.1. S₀ state optimized geometries (gas-phase) of four low-energy conformers of various *p*-R-DMArPhP calculated at the B3LYP-D3/def2-TZVP level.

Table 6.1. ZPE-corrected relative energies (E_{rel} , kJ/mol) of four conformers of various *p*-R-DMAPhP (gas-phase) calculated at the **A)** B3LYP-D3/def2-TZVP; **B)** B3LYP-D3/aug-cc-pVTZ; **C)** B3LYP-D3/6-311++G(d,p); **D)** ω B97X-D/def2-TZVP; **E)** B97-D3/aug-cc-pVTZ; **F)** B97-D3/6-311++G(d,p); and **G)** MP2/6-311++G(d,p) levels

	A				B				C			
	P1	P2	N1	N2	P1	P2	N1	N2	P1	P2	N1	N2
–NMe ₂	0.00	3.09	2.00	3.22	0.00	3.31	2.23	3.67	0.00	3.33	3.22	4.18
–NH ₂	0.00	3.15	1.93	4.17	0.00	3.33	2.19	4.57	0.00	3.38	3.08	5.18
–OH	0.00	2.55	1.55	1.90	0.00	2.75	1.78	2.32	0.00	2.77	2.65	2.83
–H	0.00	2.57	1.94	4.47	0.00	2.72	2.19	4.88	0.00	2.81	3.15	5.53
–F	0.00	2.46	1.55	3.70	0.00	2.66	1.82	4.14	0.00	2.69	2.71	4.73
–Cl	0.00	2.28	1.47	3.89	0.00	2.45	1.72	4.31	0.00	2.48	2.55	4.80
–CF ₃	0.00	1.78	0.97	3.55	0.00	1.95	1.23	3.95	0.00	1.94	2.17	4.36
–CN	0.00	1.64	0.69	3.14	0.00	1.82	1.00	3.58	0.00	1.85	1.92	4.10
–NO ₂	0.00	1.58	0.54	3.74	0.00	1.69	0.76	4.17	0.00	1.84	1.56	4.60

	D				E				F			
	P1	P2	N1	N2	P1	P2	N1	N2	P1	P2	N1	N2
–NMe ₂	0.00	3.75	1.47	2.20	0.00	2.94	4.26	6.12	0.00	3.02	4.89	6.85
–NH ₂	0.00	4.18	0.36	2.93	0.00	3.18	4.22	7.19	0.00	3.26	5.13	7.58
–OH	0.00	3.63	0.40	0.57	0.00	2.64	3.76	4.94	0.00	2.69	4.69	5.31
–H	0.00	2.71	1.21	3.74	0.00	2.57	3.89	7.10	0.00	2.59	4.70	7.81
–F	0.00	2.64	0.06	2.87	0.00	2.83	3.67	6.77	0.00	2.70	4.35	7.04
–Cl	0.00	2.73	0.56	2.65	0.00	2.34	3.40	6.53	0.00	2.45	4.23	7.28
–CF ₃	0.00	2.74	0.45	3.10	0.00	1.75	2.54	6.31	0.00	1.72	3.09	6.24
–CN	0.00	2.44	0.12	2.33	0.00	1.60	2.16	5.47	0.00	1.51	2.90	6.05
–NO ₂	0.00	2.36	0.03	2.45	0.00	1.92	1.84	6.05	0.00	1.88	2.53	6.60

	G			
	P1	P2	N1	N2
–NMe ₂	0.00	2.33	3.65	2.19
–NH ₂	0.00	2.62	3.97	3.76
–OH	0.00	2.11	2.70	1.26

-H	0.00	2.17	4.04	4.32
-F	0.00	2.29	3.58	3.41
-Cl	0.00	2.25	3.61	3.65
-CF ₃	0.00	2.69	4.43	4.49
-CN	0.00	2.10	4.41	4.04
-NO ₂	0.00	2.92	4.09	4.19

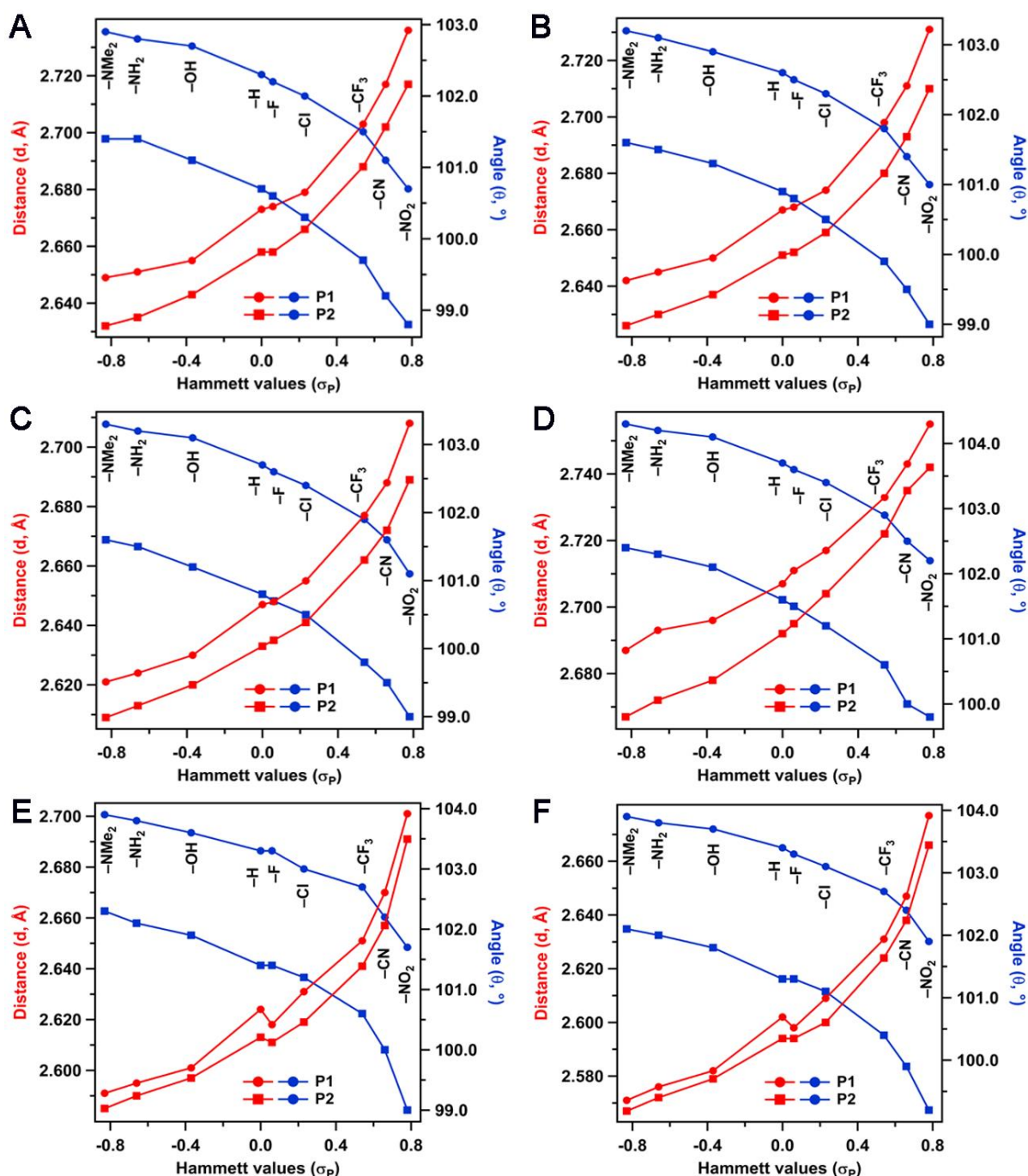


Figure 6.2. Plots of distance (*d*, red traces) between the nitrogen atom and carbonyl carbon and $\angle\text{N-C-O}$ (θ , blue traces) of P1 and P2 of various *p*-R-DMArPhP versus Hammett values

of the substituents obtained from the S_0 state optimized geometries (gas-phase) at the **A)** B3LYP-D3/def2-TZVP; **B)** B3LYP-D3/aug-cc-pVTZ; **C)** B3LYP-D3/6-311++G(d,p); **D)** ω B97X-D/def2-TZVP; **E)** B97-D3/aug-cc-pVTZ; **F)** B97-D3/6-311++G(d,p) levels. The lines connecting the data points are not fitted but are provided to guide the eyes.

Geometrical parameters such as distance (d) between the nitrogen atom and carbonyl carbon and the angle between the nitrogen atom and the carbonyl group, i.e., $\angle \text{N}-\text{C}-\text{O}$ (θ), govern the strength of the $n \rightarrow \pi^*$ interaction. The plots of these geometrical parameters in p -R-DMArPhP versus Hammett values (σ_p) of various substituents are shown in Figure 6.2. It is found that the distance is less than the sum of the van der Waals radii of the nitrogen and carbon atoms for both P1 and P2. Moreover, d (red traces) is less for the $-\text{NMe}_2$ group and increases gradually to the $-\text{NO}_2$ group, whereas θ (blue traces) deviates from the Bürgi-Dunitz trajectory for moving from EDG to EWG. In contrast, the $\text{N} \cdots \text{C}=\text{O}$ distance (d) is ~ 1.2 Å more than the sum of the van der Waals radii of carbon and nitrogen atoms for N1 and N2, which suggests the absence of the $n \rightarrow \pi^*$ interaction in these conformers. Thus, the geometrical parameters plotted in Figure 6.2 suggest that the strength of the $\text{N} \cdots \text{C}=\text{O}$ $n \rightarrow \pi^*$ interaction can be easily tuned by changing the electronic substituents of the molecule. It also suggests that P2 has a stronger $n \rightarrow \pi^*$ interaction than the P1 conformer. The $n \rightarrow \pi^*$ interaction in p -R-DMArPhP weakens the carbonyl bond. Hence, a redshift in the carbonyl stretching frequency ($\Delta\nu_{\text{C}=\text{O}}$) of p -R-DMArPhP can be observed with respect to the m -R-PhP (obtained after deleting the donor $-\text{NMe}_2$ group from p -R-DMArPhP and its further optimization) (Figure 6.3). The IR redshift can also be monitored with respect to the global minimum conformation of m -R-PhP or the N1 and N2 conformers of p -R-DMArPhP, which do not have any $n \rightarrow \pi^*$ interaction.

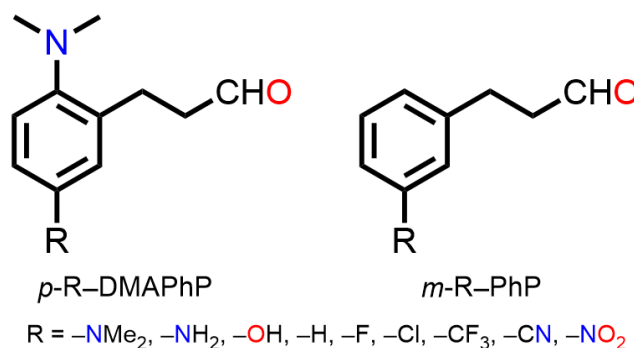


Figure 6.3. Structures of the molecules for comparing the redshift of carbonyl stretching frequency of p -R-DMArPhP with respect to the m -R-PhP (obtained after deleting the $n \rightarrow \pi^*$ donor $-\text{NMe}_2$ group from p -R-DMArPhP and its further optimization).

Figure 6.4 shows the plots of the $\Delta\nu_{\text{C=O}}$ values of the P1 and P2 of *p*-R-DMAPhP versus the Hammett values of the substituents. It is found that the $\Delta\nu_{\text{C=O}}$ values systematically decrease for both P1 and P2 as we move from the EDGs to EWGs. $\Delta\nu_{\text{C=O}}$ values of $\sim 30\text{ cm}^{-1}$ are observed in the P1 and P2 of *p*-R-DMAPhP, with respect to *m*-R-PhP (Figure 6.4). On the other hand, a negligible $\Delta\nu_{\text{C=O}}$ of $\sim 2\text{ cm}^{-1}$ is observed in N1 and N2 with respect to that in *m*-R-PhP. Further, a larger redshift in P2 than in P1 suggests that the $n\rightarrow\pi^*$ interaction is stronger in P2 than in P1. Figure 6.4 also shows that the WBI of the carbonyl bond in P1 and P2 increases as the substitution varies from the EDGs to EWGs. Hence, the $\Delta\nu_{\text{C=O}}$ is due to a decrease in the carbonyl bond order because of the electron delocalization from the nitrogen atom.

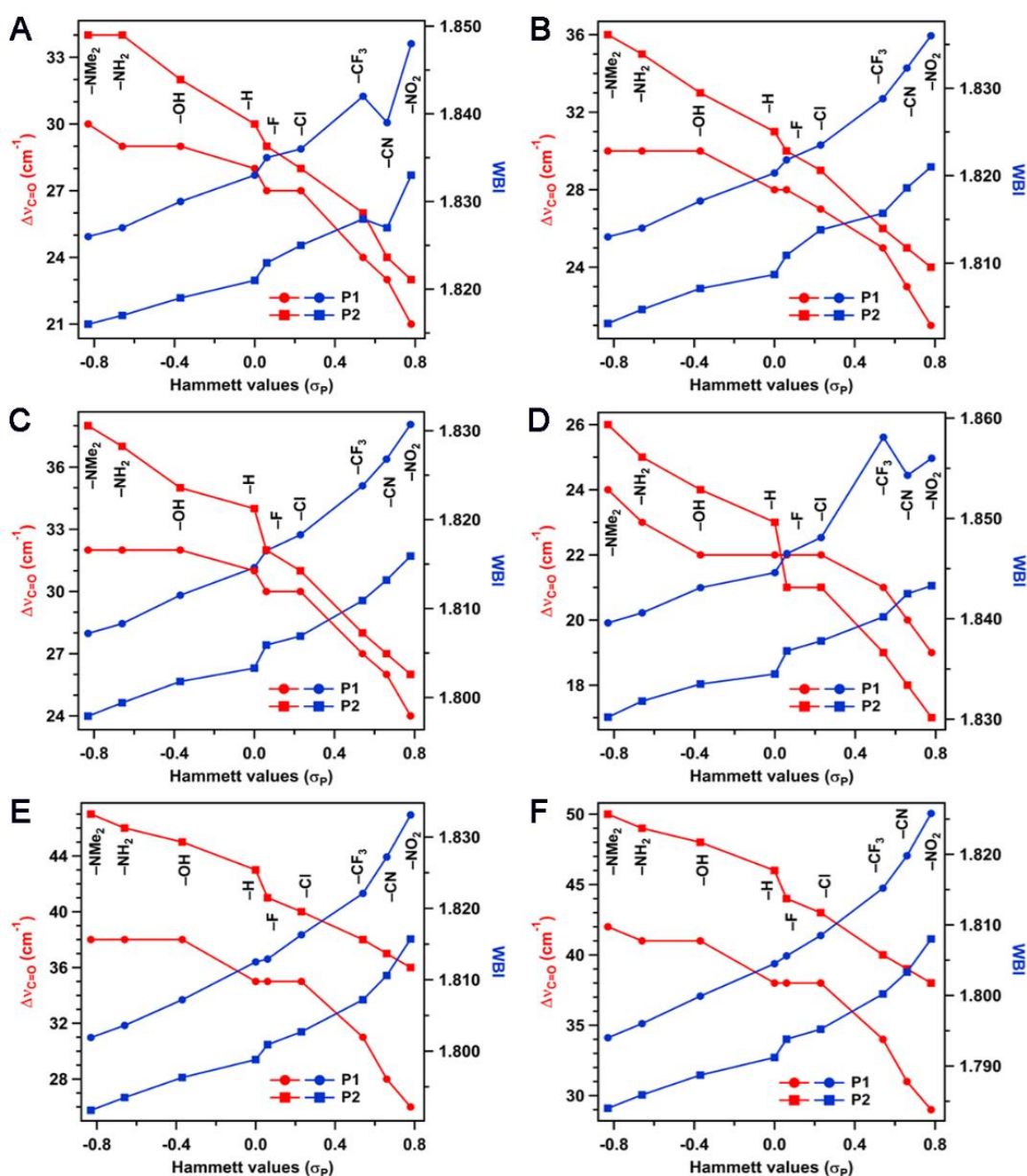


Figure 6.4. Plots of redshift ($\Delta\nu_{\text{C=O}}$, cm^{-1}) in carbonyl stretching frequency (red traces) and WBI (blue traces) of the carbonyl bond of P1 and P2 of various *p*-R–DMAPhP (gas-phase) versus Hammett values of the substituents calculated at the **A)** B3LYP-D3/def2-TZVP; **B)** B3LYP-D3/aug-cc-pVTZ; **C)** B3LYP-D3/6-311++G(d,p); **D)** ω B97X-D/def2-TZVP; **E)** B97-D3/aug-cc-pVTZ; and **F)** B97-D3/6-311++G(d,p) levels. The lines connecting the data points are not fitted but are provided to guide the eyes.

As stated, the carbonyl bond weakens due to the delocalization of the lone pair electron density of the nitrogen atom into its π^* orbital. Hence, the occupancies of the donor and acceptor orbitals in the *p*-R–DMAPhP are scrutinized. Lesser lone pair orbital occupancies of the nitrogen atom in P1 and P2 than in N1 and N2 confirm the presence of the $n \rightarrow \pi^*$ interaction in the former ones. Further higher strength of the $n \rightarrow \pi^*$ interaction in P2 than P1 is also reflected by their lone pair occupancies of the nitrogen atom. The impact of the $n \rightarrow \pi^*$ interaction on the nitrogen lone pair orbital occupancy can be determined by comparing the occupancy in *p*-R–DMAPhP with that in *p*-R–DMAPh (obtained after deleting the propanal from *p*-R–DMAPhP, i.e., unoptimized *p*-R–DMAPh) without having the propanal group, which is the $n \rightarrow \pi^*$ acceptor. Surprisingly, the nitrogen lone pair orbital orientation in *p*-R–DMAPhP changed from $\sim 30^\circ$ to 90° in the optimized *p*-R–DMAPh. Hence, the nitrogen lone pair orbital occupancies in *p*-R–DMAPhP is compared with those in the unoptimized *p*-R–DMAPh (Table 6.2). The occupancies of the lone pair orbital on the nitrogen atom of the unoptimized *p*-R–DMAPh are more than those for P1 and P2, while those are similar to N1 and N2.

Table 6.2. Occupancy of the lone pair orbital of the nitrogen atom and π^* orbital of four conformers of various *p*-R–DMAPhP (gas-phase) calculated at the B3LYP-D3/def2-TZVP level

	LP _N (<i>p</i> -R–DMAPhP)				LP _N (Unoptimized <i>p</i> -R–DMAPh)			
	P1	P2	N1	N2	P1	P2	N1	N2
–NMe ₂	1.816	1.806	1.850	1.855	1.852	1.845	1.850	1.854
–NH ₂	1.815	1.806	1.849	1.854	1.852	1.844	1.849	1.854
–OH	1.816	1.806	1.848	1.853	1.851	1.843	1.847	1.852
–H	1.810	1.799	1.836	1.842	1.841	1.832	1.835	1.841
–F	1.811	1.800	1.838	1.843	1.842	1.834	1.837	1.842

–Cl	1.811	1.800	1.836	1.842	1.840	1.832	1.835	1.840
–CF ₃	1.804	1.792	1.824	1.832	1.829	1.820	1.821	1.829
–CN	1.808	1.796	1.831	1.838	1.836	1.826	1.829	1.835
–NO ₂	1.791	1.777	1.801	1.813	1.809	1.800	1.797	1.807

	$\pi^*_{C=O}$ (<i>p</i> -R–DMAPhP)				$\pi^*_{C=O}$ (Unoptimized <i>m</i> -R–PhP)			
	P1	P2	N1	N2	P1	P2	N1	N2
–NMe ₂	0.098	0.099	0.059	0.057	0.052	0.048	0.056	0.054
–NH ₂	0.098	0.098	0.058	0.056	0.052	0.048	0.055	0.054
–OH	0.096	0.096	0.058	0.057	0.051	0.048	0.055	0.054
–H	0.093	0.094	0.058	0.056	0.051	0.047	0.054	0.053
–F	0.092	0.093	0.058	0.056	0.051	0.047	0.054	0.053
–Cl	0.091	0.092	0.057	0.056	0.051	0.047	0.054	0.053
–CF ₃	0.086	0.088	0.057	0.055	0.050	0.046	0.053	0.052
–CN	0.089	0.089	0.057	0.055	0.050	0.046	0.053	0.052
–NO ₂	0.081	0.084	0.056	0.055	0.049	0.045	0.052	0.052

Figure 6.5 shows the plots of the difference in the nitrogen atom lone pair orbital occupancies of P1 and P2 in *p*-R–DMAPhP with those of the unoptimized *p*-R–DMAPh [$\Delta LP_N(P1)$, $\Delta LP_N(P2)$] as a function of the σ_p values. It is found that both $\Delta LP_N(P1)$ and $\Delta LP_N(P2)$ decrease as the substituents vary from the EDGs to the EWGs. It is noteworthy that $\Delta LP_N(P2)$ is more than $\Delta LP_N(P1)$. Occupancy of the π^* orbital of the carbonyl group ($\pi^*_{C=O}$) is also found to be affected by $n \rightarrow \pi^*$ interaction. Larger $\pi^*_{C=O}$ values in P1 and P2 than in N1 and N2 indicate the presence of $n \rightarrow \pi^*$ interaction in the former ones. The $\pi^*_{C=O}$ values also support a relatively stronger $n \rightarrow \pi^*$ interaction in P2 than in P1. Further, it can be noticed that the $\pi^*_{C=O}$ values of the P1 and P2 of *p*-R–DMAPhP on the deletion of the $n \rightarrow \pi^*$ donor group, i.e., –NMe₂ (*m*-R–PhP) are less than those for P1 and P2 with the donor group (Table 6.2). However, no change in the $\pi^*_{C=O}$ values has been observed for the N1 and N2, while the $n \rightarrow \pi^*$ donor group is deleted (Table 6.2). The difference in the $\pi^*_{C=O}$ values in P1 ($\Delta \pi^*_{C=O}$, P1) and P2 ($\Delta \pi^*_{C=O}$, P2) with respect to those in unoptimized *m*-R–PhP is plotted as a function of the σ_p values of the substituents in Figure 6.5. It is found that the $\Delta \pi^*_{C=O}$ values decrease as the substitutions are changed from the EDGs to EWGs.

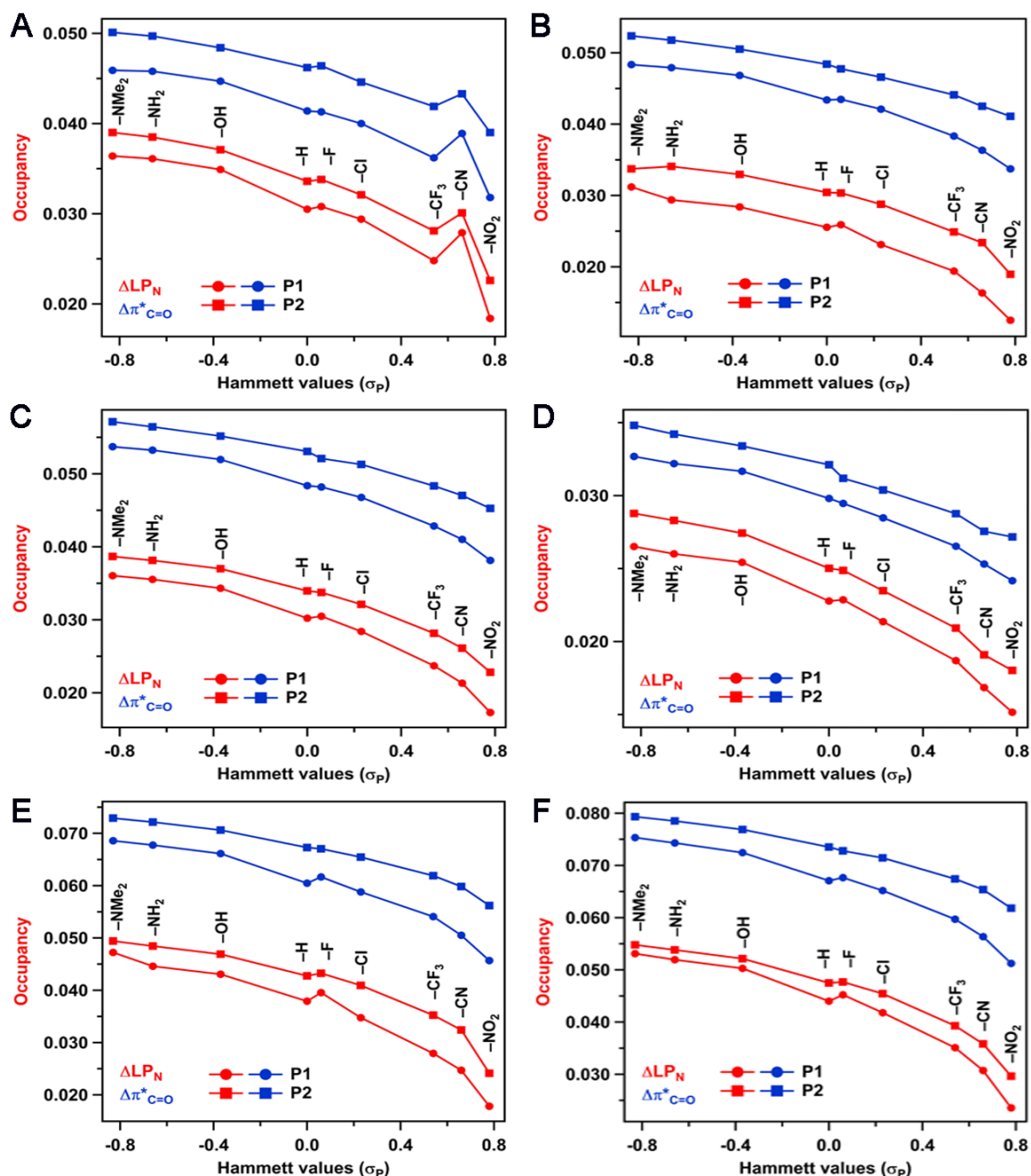


Figure 6.5. Plots of difference in occupancy of the lone pair orbital of the nitrogen atom (red traces) and π^* orbital (blue traces) of P1 and P2 in various *p*-R-DMApH (gas-phase) with the respective unoptimized *p*-R-DMApH and unoptimized *m*-R-PhP, respectively, versus Hammett values calculated at the **A)** B3LYP-D3/def2-TZVP; **B)** B3LYP-D3/aug-cc-pVTZ; **C)** B3LYP-D3/6-311++G(d,p); **D)** ω B97X-D/def2-TZVP; **E)** B97-D3/aug-cc-pVTZ; and **F)** B97-D3/6-311++G(d,p) levels. The lines connecting the data points are not fitted but are provided to guide the eyes.

The strength of the $n \rightarrow \pi^*$ interaction in P1 and P2 of *p*-R-DMApH has been determined from $E^{(2)}$ values obtained from the NBO calculation. $E^{(2)}$ values signify the

overlap between the lone pair orbital of the nitrogen atom and the π^* orbital of the carbonyl group. Figure 6.6 shows the plots for the $E^{(2)}$ values in P1 and P2 as a function of the σ_p values of the substituents. It is found that the $E^{(2)}$ values decrease as the substitution is varied from the EDGs to EWGs.

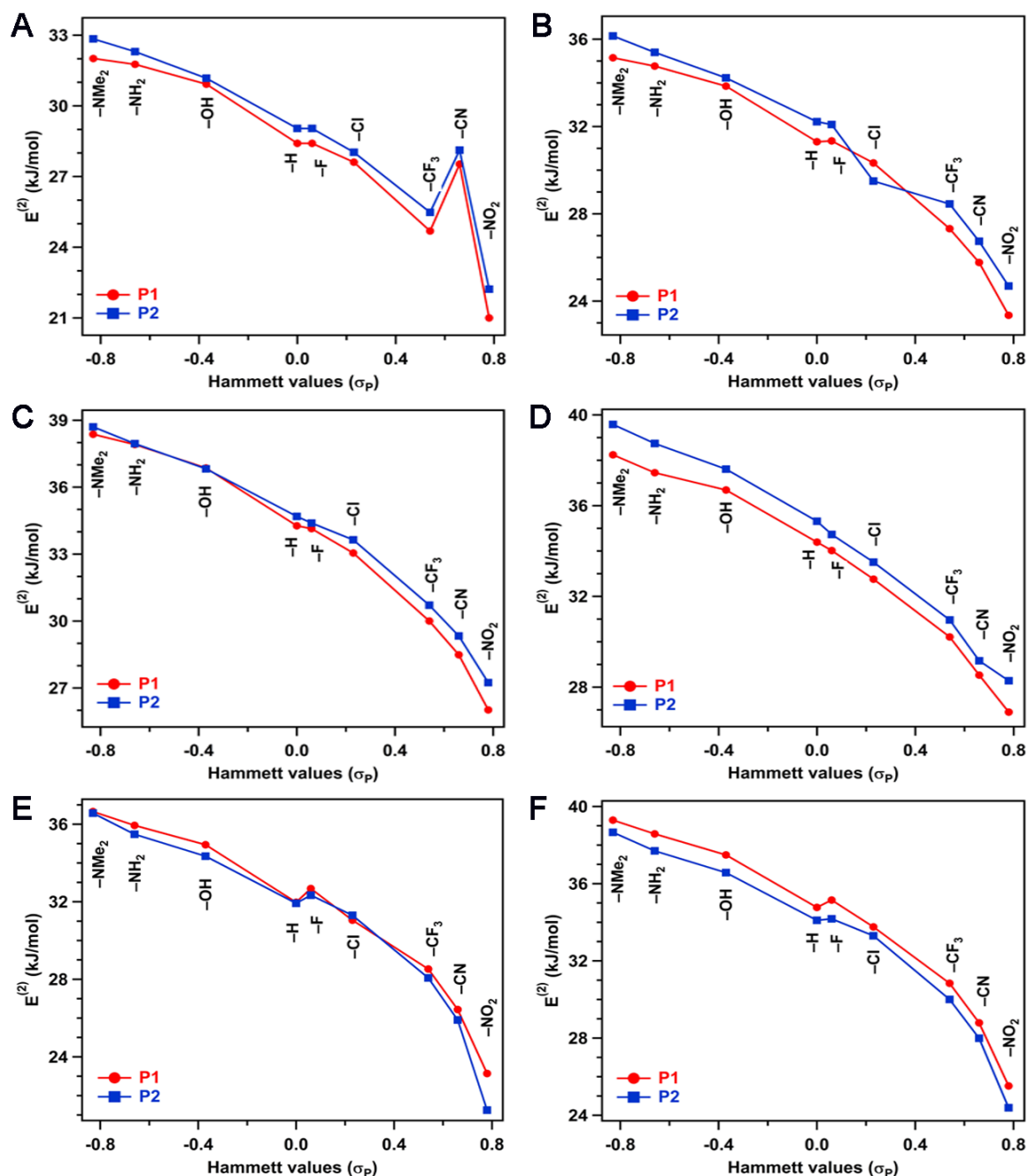


Figure 6.6. Plots of $E^{(2)}$ values (kJ/mol) of $n \rightarrow \pi^*$ interaction in P1 and P2 of various *p*-R-DMAPhP (gas-phase) versus Hammett values of the substituents calculated at the **A)** B3LYP-D3/def2-TZVP; **B)** B3LYP-D3/aug-cc-pVTZ; **C)** B3LYP-D3/6-311++G(d,p); **D)** ω B97X-D/def2-TZVP; **E)** B97-D3/aug-cc-pVTZ; and **F)** B97-D3/6-311++G(d,p) levels. The lines connecting the data points are not fitted but are provided to guide the eyes.

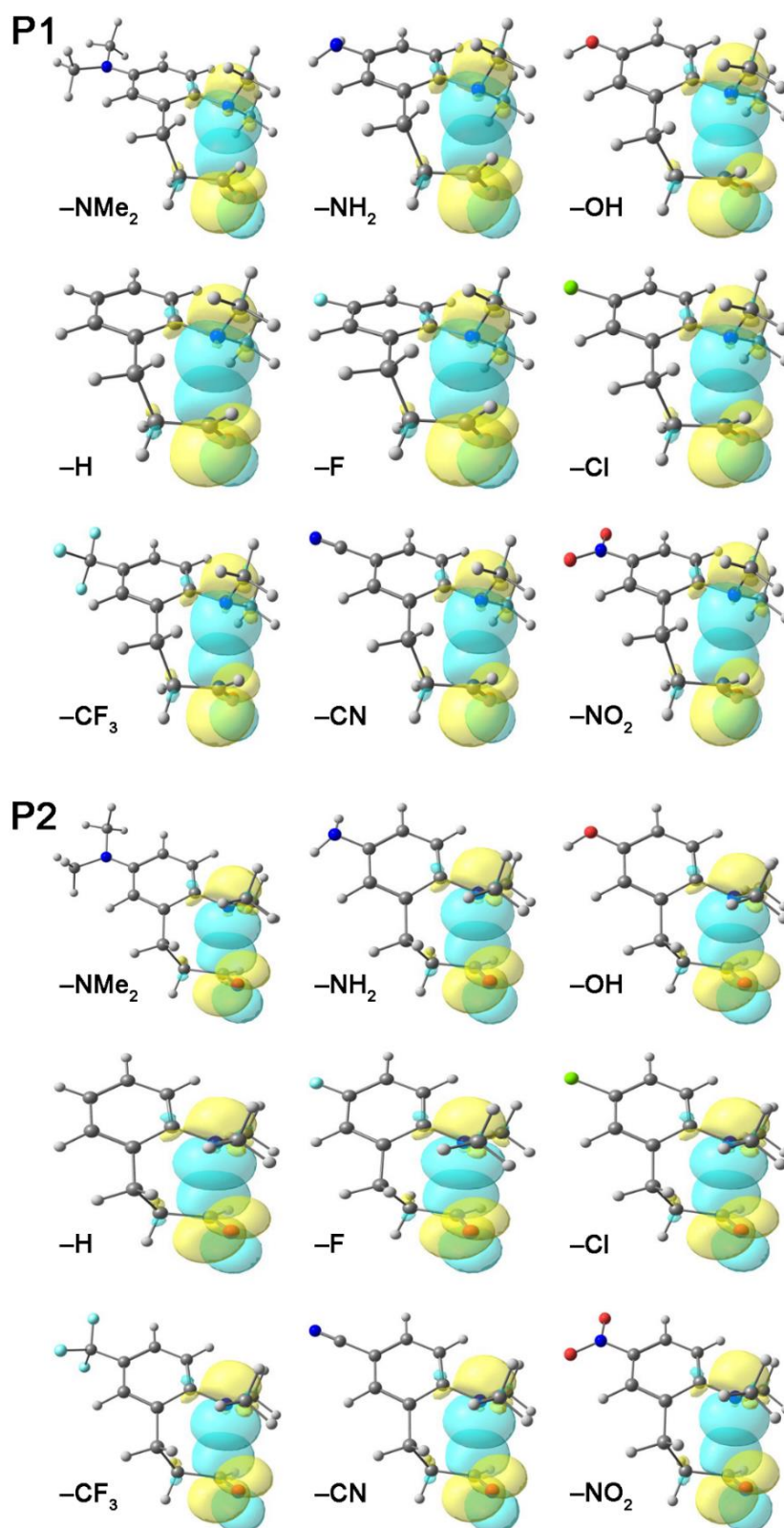


Figure 6.7. NBO orbital overlap for $n \rightarrow \pi^*$ interaction in P1 and P2 of various *p*-R-DMArPhP (gas-phase) calculated at the B3LYP-D3/def2-TZVP level.

Orbital overlap for the P1 and P2 of *p*-R-DMArPhP are shown in Figure 6.7. It is worth mentioning that the strength of $n \rightarrow \pi^*$ interaction in P2 is more than in P1,

although the latter is more stable than the former. It has been found from the NSA¹¹⁰ that the steric repulsion energy between the lone pair orbital of the nitrogen atom and σ/π orbitals of the carbonyl group is higher in P2 than in P1 (Table 6.3). Thus, the steric calculation qualitatively explains the trend in the energy order of P1 and P2.⁶¹

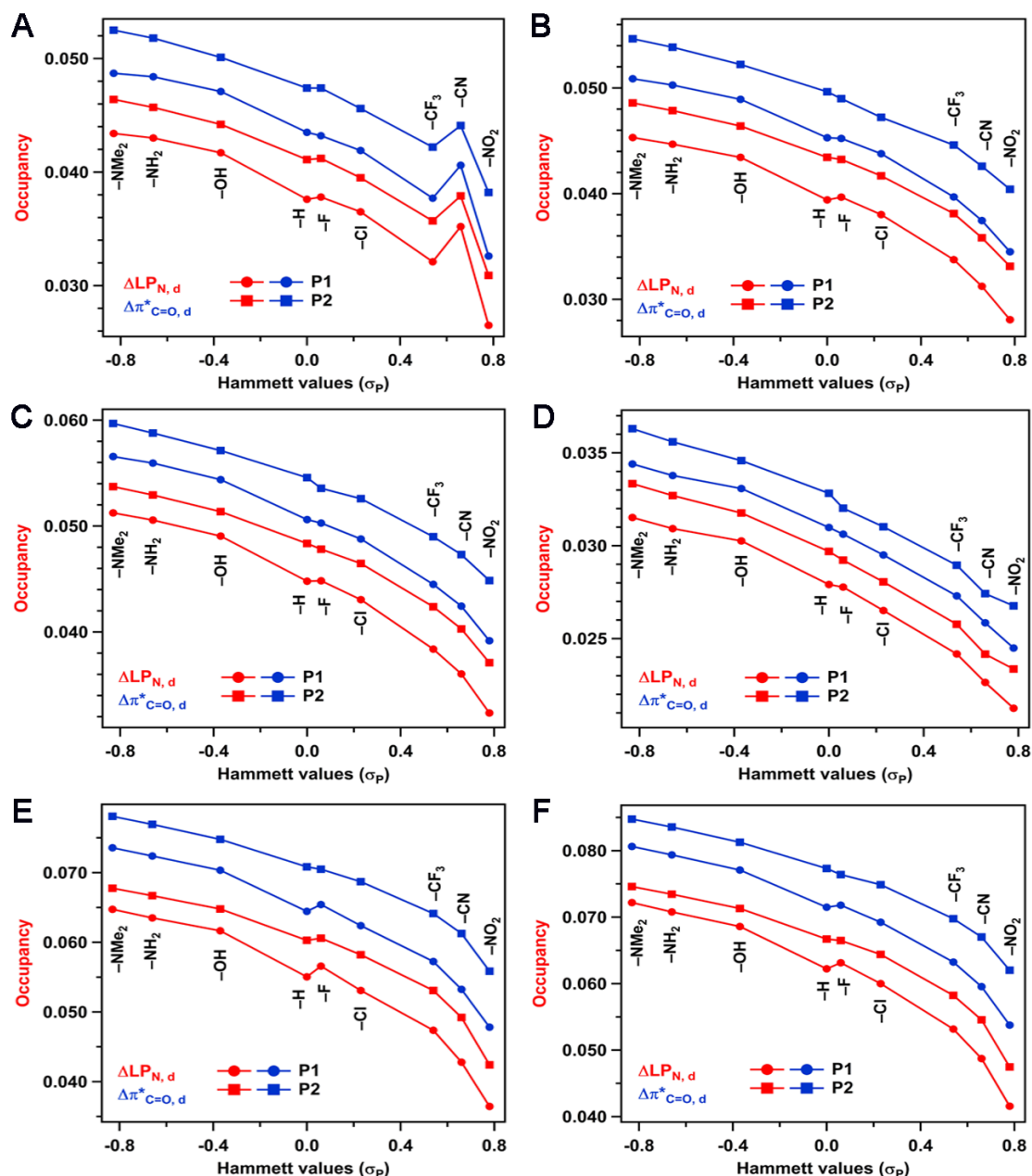


Figure 6.8. Plots of difference in occupancy of lone pair orbital of the nitrogen atom (red traces) and π^* orbital (blue traces) of P1 and P2 in various *p*-R-DMAPhP (gas-phase) after deleting $n \rightarrow \pi^*$ interaction from these molecules versus Hammett values calculated at the **A)** B3LYP-D3/def2-TZVP; **B)** B3LYP-D3/aug-cc-pVTZ; **C)** B3LYP-D3/6-311++G(d,p); **D)** ω B97X-D/def2-TZVP; **E)** B97-D3/aug-cc-pVTZ; and **F)** B97-D3/6-311++G(d,p) levels. The lines connecting the data points are not fitted but are provided to guide the eyes.

Table 6.3. Steric repulsion energy (kJ/mol) between the lone pair orbital of the nitrogen atom and σ/π orbitals of the carbonyl group of the P1 and P2 of various *p*-R–DMAPhP (gas-phase) molecules calculated at the B3LYP-D3/def2-TZVP level

	–NMe ₂	–NH ₂	–OH	–H	–F	–Cl	–CF ₃	–CN	–NO ₂
P1	22.51	22.47	22.22	20.75	21.34	21.00	19.71	21.17	17.28
P2	23.51	23.35	22.84	21.88	21.80	21.34	19.79	21.21	18.24

NBO deletion analysis is performed further to verify the presence of the $n \rightarrow \pi^*$ interaction in P1 and P2. The deletion analysis calculates the occupancies of the orbitals after deleting the $n \rightarrow \pi^*$ interaction present in the conformers. Interestingly, it is found that the occupancies of the lone pair orbital of the nitrogen atom and π^* orbital of the carbonyl group increase and decrease, respectively, upon the deletion of the $n \rightarrow \pi^*$ interaction in the P1 and P2 of *p*-R–DMAPhP (Figure 6.8 and Table 6.4). It reconfirms that the electron density delocalizes from the nitrogen atom to the π^* orbital of the carbonyl group.

Table 6.4. Comparison of occupancies of the lone pair orbital of the nitrogen atom and π^* orbitals of the P1 and P2 upon the deletion of $n \rightarrow \pi^*$ interaction from *p*-R–DMAPhP calculated at the B3LYP-D3/def2-TZVP level

	Before deletion of $n \rightarrow \pi^*$ interaction				After deletion of $n \rightarrow \pi^*$ interaction			
	LP _N		$\pi^*_{C=O}$		LP _{N, d}		$\pi^*_{C=O, d}$	
	P1	P2	P1	P2	P1	P2	P1	P2
–NMe ₂	1.8159	1.8059	0.0980	0.0985	1.8593	1.8523	0.0493	0.0460
–NH ₂	1.8154	1.8056	0.0976	0.0977	1.8584	1.8513	0.0492	0.0459
–OH	1.8156	1.8057	0.0959	0.0959	1.8573	1.8499	0.0488	0.0458
–H	1.8104	1.7988	0.0928	0.0936	1.8480	1.8399	0.0493	0.0462
–F	1.8114	1.8002	0.0920	0.0930	1.8492	1.8414	0.0488	0.0456
–Cl	1.8109	1.7997	0.0907	0.0915	1.8474	1.8392	0.0488	0.0459
–CF ₃	1.8043	1.7920	0.0863	0.0882	1.8364	1.8277	0.0486	0.0460
–CN	1.8079	1.7957	0.0892	0.0894	1.8431	1.8336	0.0486	0.0453
–NO ₂	1.7906	1.7771	0.0809	0.0842	1.8171	1.8080	0.0483	0.0460

QTAIM and NCI analyses are performed to gain insight into the $n \rightarrow \pi^*$ interaction in *p*-R–DMAPhP. Plots of various AIM parameters shown in Figure 6.9 suggest that the $n \rightarrow \pi^*$ interaction in *p*-R–DMAPhP weakens with the variation of the

substituents from the EDGs to the EWGs. AIM molecular graphs depicting the $n \rightarrow \pi^*$ interaction in P1 and P2 conformers of *p*-R–DMAPhP are shown in Figure 6.10.

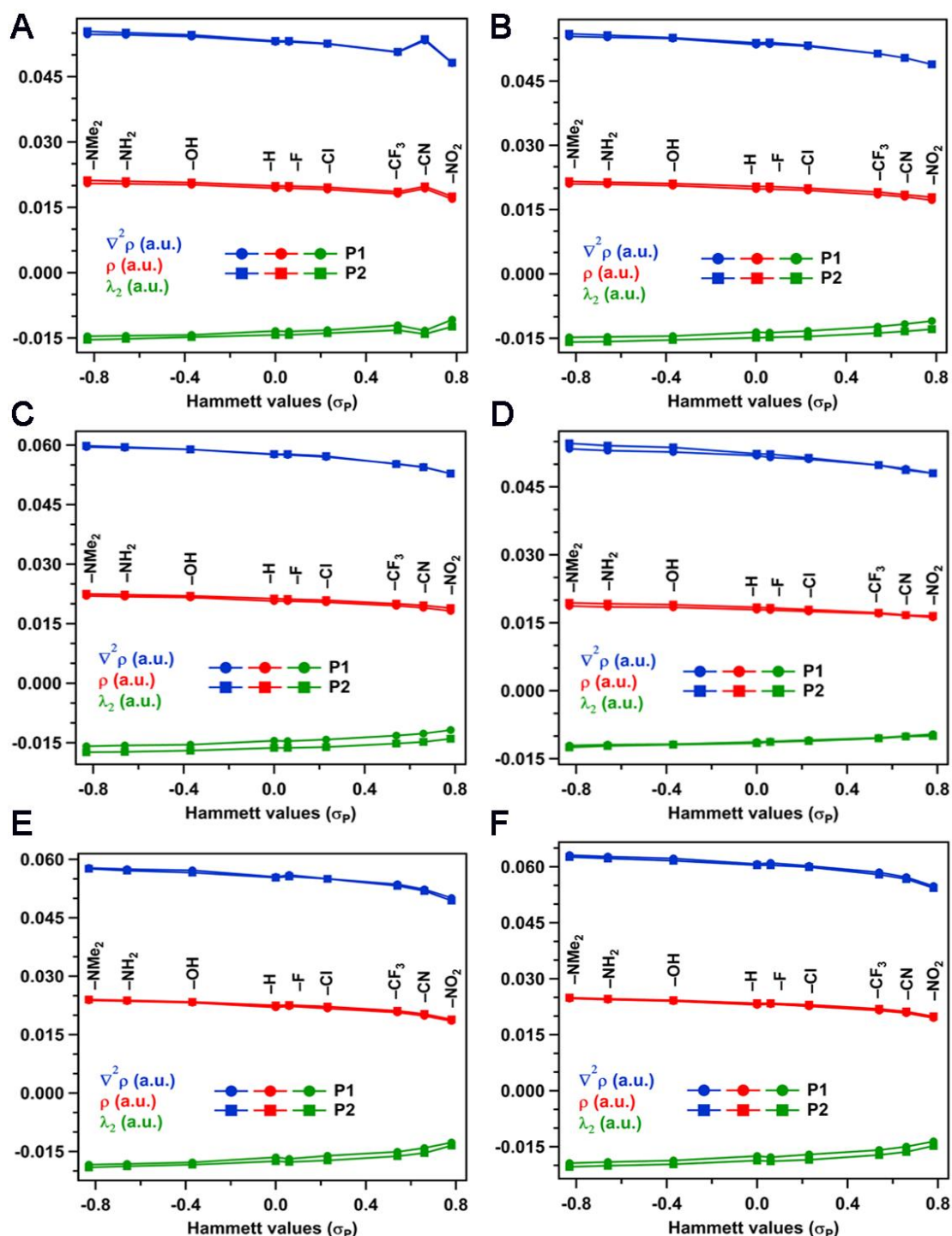


Figure 6.9. Plots of AIM parameters of various *p*-R–DMAPhP (gas-phase) at the BCP of $n \rightarrow \pi^*$ interaction versus Hammett values of the substituents calculated at the **A)** B3LYP-D3/def2-TZVP; **B)** B3LYP-D3/aug-cc-pVTZ; **C)** B3LYP-D3/6-311++G(d,p); **D)** ω B97X-D/def2-TZVP; **E)** B97-D3/aug-cc-pVTZ; and **F)** B97-D3/6-311++G(d,p) levels. The lines connecting the data points are not fitted but are provided to guide the eyes.

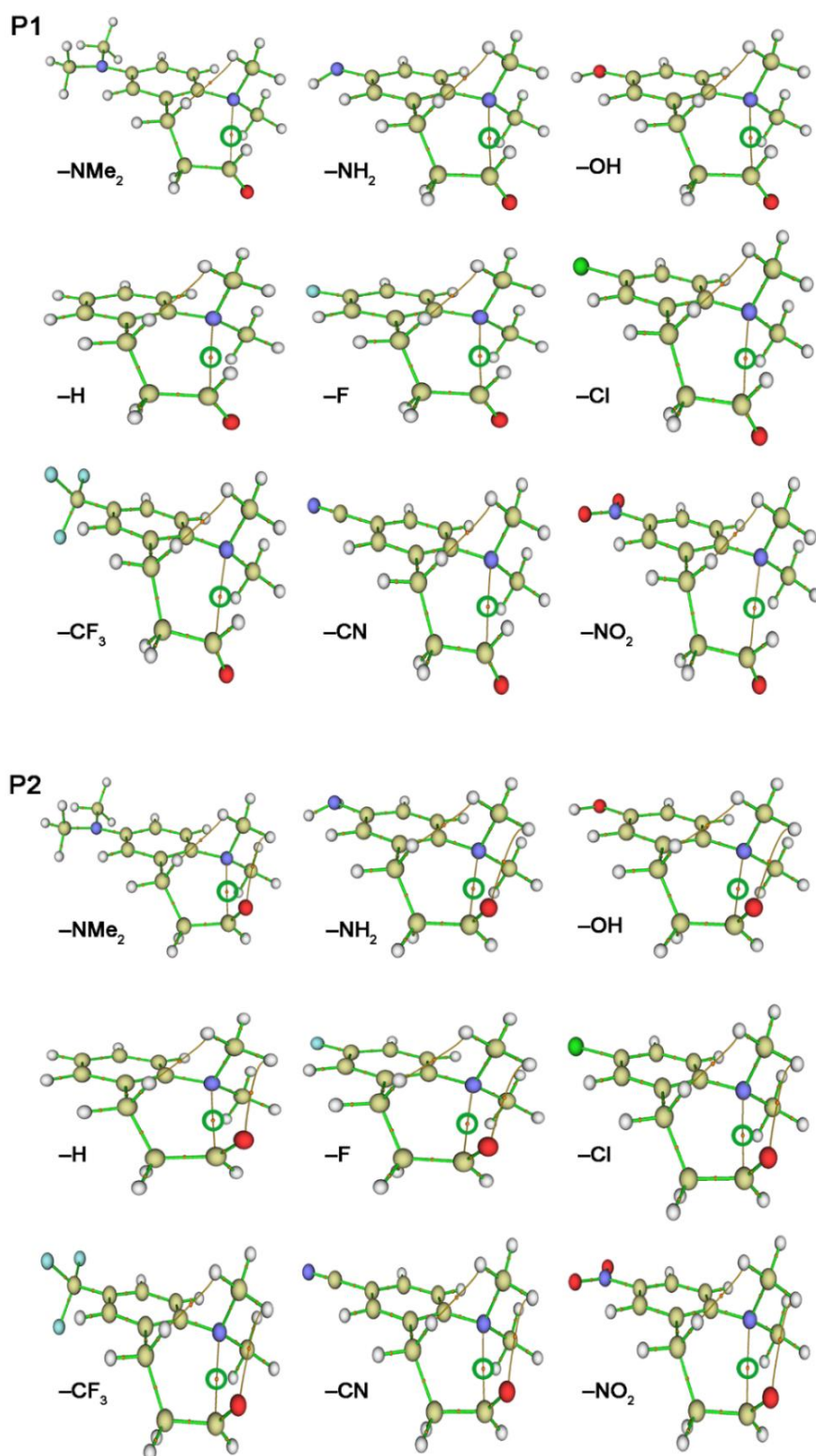


Figure 6.10. AIM molecular graphs for P1 and P2 of various *p*-R-DMArPhP (gas-phase), representing BCP for $N\cdots C=O$ $n\rightarrow\pi^*$ interaction marked with green circles calculated at the B3LYP-D3/def2-TZVP level.

The NCI calculations for the P1 and P2 exhibit the isosurface and minima in the RDG plot versus $\text{Sign}(\lambda_2)\rho(r)$ for the $n\rightarrow\pi^*$ interaction (Figures 6.11 and 6.12). It can

be noticed that the minima corresponding to $n \rightarrow \pi^*$ interaction moves toward the right side as electronic substitution varies from the EDGs to EWGs. Overall results suggest that the strength of the intramolecular $n \rightarrow \pi^*$ interaction can be modulated systematically by varying the substituents at the *para* position of the $n \rightarrow \pi^*$ donor.

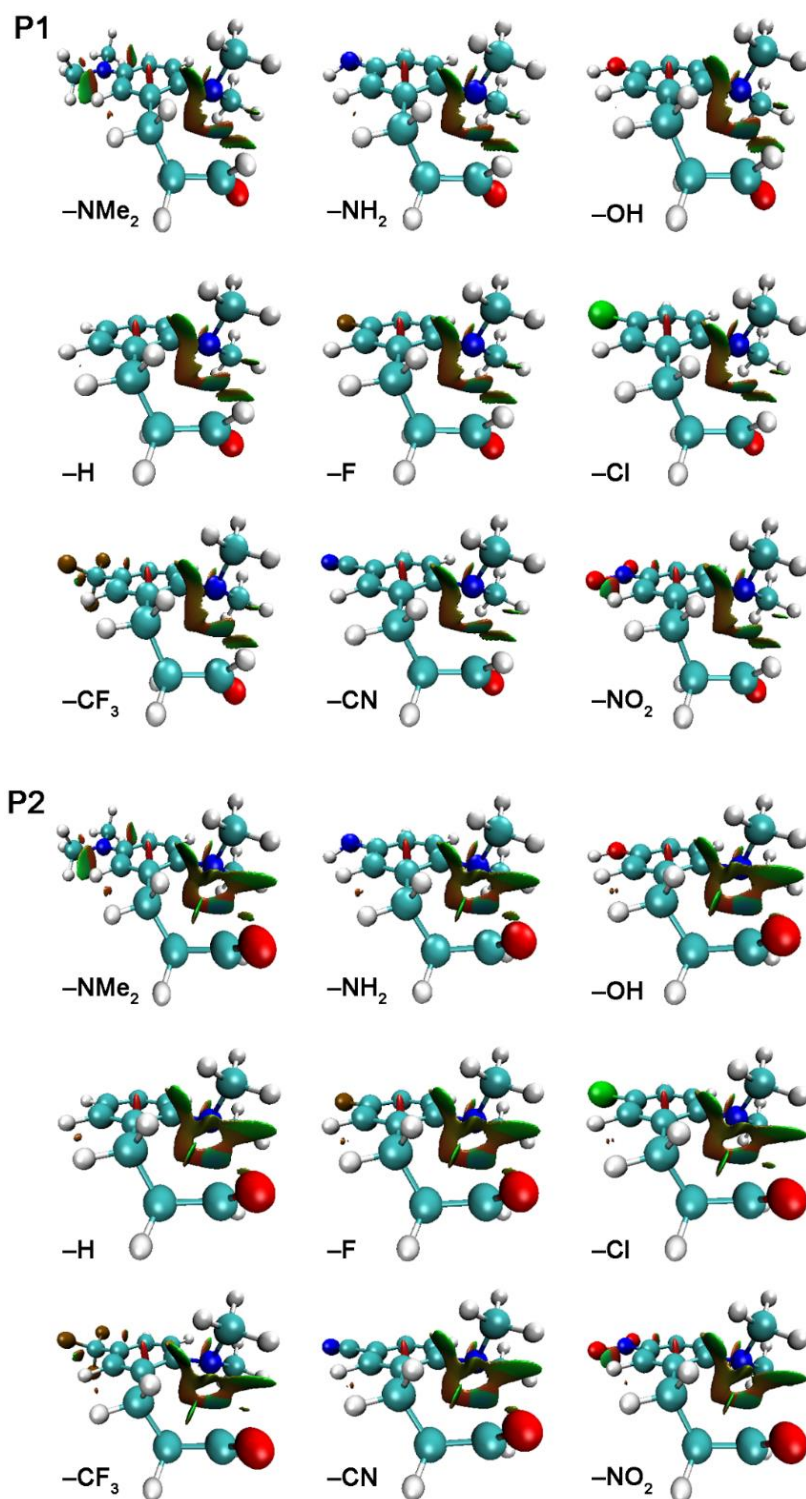


Figure 6.11. NCI isosurface plots for P1 and P2 of various *p*-R-DMArPhP (gas-phase) calculated at the B3LYP-D3/def2-TZVP level.

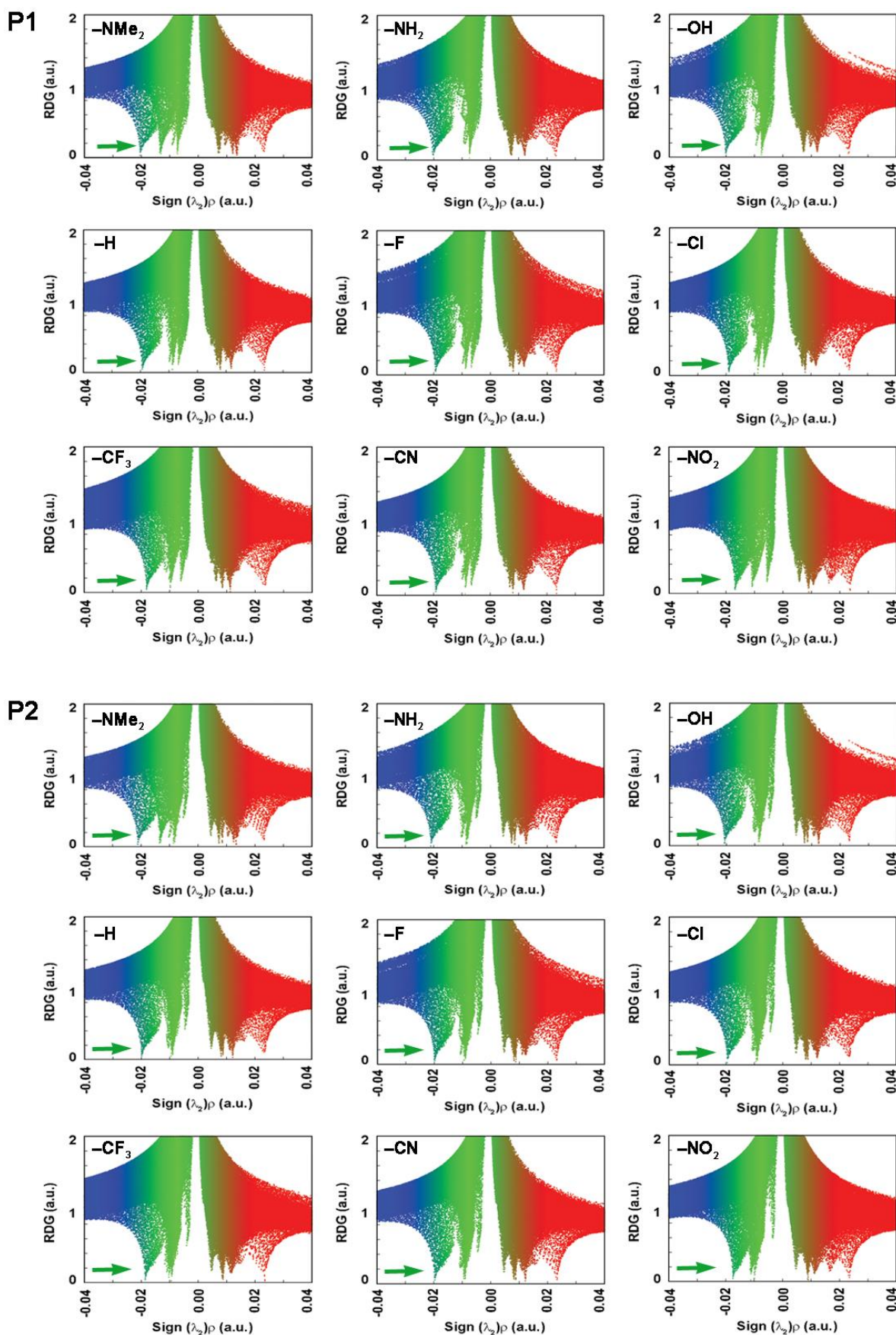


Figure 6.12. NCI RDG plots for P1 and P2 of various *p*-R-DMArPhP (gas-phase) calculated at the B3LYP-D3/def2-TZVP level.

Similar results were obtained at the MP2/6-311++G(d,p) level. Table 6.5 shows various geometrical and electronic parameters for *p*-R-DMArPhP obtained at the MP2/6-311++G(d,p) level. It should be mentioned here that the optimized geometries at the MP2 level are similar to those observed at several DFT levels.

Table 6.5. Relevant geometrical parameters such as distance (*d*, Å) and $\angle\text{N-C-O}$ (θ) of the P1 and P2 of various *p*-R-DMArPhP (gas-phase) calculated at the MP2/6-311++G(d,p) level. $E^{(2)}$ values (kJ/mol) of $n \rightarrow \pi^*$ interaction are calculated at the HF/6-311++G(d,p) level on the geometries optimized at the MP2/6-311++G(d,p) level

R	d		θ		$E^{(2)}$		Hammett (σ_p)
	P1	P2	P1	P2	P1	P2	
-N(CH ₃) ₂	2.691	2.579	100.4	102.0	33.05	49.41	-0.83
-NH ₂	2.705	2.580	100.1	102.0	31.25	48.99	-0.66
-OH	2.719	2.584	99.8	101.9	29.33	48.07	-0.37
-H	2.726	2.592	99.3	101.5	27.95	46.23	0.00
-F	2.764	2.597	98.3	101.4	23.51	45.27	0.06
-Cl	2.755	2.600	98.3	101.2	24.35	44.64	0.23
-CF ₃	2.789	2.616	97.0	100.8	20.50	41.92	0.54
-CN	2.797	2.622	96.6	100.5	19.50	40.58	0.66
-NO ₂	2.821	2.624	95.9	100.5	17.24	40.00	0.78

The role of solvents with different polarity, such as water (H₂O, polar protic), dichloromethane (CH₂Cl₂, polar aprotic), and carbon tetrachloride (CCl₄, non-polar) on $n \rightarrow \pi^*$ interaction was also determined using the IEFPCM calculations at the B3LYP-D3/def2-TZVP level.^{170, 171} It should be mentioned here that the PCM model does not change the overall molecular geometries of any conformers of *p*-R-DMArPhP as compared to the obtained from the gas-phase calculations. However, there are some changes in the geometrical parameters, such as the distance ($d_{\text{N}\cdots\text{C}=\text{O}}$, Å) between the nitrogen atom ($n \rightarrow \pi^*$ donor) and the carbonyl carbon ($n \rightarrow \pi^*$ acceptor) as well as in the $\angle\text{N-C-O}$ (θ) between the nitrogen atom and carbonyl group. These geometrical parameters (Tables 6.6-6.7) and other parameters such as redshift ($\Delta\nu_{\text{C}=\text{O}}$, cm⁻¹) in the carbonyl stretching frequency (Table 6.8) and $E^{(2)}$ values (kJ/mol) for the $n \rightarrow \pi^*$ interaction (Table 6.9) were also scrutinized for the different solvents with the gas-phase. It is intriguing that the trend of the results, i.e., the overall electronic effect of various substituents on the $n \rightarrow \pi^*$ interaction obtained from the PCM calculations

performed in all three solvents, is similar to those obtained from the gas-phase calculations. However, it should be emphasized that the polarity of the solvents plays a role in the strength of the $n \rightarrow \pi^*$ interaction. The results presented in Tables 6.6-6.9 state that the strength of the $n \rightarrow \pi^*$ interaction decreases as the polarity of the solvents decreases, i.e., the order of the interaction strength follows the trend $\text{H}_2\text{O} > \text{CH}_2\text{Cl}_2 > \text{CCl}_4 > \text{gas-phase}$. Interestingly, the gas-phase results are close to those obtained in the non-polar solvent (CCl_4).

Table 6.6. Comparison of the relevant geometrical parameters such as distance (d, Å) of the P1 and P2 of various *p*-R-DMAPhP in different solvents with the gas-phase calculated at the B3LYP-D3/def2-TZVP level

	H ₂ O		CH ₂ Cl ₂		CCl ₄		Gas-phase		Hammett (σ_p)
	P1	P2	P1	P2	P1	P2	P1	P2	
-N(CH ₃) ₂	2.609	2.586	2.612	2.594	2.629	2.613	2.649	2.632	-0.83
-NH ₂	2.608	2.589	2.612	2.597	2.630	2.616	2.651	2.635	-0.66
-OH	2.624	2.599	2.624	2.607	2.639	2.624	2.655	2.643	-0.37
-H	2.645	2.617	2.644	2.624	2.652	2.641	2.673	2.658	0.00
-F	2.649	2.616	2.653	2.623	2.663	2.641	2.674	2.658	0.06
-Cl	2.655	2.626	2.655	2.633	2.665	2.649	2.679	2.666	0.23
-CF ₃	2.691	2.649	2.693	2.656	2.698	2.673	2.703	2.688	0.54
-CN	2.719	2.673	2.712	2.679	2.716	2.690	2.717	2.702	0.66
-NO ₂	2.780	2.767	2.759	2.723	2.740	2.712	2.736	2.717	0.78

Table 6.7. Comparison of the relevant geometrical parameters such as $\angle \text{N-C-O}$ (θ) of the P1 and P2 of various *p*-R-DMAPhP in different solvents with the gas-phase calculated at the B3LYP-D3/def2-TZVP level

	H ₂ O		CH ₂ Cl ₂		CCl ₄		Gas-phase		Hammett (σ_p)
	P1	P2	P1	P2	P1	P2	P1	P2	
-N(CH ₃) ₂	104.1	103.1	104.2	102.9	103.8	102.3	102.9	101.4	-0.83
-NH ₂	104.2	103.0	104.2	102.8	103.7	102.2	102.8	101.4	-0.66
-OH	104.1	102.7	104.0	102.6	103.6	102.0	102.7	101.1	-0.37
-H	103.8	102.5	103.6	102.3	103.1	101.6	102.3	100.7	0.00
-F	103.8	102.4	103.8	102.2	103.2	101.5	102.2	100.6	0.06
-Cl	103.6	102.2	103.5	101.9	103.0	101.2	102.0	100.3	0.23

-CF ₃	103.4	101.7	103.3	101.4	102.6	100.6	101.5	99.7	0.54
-CN	103.2	101.2	103.0	100.9	102.3	100.2	101.1	99.2	0.66
-NO ₂	102.5	99.5	102.5	99.8	101.8	99.6	100.7	98.8	0.78

Table 6.8. Comparison of the redshift in the carbonyl stretching frequency ($\Delta\nu_{\text{C=O}}$, cm^{-1}) in the P1 and P2 of various *p*-R–DMAPhP with respect to the *m*-R–PhP in different solvents with the gas-phase calculated at the B3LYP-D3/def2-TZVP level

	H ₂ O		CH ₂ Cl ₂		CCl ₄		Gas-phase		Hammett (σ_{P})
	P1	P2	P1	P2	P1	P2	P1	P2	
-N(CH ₃) ₂	40	45	38	43	30	37	22	31	-0.83
-NH ₂	38	42	40	40	28	35	22	31	-0.66
-OH	38	42	34	39	27	34	19	29	-0.37
-H	33	38	30	36	25	33	20	30	0.00
-F	32	37	29	35	24	32	18	28	0.06
-Cl	31	36	28	34	23	31	19	29	0.23
-CF ₃	29	36	26	33	19	29	15	26	0.54
-CN	26	33	23	31	17	27	12	24	0.66
-NO ₂	20	28	19	29	15	26	11	23	0.78

Table 6.9. Comparison of the $E^{(2)}$ values (kJmol) of $n \rightarrow \pi^*$ interaction in the P1 and P2 of various *p*-R–DMAPhP in different solvents with the gas-phase calculated at the B3LYP-D3/def2-TZVP level

	H ₂ O		CH ₂ Cl ₂		CCl ₄		Gas-phase		Hammett (σ_{P})
	P1	P2	P1	P2	P1	P2	P1	P2	
-N(CH ₃) ₂	39.54	41.59	38.74	39.96	35.48	36.32	32.01	32.84	-0.83
-NH ₂	39.46	40.84	38.49	39.29	35.23	35.73	31.76	32.30	-0.66
-OH	36.86	38.99	36.53	37.61	33.81	34.35	30.92	31.17	-0.37
-H	33.68	36.15	33.43	34.85	31.59	31.88	28.41	29.04	0.00
-F	33.22	36.19	32.38	34.89	30.42	31.80	28.41	29.04	0.06
-Cl	32.26	34.69	31.84	33.43	29.96	30.71	27.61	28.03	0.23
-CF ₃	27.74	31.46	27.28	30.29	26.02	27.78	24.69	25.48	0.54
-CN	24.43	28.28	24.27	27.41	23.85	25.61	27.53	28.12	0.66
-NO ₂	18.66	17.61	20.17	22.01	21.25	23.14	21.00	22.22	0.78

Literature reports from both experiment and computation have demonstrated the electronic effects on the strength of the $n \rightarrow \pi^*$ interaction.⁵²⁻⁶² Sarma and co-workers have shown from FTIR and NMR spectroscopy combined with calculations that the strength of the $n \rightarrow \pi^*$ interaction can be modulated by introducing EDG and EWG at the $n \rightarrow \pi^*$ acceptor site.⁵⁸ Raines and co-workers have demonstrated through NMR spectroscopy and calculations that the strength of the $n \rightarrow \pi^*$ interaction can be varied by changing the acyl donor and acceptor in *N*-acyl prolyl ester (Ac-Pro-OMe) model.^{55, 56} However, none of these reports dealt where the $n \rightarrow \pi^*$ acceptor, i.e., carbonyl group, was either free from hyperconjugation from nearby heteroatom or perturbation from the adjacent aromatic ring. The similar electronic effects on the strength of the $n \rightarrow \pi^*$ interaction have been studied in the present work by bridging this gap with the earlier reports.

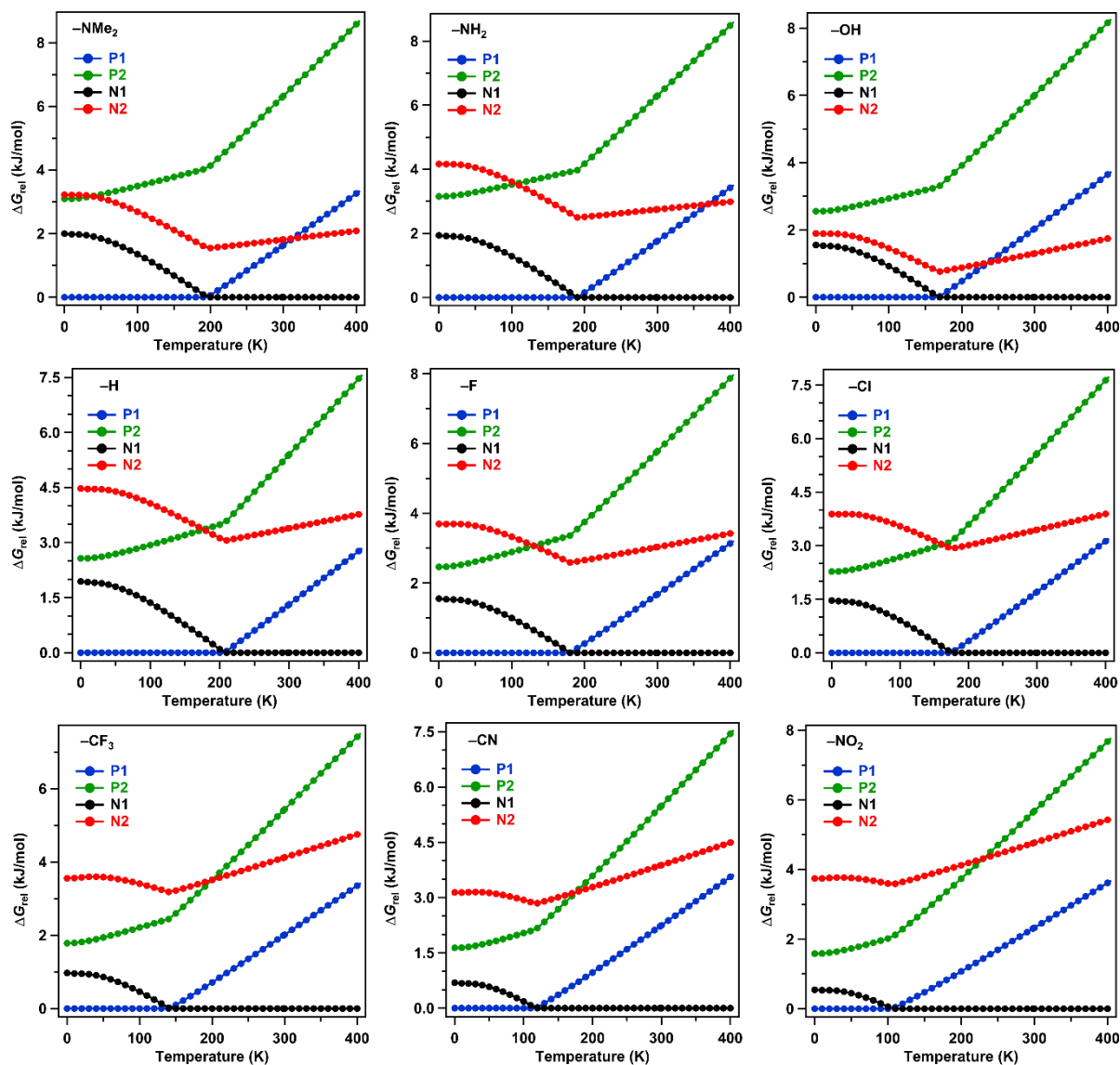


Figure 6.13. Plots of ΔG_{rel} values (kJ/mol) of various *p*-R–DMAPhP (gas-phase) as the function of temperature (0–400 K) calculated at the B3LYP-D3/def2-TZVP level. The lines connecting the data points are not fitted but are provided to guide the eyes.

6.4 Effect of $n \rightarrow \pi^*$ interaction on folding the P1 and P2

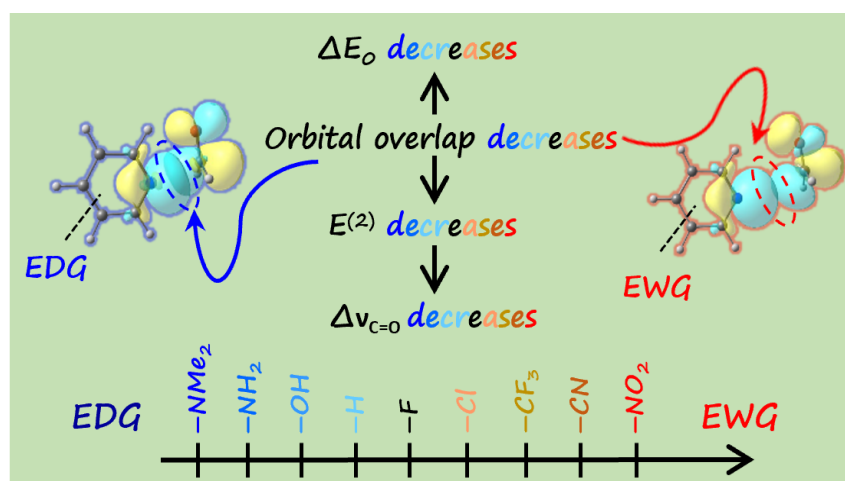
Various *p*-R–DMAPhP have a propanal side-chain at the *ortho* position to the $-\text{NMe}_2$ group. Figure 6.1 shows that the propanal side-chain is close to the $-\text{NMe}_2$ group for the P1 and P2 and favorable for the $n \rightarrow \pi^*$ interaction in them. Hence, due to this interaction, the propanal side-chain folds towards the $n \rightarrow \pi^*$ donor in P1 and P2 (folded conformers). There are many reports on folding molecular structures due to hydrogen bonds.^{184, 185, 226–228} The change in relative Gibbs free energy (ΔG) has been calculated for the *p*-R–DMAPhP to correct their relative electronic energies in the temperature range of 0–400 K. It is found that the ΔG values of P1 and P2 increase with the increase in temperature. In contrast, ΔG values of N1 (extended conformer) decrease with the increase in temperature and become the most stable conformer. Stabilizing extended over folded conformers at higher temperatures (~ 150 K) suggests the involvement of the entropy factor in stabilizing the N1 over P1/P2 at higher temperatures. ΔG values of various *p*-R–DMAPhP are given in Figure 6.13. It can be noticed that the temperature for the destabilization of the P1 decreases as we move from the EDGs (200 K) to EWGs (110 K).

6.5 Conclusion

Modulation of the intramolecular $n \rightarrow \pi^*$ interaction in *p*-R–DMAPhP by varying the R group with EDGs and EWGs has been investigated in detail using DFT, MP2, and PCM calculations. It is found through the NBO, QTAIM, and NCI analyses that the strength of the $n \rightarrow \pi^*$ interaction increases systematically as the *para* substitution to the $-\text{NMe}_2$ ($n \rightarrow \pi^*$ donor) of *p*-R–DMAPhP varies from the EWGs to EDGs. The two most stable conformers, P1 and P2, of the flexible amino-aldehyde are found to be stabilized by $\text{N} \cdots \text{C}=\text{O}$ the $n \rightarrow \pi^*$ interaction. The redshift in the carbonyl stretching frequency in the P1 and P2 is mainly due to the $n \rightarrow \pi^*$ interaction, as the carbonyl group is free from any hyperconjugation, which is the case with the amides and esters molecules. Plots of various electronic parameters and energetics involving $n \rightarrow \pi^*$ interaction as a function of the Hammett values of the substituents demonstrate that the $n \rightarrow \pi^*$ interaction can be fine-tuned by varying the electron density at the lone pair orbital of the $n \rightarrow \pi^*$ donor group. Folding of the flexible side-chain in *p*-R–DMAPhP through $n \rightarrow \pi^*$ interaction

has been found to resemble the hydrogen bonding interaction in the peptide backbone to form the secondary structures of proteins. The role of entropy in the stabilization of N1 and destabilization of the P1/P2 at higher temperatures has been observed from the relative Gibbs free energy calculation. The present work has implications in exploiting the $n \rightarrow \pi^*$ interaction toward improved drug designing and supramolecular assemblies.

Chapter 7: Intermolecular Modulation of $\text{N}\cdots\text{C}=\text{O}$ $\text{n}\rightarrow\pi^*$ Interaction and its Role in Stabilizing Molecular Complexes of *p*-Substituted Pyridines with Aldehydes



Adapted from: **P. Panwaria** and A. Das*, Modulation of $\text{n} \rightarrow \pi^*$ Interaction in the Complexes of *p*-Substituted Pyridines with Aldehydes: A Theoretical Study. *J. Phys. Chem. A* **2023**, 127, 6081-6090.

7.1 Motivation of this work

In Chapter 6, we have discussed the modulation of the strength of an intramolecular $N\cdots C=O$ $n\rightarrow\pi^*$ interaction by varying the *para* substituent of an $n\rightarrow\pi^*$ donor group from the EDG to the EWG using quantum chemistry calculations. We have also shown that the $N\cdots C=O$ $n\rightarrow\pi^*$ interaction has similarity with the hydrogen bonding in terms of the folding of the flexible propanal side-chain of 3-[2-(dimethylamino) phenyl] propanal. Moreover, it is found that their destabilization temperature decreases with the weakening of the $n\rightarrow\pi^*$ interaction. However, reports on the modulation of the intermolecular $n\rightarrow\pi^*$ interaction are scarce. This chapter aims to study the intermolecular $n\rightarrow\pi^*$ interaction, which primarily stabilizes molecular complexes.

7.2 Introduction

Modulation of the strength of the $n\rightarrow\pi^*$ interaction can be monitored by IR and NMR spectroscopy as well as quantum chemistry calculations.^{45, 52, 62, 69} The redshift observed in the carbonyl stretching frequency involved in the $n\rightarrow\pi^*$ interaction determines its strength. However, due to its weak nature, IR spectroscopic studies in the solution and gas-phase are limited. Our group has reported gas-phase IR spectroscopic evidence of the $n\rightarrow\pi^*$ interaction in capped 4*R*-hydroxyproline and phenyl formate.^{92, 93} It should be noted here that the carbonyl stretching frequencies of the above-mentioned molecular systems are affected by the $n\rightarrow\pi^*$ interaction as well as hyperconjugation from nearby etheral oxygen. Although the hyperconjugation effects are present in both the conformers with and without the $n\rightarrow\pi^*$ interaction, those are not similar in magnitude. Hence, the hyperconjugation effects and $n\rightarrow\pi^*$ interaction together contribute to the redshift of the carbonyl stretching frequency in the conformer having the $n\rightarrow\pi^*$ interaction with respect to the one without the $n\rightarrow\pi^*$ interaction. Deb *et al.* have demonstrated the presence of the $n\rightarrow\pi^*$ interaction in the aqueous tetrahydrofuran (THF) solutions of phenyl formate using FTIR and 2D-IR spectroscopy techniques.¹⁴¹ Raines and co-workers studied various proline derivatives using IR and NMR spectroscopy to determine the $n\rightarrow\pi^*$ interaction.^{45, 90, 105, 107} They have reported a redshift in the ester carbonyl stretching frequency of the *exo* conformer compared to that of the *endo* conformer of 4-fluoro *N*-acetyl prolyl methyl ester.⁹⁰ The $E^{(2)}$ value of the $n\rightarrow\pi^*$ interaction in *exo* and *endo* conformers of 4-fluoro *N*-acetyl prolyl methyl ester was 10.88 and 0.67 kJ/mol, respectively.⁵² Sarma and co-workers studied $n_N(\text{amide})\rightarrow\pi^*(\text{aromatic})$ interaction in *N*-alkyl- *N*, *N'*-diacylhydrazines by substituting a series of EDGs to EWGs at the *para* position of the phenyl ring.⁵⁸ They observed a

systematic IR redshift in N–H stretching frequency, albeit of very small magnitude, for moving from EDGs to EWGs at the $n \rightarrow \pi^*$ acceptor site, i.e., increasing the acceptor ability of the aryl ring.

Spectroscopic studies of the intermolecular $n \rightarrow \pi^*$ interactions are further limited in the literature. Although there are reports of some microwave studies on the intermolecular $n \rightarrow \pi^*$ interaction, no such studies by IR spectroscopy have been delineated yet. Das and co-workers reported an indirect probe of the $n \rightarrow \pi^*$ interaction in 7-azaindole...2,6-fluoropyridines complexes by measuring the redshift in N–H stretching frequency, which is hydrogen-bonded and affected by the $n \rightarrow \pi^*$ interaction.⁴⁹ Pate and co-workers observed the $n \rightarrow \pi^*$ interaction in β -propiolactone...(H₂O)_{n=2,3} complexes using microwave spectroscopy.²³⁰ Later, Lopez and co-workers reported the observation of the $n \rightarrow \pi^*$ interaction in the complexes of pyridine with several aldehydes and ketones using microwave spectroscopy.¹³⁵⁻¹³⁷ From the viewpoint of quantum chemistry calculations, Das and co-workers reported the effect of substituents on the $n \rightarrow \pi^*$ interaction in 7-azaindole...2,6-fluoropyridines complexes by introducing the substituents on both donor and acceptor moieties.^{59, 125} Later, Sarma and co-workers investigated intermolecular C=O...C=O $n \rightarrow \pi^*$ interaction from computational and CSD studies.²³¹ In this chapter, we have discussed intermolecular N...C=O $n \rightarrow \pi^*$ interactions in the complexes of *p*-substituted pyridines (*p*-R-Py) with HCHO, HCOCl, and CH₃CHO using quantum chemistry calculations. Specifically, we have studied *p*-R-Py...S complexes, where R = –NMe₂, –NH₂, –OH, –H, –F, –Cl, –CF₃, –CN, and –NO₂ while S = HCHO, HCOCl, and CH₃CHO. The present investigation aims to have a systematic study on the modulation of the $n \rightarrow \pi^*$ interaction by varying the substituent from EDGs to EWGs at the $n \rightarrow \pi^*$ donor/acceptor sites. Most importantly, we have determined a correlation between the $n \rightarrow \pi^*$ interaction and theoretical redshift in the carbonyl stretching frequency for variation of a wide range of EDGs and EWGs at the donor/acceptor sites.

7.3 Results and Discussion

Various *p*-R-Py...S complexes calculated at the B3LYP-D3/def2-TZVP level (Figure 7.1) are studied to investigate the effect of electronic substitution (EDGs to EWGs) at the *para* position of the pyridine ring (donor site) on the $n \rightarrow \pi^*$ interaction (discussed in the first part of the chapter). Further, the effect of methyl (EDG) and chloro (EWG) substitution at the acceptor site (HCHO, HCOCl, and CH₃CHO) on the $n \rightarrow \pi^*$ interaction was also studied by keeping the

para substitution of the pyridine ring fixed (discussed in the second part of the chapter). Generally, the EDGs at the *para* position of the pyridine ring will push the electron density towards the nitrogen atom and strengthen the $n \rightarrow \pi^*$ interaction, while the interaction will be weaker with the EWGs. On the other hand, substituting one of the hydrogen atoms of the HCHO with the methyl group will populate the π^* orbital of the carbonyl group by pushing the electron density and making it less susceptible to the formation of the $n \rightarrow \pi^*$ interaction. However, the Cl substitution at the HCHO is interesting as it has both the -I and +I effects.

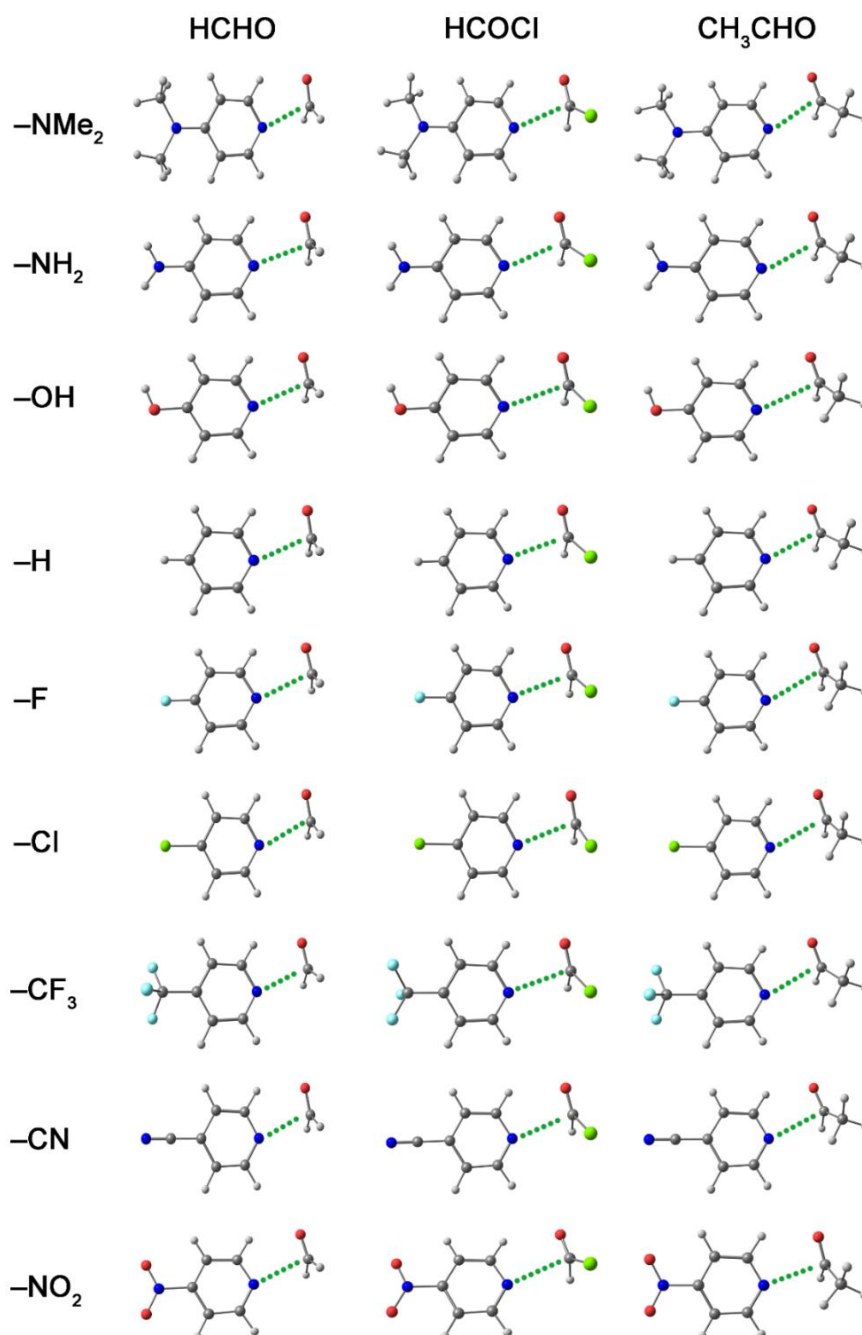


Figure 7.1. S_0 state optimized geometries (gas-phase) of p -R-Py $\cdots$ S complexes calculated at the B3LYP-D3/def2-TZVP level.

7.3.1 Electronic substitution at the *para* position of the pyridine ring ($n \rightarrow \pi^*$ donor site)

The strength of the $n \rightarrow \pi^*$ interaction depends on the Bürgi-Dunitz trajectory, i.e., distance (d) and $\angle N-C-O$ (θ) between the nitrogen atom and the carbonyl carbon. Figure 7.2a-c shows the plots of distance and angle versus Hammett values (σ_p) for p -R-Py $\cdots$ HCHO, p -R-Py $\cdots$ HCOCl, and p -R-Py $\cdots$ CH₃CHO complexes at the different DFT levels. It can be found that the d value is least for the strongest EDG and gradually increases linearly up to the maximum for the strongest EWG.

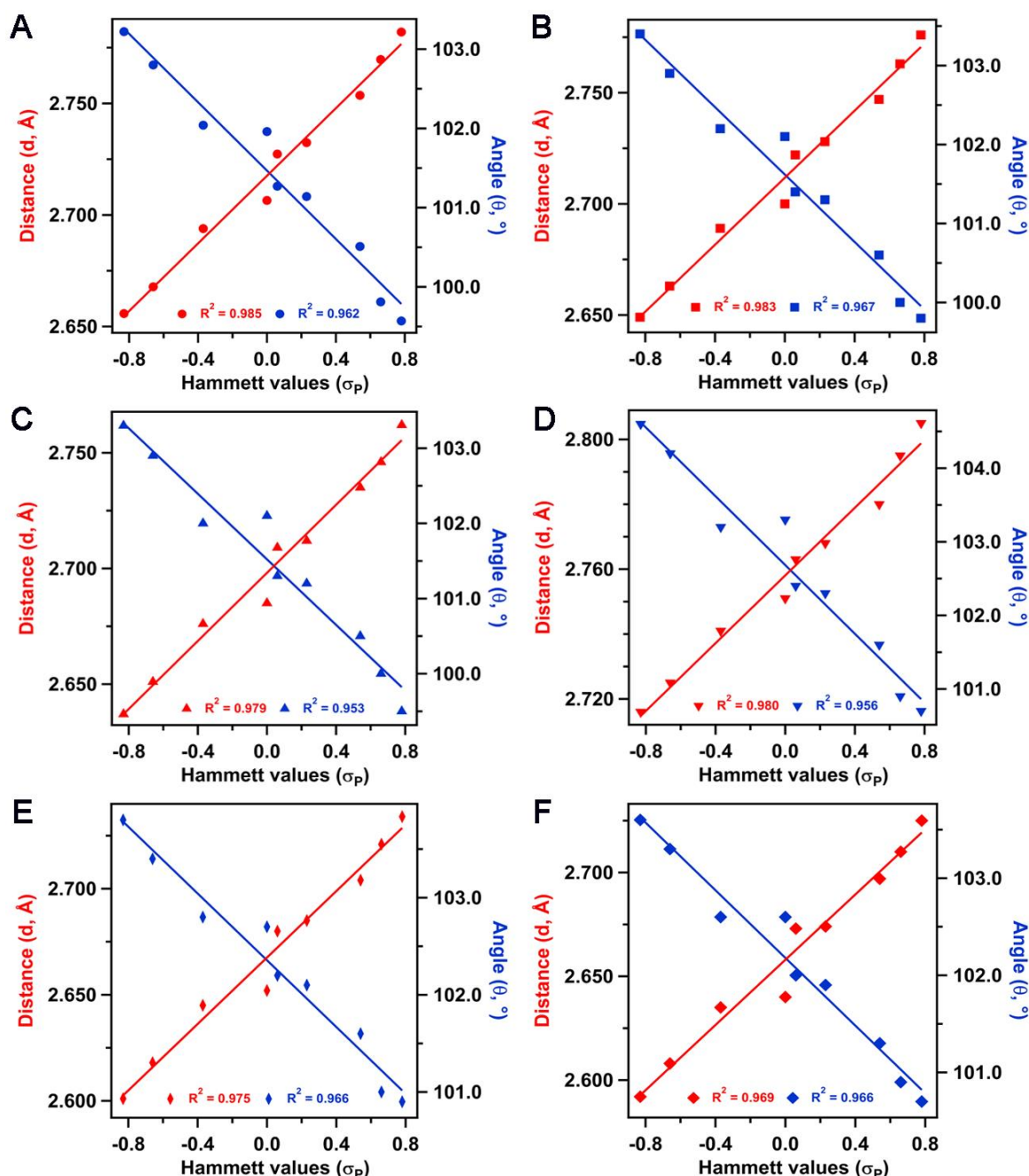


Figure 7.2a. Plots of distance (red trace) between the nitrogen atom and carbonyl carbon and $\angle N-C-O$ (blue trace) of p -R-Py $\cdots$ HCHO complexes versus Hammett values of the

substituents obtained from the S_0 state optimized geometries (gas-phase) at the **A)** B3LYP-D3/def2-TZVP; **B)** B3LYP-D3/aug-cc-pVTZ; **C)** B3LYP-D3/6-311++G(d,p); **D)** ω B97X-D/def2-TZVP; **E)** B97-D3/aug-cc-pVTZ; and **F)** B97-D3/6-311++G(d,p) levels.

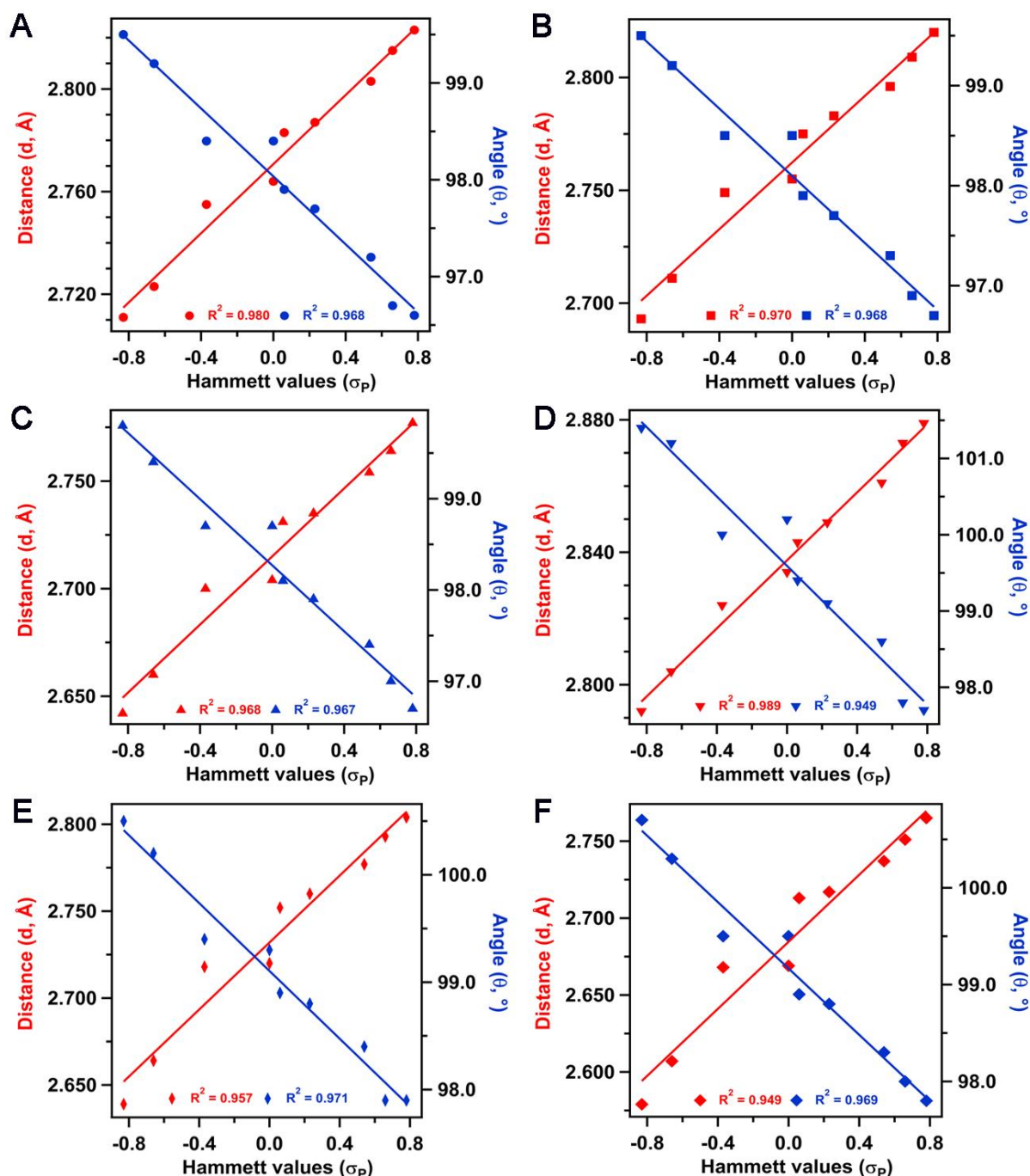


Figure 7.2b. Plots of distance (red trace) between the nitrogen atom and carbonyl carbon and $\angle$ N-C-O (blue trace) of p -R-Py...HCOCl complexes versus Hammett values of the substituents obtained from the S_0 state optimized geometries (gas-phase) at the **A)** B3LYP-D3/def2-TZVP; **B)** B3LYP-D3/aug-cc-pVTZ; **C)** B3LYP-D3/6-311++G(d,p); **D)** ω B97X-D/def2-TZVP; **E)** B97-D3/aug-cc-pVTZ; and **F)** B97-D3/6-311++G(d,p) levels.

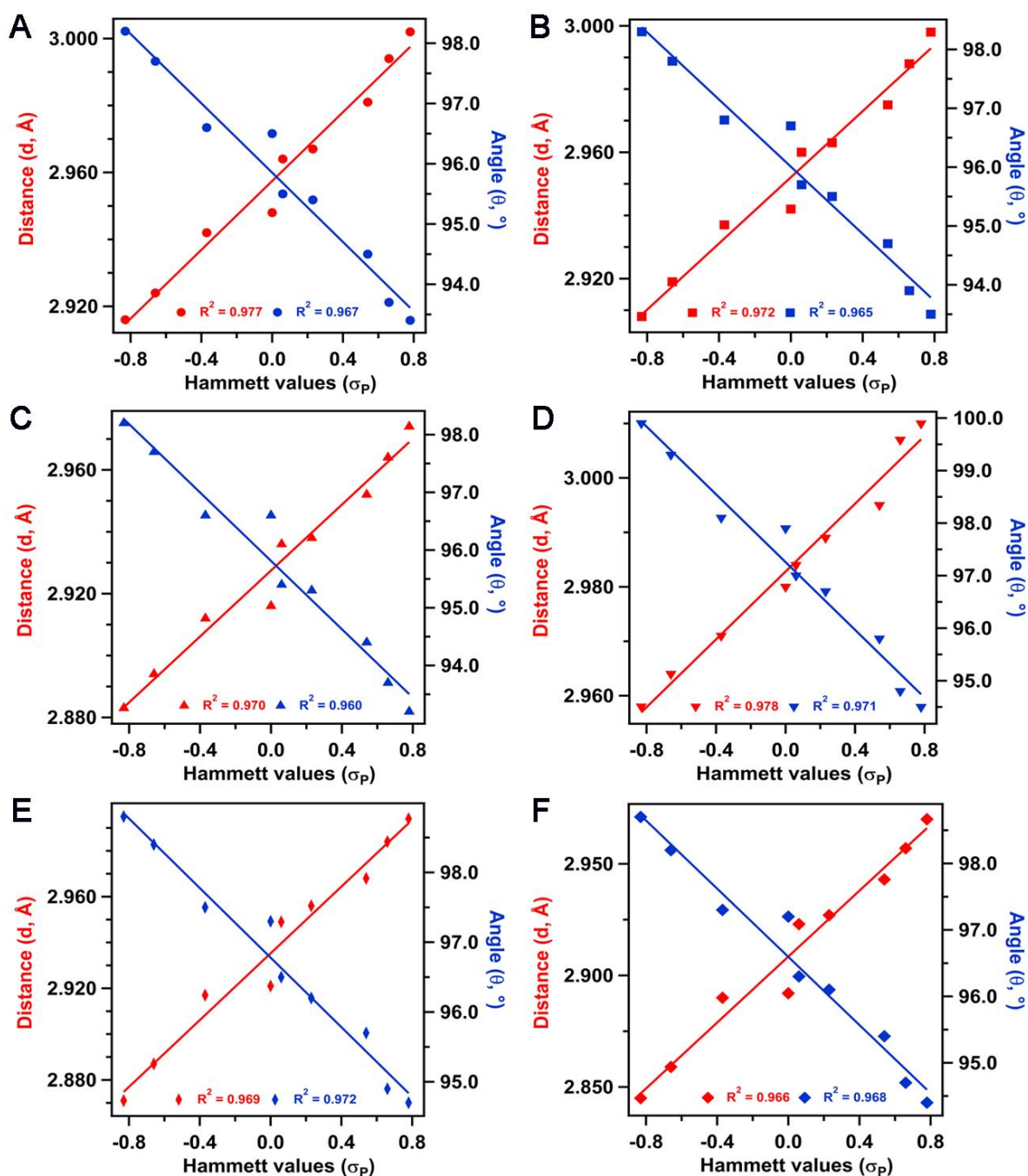


Figure 7.2c. Plots of distance (red trace) between the nitrogen atom and carbonyl carbon and $\angle$ N–C–O (blue trace) of p -R-Py...CH₃CHO complexes versus Hammett values of the substituents obtained from the S_0 state optimized geometries (gas-phase) at the **A**) B3LYP-D3/def2-TZVP; **B**) B3LYP-D3/aug-cc-pVTZ; **C**) B3LYP-D3/6-311++G(d,p); **D**) ω B97X-D/def2-TZVP; **E**) B97-D3/aug-cc-pVTZ; and **F**) B97-D3/6-311++G(d,p) levels.

Similarly, linear Hammett plots are observed for $\angle$ N–C–O, which decreases gradually from EDG to EWG, i.e., deviation of $\angle$ N–C–O from the Bürgi-Dunitz trajectory. It can be inferred that the strength of the $n \rightarrow \pi^*$ interaction in the p -R–

Py $\cdots$ HCHO, *p*-R-Py $\cdots$ HCOCl, and *p*-R-Py $\cdots$ CH₃CHO complexes decreases as we move from the EDGs to EWGs substitutions at the *para* position of the pyridine ring. The stability of an intermolecular complex depends on its binding energy, which arises from various types of intermolecular interactions binding the monomers together. Figure 7.3a-c shows that the ZPE and BSSE corrected binding energies (ΔE_0) of *p*-R-Py $\cdots$ HCHO, *p*-R-Py $\cdots$ HCOCl, and *p*-R-Py $\cdots$ CH₃CHO complexes calculated at the B3LYP-D3/def2-TZVP level decrease for moving from the EDGs to EWGs. The binding energy versus Hammett plot reveals that the intermolecular forces become weak as the *para* position of the pyridine ring is substituted by the EWGs.

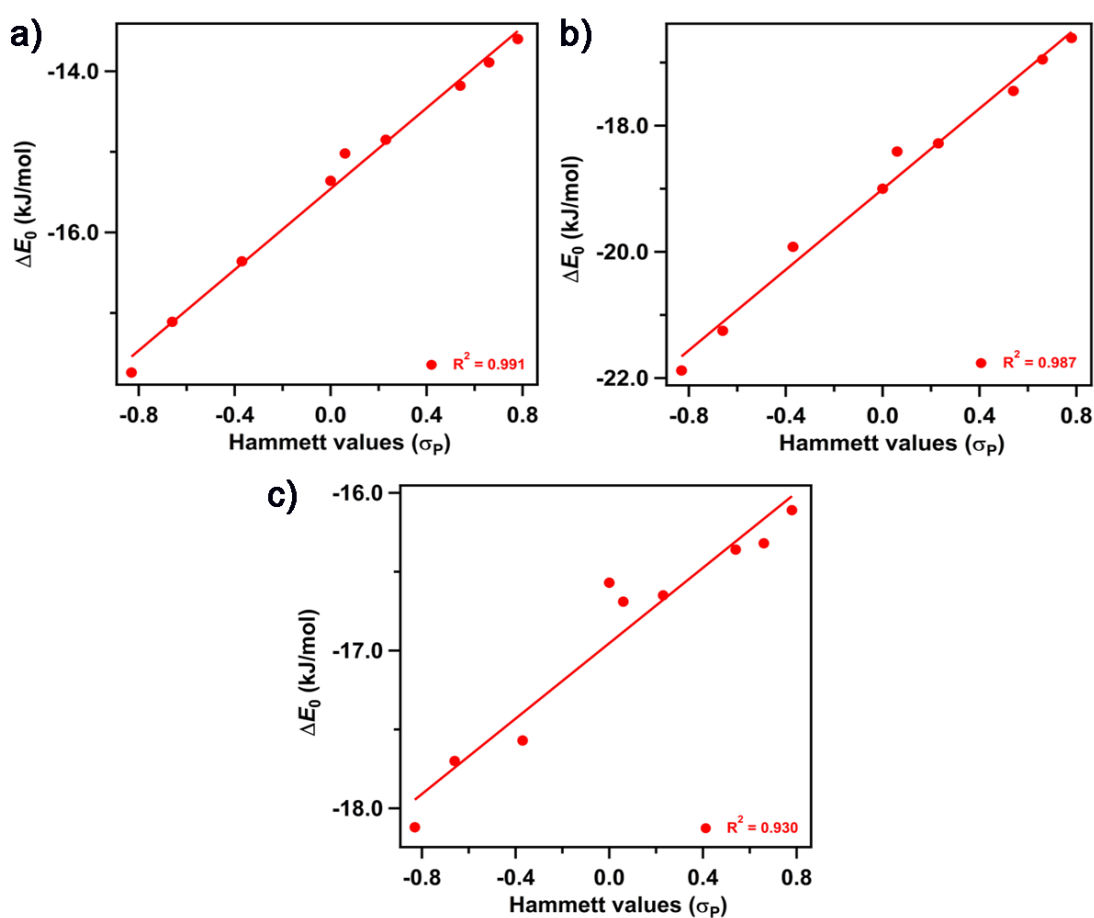


Figure 7.3. Plots of BSSE and ZPE corrected binding energy (ΔE_0 , kJ/mol) of a) *p*-R-Py $\cdots$ HCHO; b) *p*-R-Py $\cdots$ HCOCl; and c) *p*-R-Py $\cdots$ CH₃CHO complexes (gas-phase) against the Hammett values of the substituents calculated at the B3LYP-D3/def2-TZVP level.

In general, perturbation of the IR frequency of the functional group delineates the proof of the non-covalent interaction present in the molecular systems. In the case of the $n \rightarrow \pi^*$ interaction studied here, delocalization of the electron density results in the decrement of the bond order of the carbonyl group. Hence, a redshift in the carbonyl

stretching frequency ($\Delta\nu_{\text{C=O}}$) is observed in the $p\text{-R-Py}\cdots\text{S}$ complexes than in the S monomer. The decrease in the bond order of the carbonyl bond can be noticed from the decrease in WBI of the carbonyl bond, calculated from the NBO analysis. Figure 7.4a-c shows the plots of $\Delta\nu_{\text{C=O}}$ as well as WBI of $p\text{-R-Py}\cdots\text{HCHO}$, $p\text{-R-Py}\cdots\text{HCOCl}$, and $p\text{-R-Py}\cdots\text{CH}_3\text{CHO}$ complexes as a function of the σ_p of the substituents calculated at the B3LYP-D3/def2-TZVP level. It is found that $\Delta\nu_{\text{C=O}}$ values decrease for moving from EDGs to EWGs, and the corresponding WBI values increase. Thus, redshift and WBI values of the carbonyl group of the complexes demonstrate that the strength of the $n\rightarrow\pi^*$ interaction increases by changing the *para* substituent from EWGs to EDGs. The change in the strength of the $n\rightarrow\pi^*$ interaction with the variation of the *para* substituents on the pyridine ring is also reflected by the change in occupancy of the nitrogen lone pair orbital in the complexes with respect to the $p\text{-R-Py}$ monomer (ΔLP_N) and the occupancy of the $\pi^*_{\text{C=O}}$ orbital.

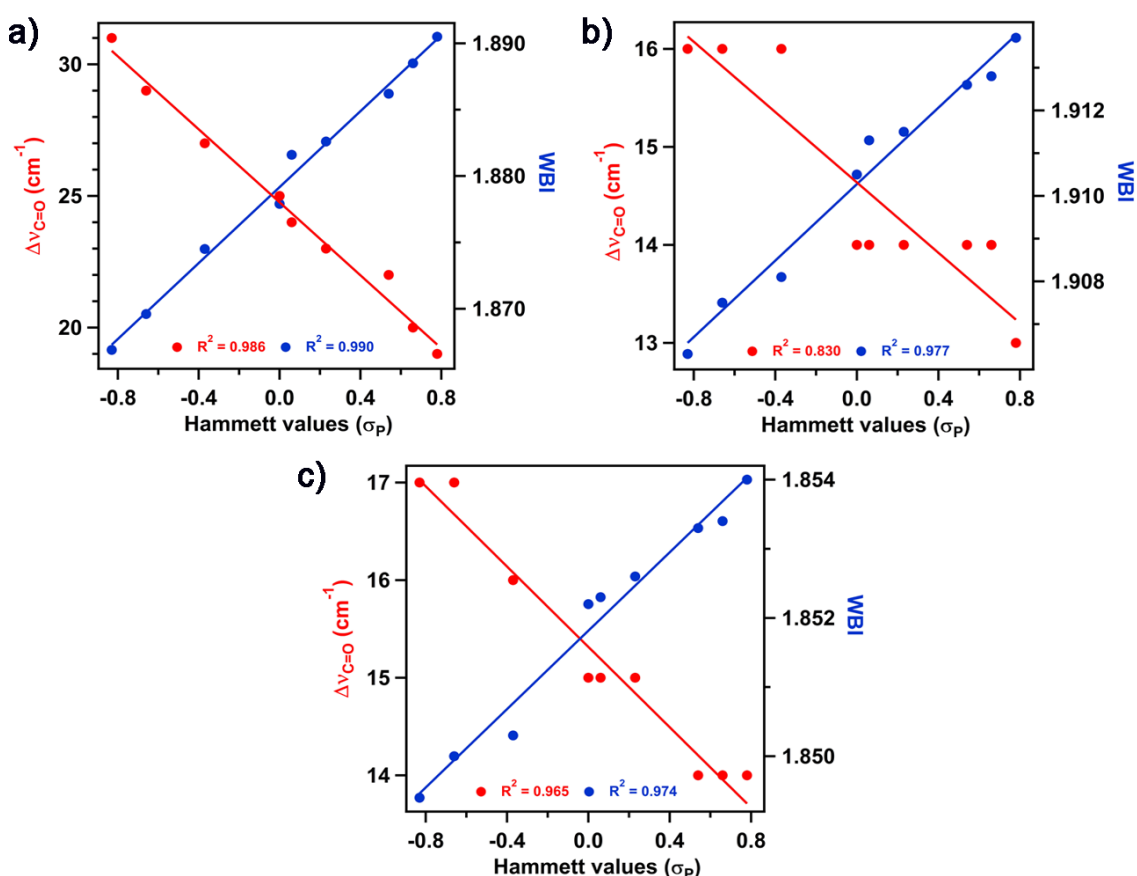


Figure 7.4. Plots of redshift ($\Delta\nu_{\text{C=O}}$, cm⁻¹) in carbonyl stretching frequency (red trace) and WBI (blue trace) of the carbonyl bond of a) $p\text{-R-Py}\cdots\text{HCHO}$; b) $p\text{-R-Py}\cdots\text{HCOCl}$; and c) $p\text{-R-Py}\cdots\text{CH}_3\text{CHO}$ complexes (gas-phase) versus Hammett values of the substituents calculated at the B3LYP-D3/def2-TZVP level.

It is worth mentioning here that the redshift observed in the carbonyl stretching frequencies of these complexes is due to the presence of the $n \rightarrow \pi^*$ interaction without having any interference due to the hyperconjugation from any neighboring oxygen or nitrogen atoms, which is present in the esters or amides, respectively. Hence, the observed change in the occupancy of the $\pi^*_{C=O}$ orbital should be due to the $n \rightarrow \pi^*$ interaction. The $\pi^*_{C=O}$ orbital occupancy is expected to be more for the EDGs and less for the EWGs substituted on the pyridine ring. Figure 7.5a-c shows linear plots for the occupancy of $\pi^*_{C=O}$ and ΔLP_N of the p -R-Py $\cdots$ HCHO, p -R-Py $\cdots$ HCOCl, and p -R-Py $\cdots$ CH₃CHO complexes calculated at the B3LYP-D3/def2-TZVP level as a function of the σ_p values. A systematic decrease of both $\pi^*_{C=O}$ orbital and ΔLP_N occupancies with the change of substituents from EDGs to EWGs correlates with the corresponding decrease in the strength of the $n \rightarrow \pi^*$ interaction in the p -R-Py $\cdots$ HCHO, p -R-Py $\cdots$ HCOCl, and p -R-Py $\cdots$ CH₃CHO complexes.

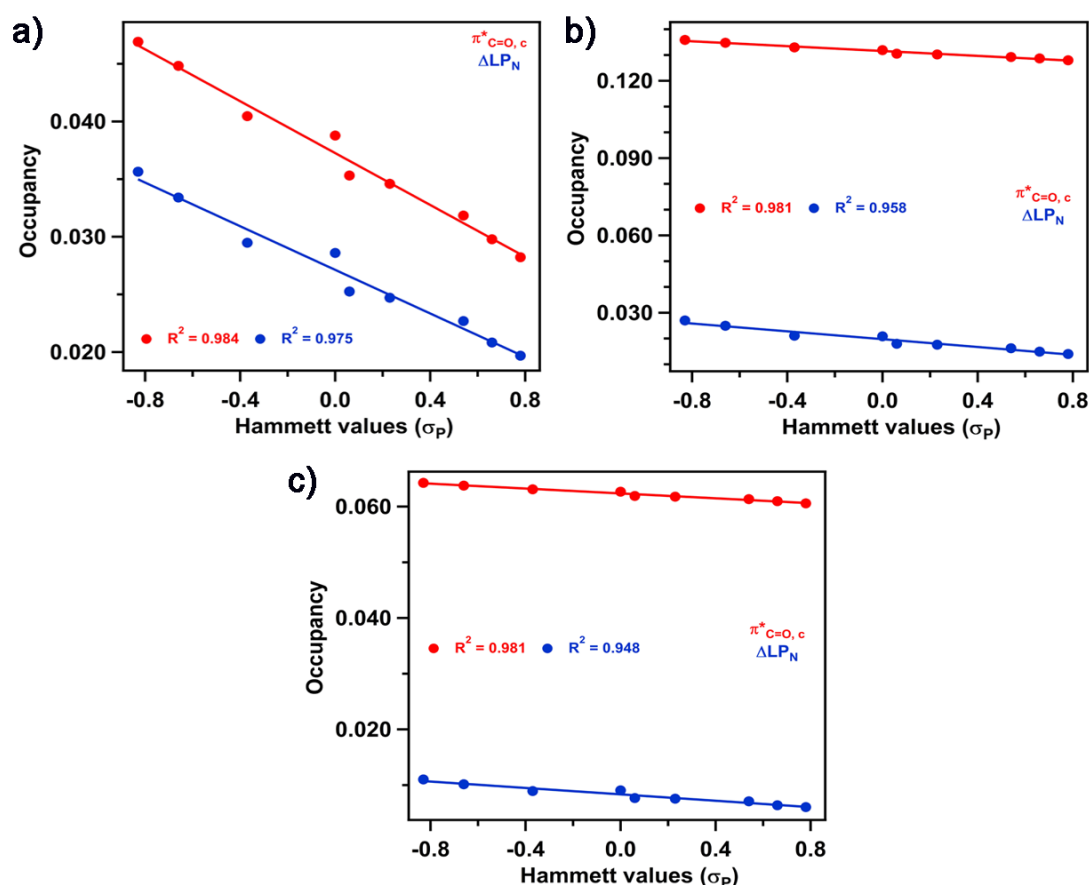


Figure 7.5. Plots of change in occupancy of the nitrogen atom (ΔLP_N) after the formation of the complex (blue trace) and π^* orbital of the carbonyl bond ($\pi^*_{C=O, c}$) (red trace) of a) p -R-Py $\cdots$ HCHO; b) p -R-Py $\cdots$ HCOCl; and c) p -R-Py $\cdots$ CH₃CHO complexes (gas-phase) versus Hammett values of the substituents calculated at the B3LYP-D3/def2-TZVP level.

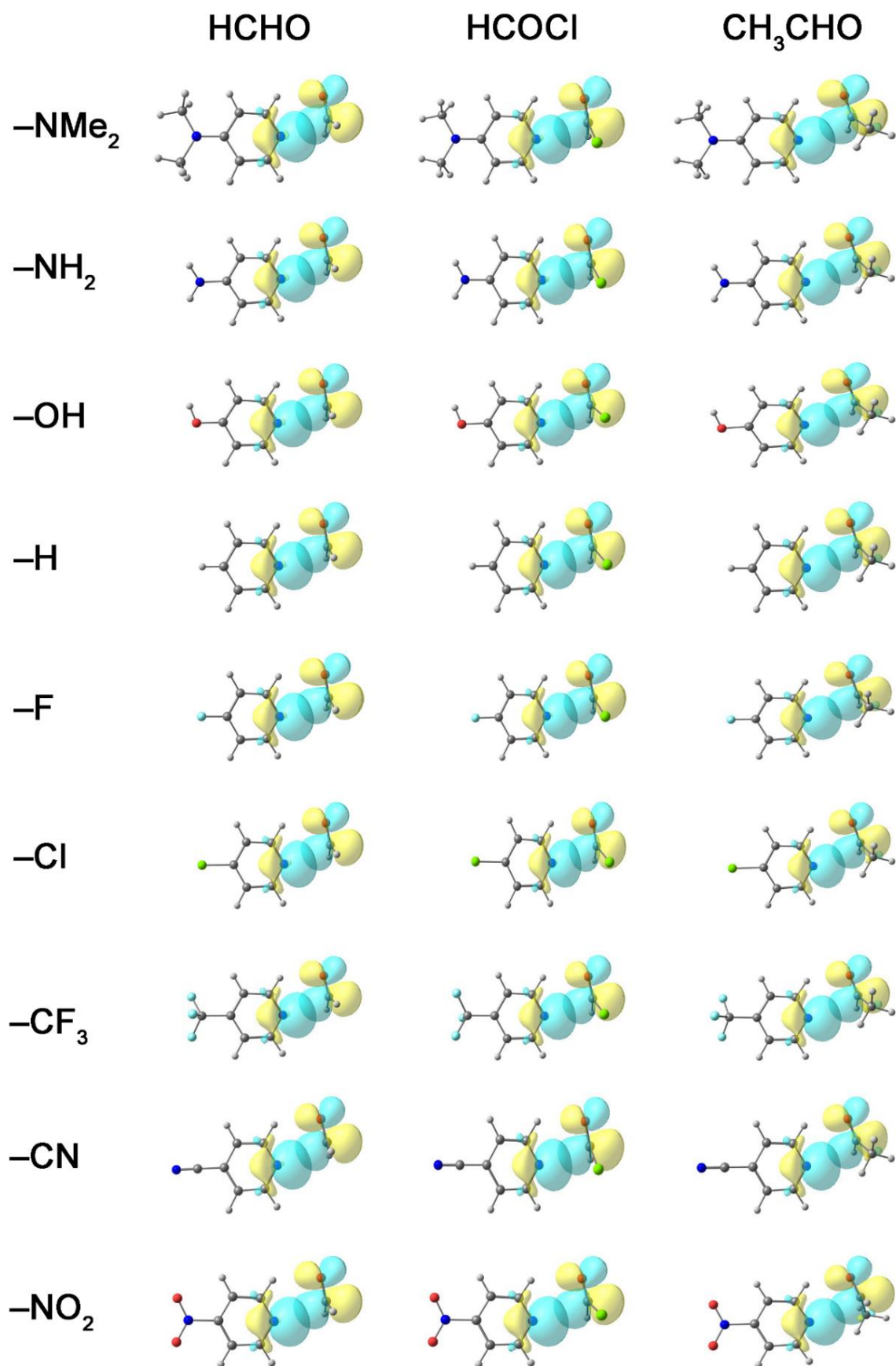


Figure 7.6. NBO orbital overlap for $n \rightarrow \pi^*$ interaction in various p -R-Py $\cdots$ S complexes (gas-phase) calculated at the B3LYP-D3/def2-TZVP level.

NBO analysis provides a qualitative understanding of the non-covalent interactions present in molecular systems. $E^{(2)}$ values (kJ/mol) obtained from the NBO analysis qualitatively represent the strength of the $n \rightarrow \pi^*$ interaction present in the p -R–Py $\cdots$ HCHO, p -R–Py $\cdots$ HCOCl, and p -R–Py $\cdots$ CH₃CHO complexes. The overlap of the NBO orbitals for the $n \rightarrow \pi^*$ interactions present in the p -R–Py $\cdots$ S complexes calculated at the B3LYP-D3/def2-TZVP level are shown in Figure 7.6. Figure 7.7a-c shows a linear relationship between the $E^{(2)}$ and σ_p values of the substituents in the p -R–Py $\cdots$ HCHO, p -R–Py $\cdots$ HCOCl, and p -R–Py $\cdots$ CH₃CHO complexes calculated at the different DFT level. The strength of the $n \rightarrow \pi^*$ interaction decreases systematically as we move from the EDGs to EWGs.

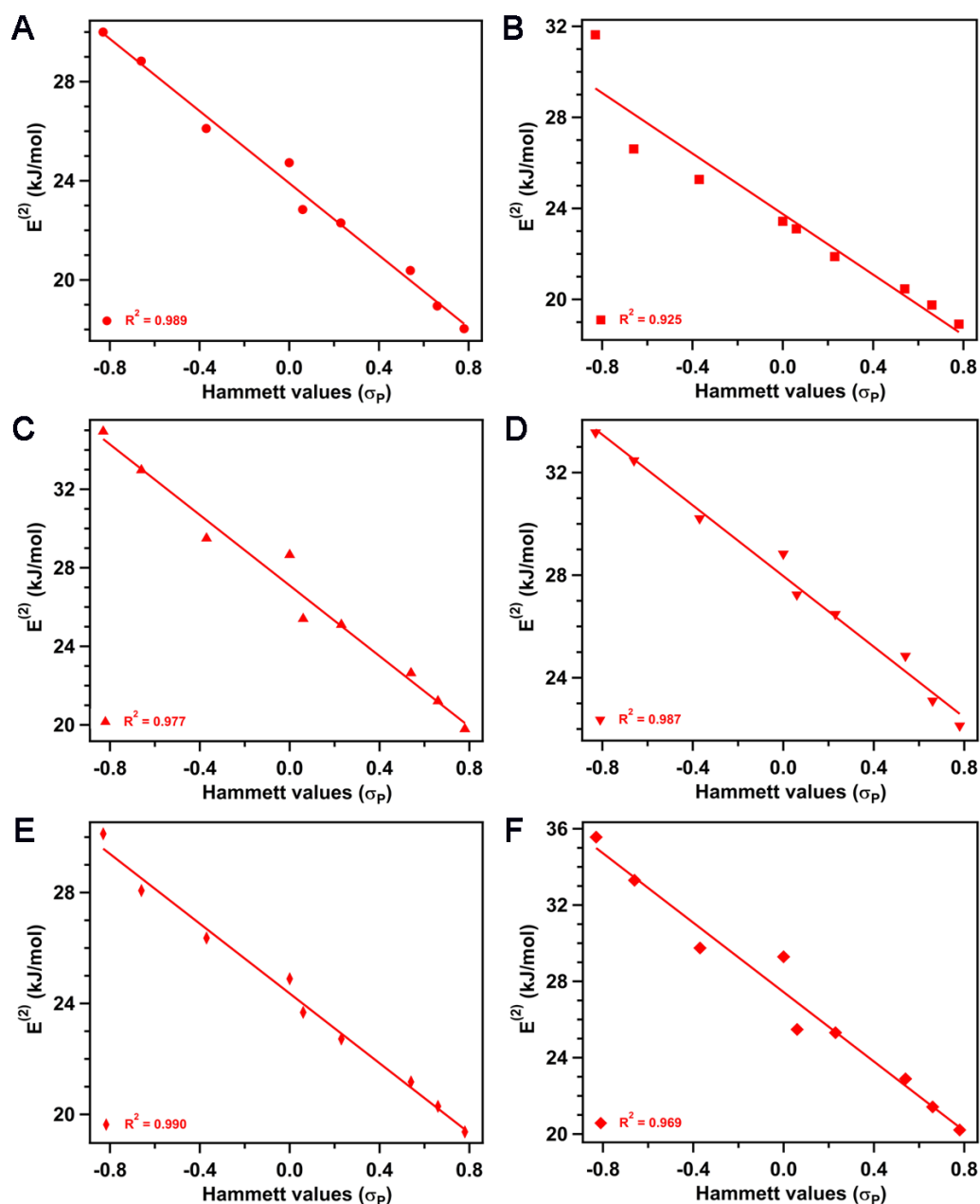


Figure 7.7a. Plots of $E^{(2)}$ values in kJ/mol of $n \rightarrow \pi^*$ interaction in various p -R-Py $\cdots$ HCHO complexes (gas-phase) versus Hammett values of the substituents calculated at the **A)** B3LYP-D3/def2-TZVP; **B)** B3LYP-D3/aug-cc-pVTZ; **C)** B3LYP-D3/6-311++G(d,p); **D)** ω B97X-D/def2-TZVP; **E)** B97-D3/aug-cc-pVTZ; and **F)** B97-D3/6-311++G(d,p) levels.

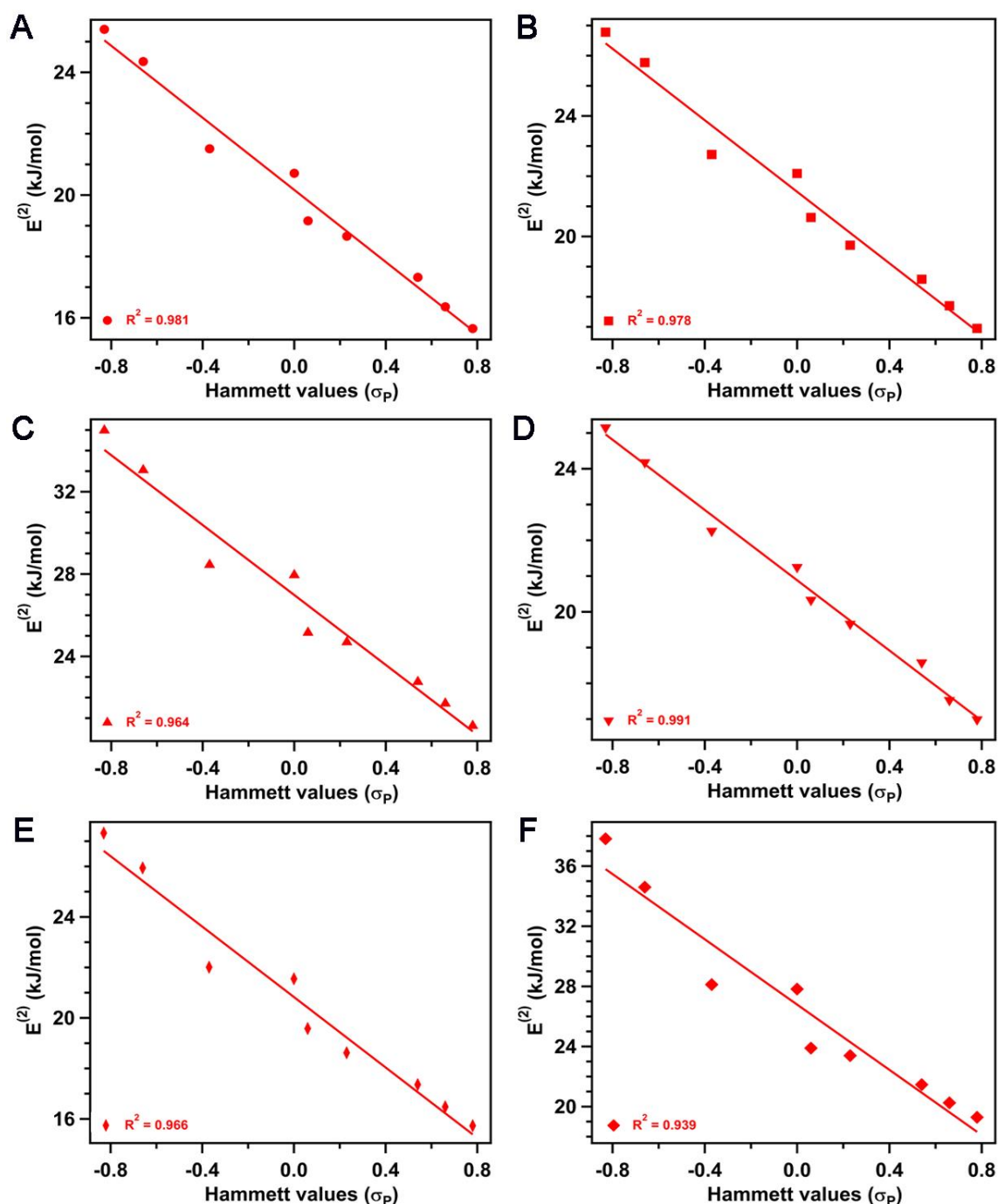


Figure 7.7b. Plots of $E^{(2)}$ values in kJ/mol of $n \rightarrow \pi^*$ interaction in various p -R-Py $\cdots$ HCOC1 complexes (gas-phase) versus Hammett values of the substituents calculated at the **A)** B3LYP-D3/def2-TZVP; **B)** B3LYP-D3/aug-cc-pVTZ; **C)** B3LYP-D3/6-311++G(d,p); **D)** ω B97X-D/def2-TZVP; **E)** B97-D3/aug-cc-pVTZ; and **F)** B97-D3/6-311++G(d,p) levels.

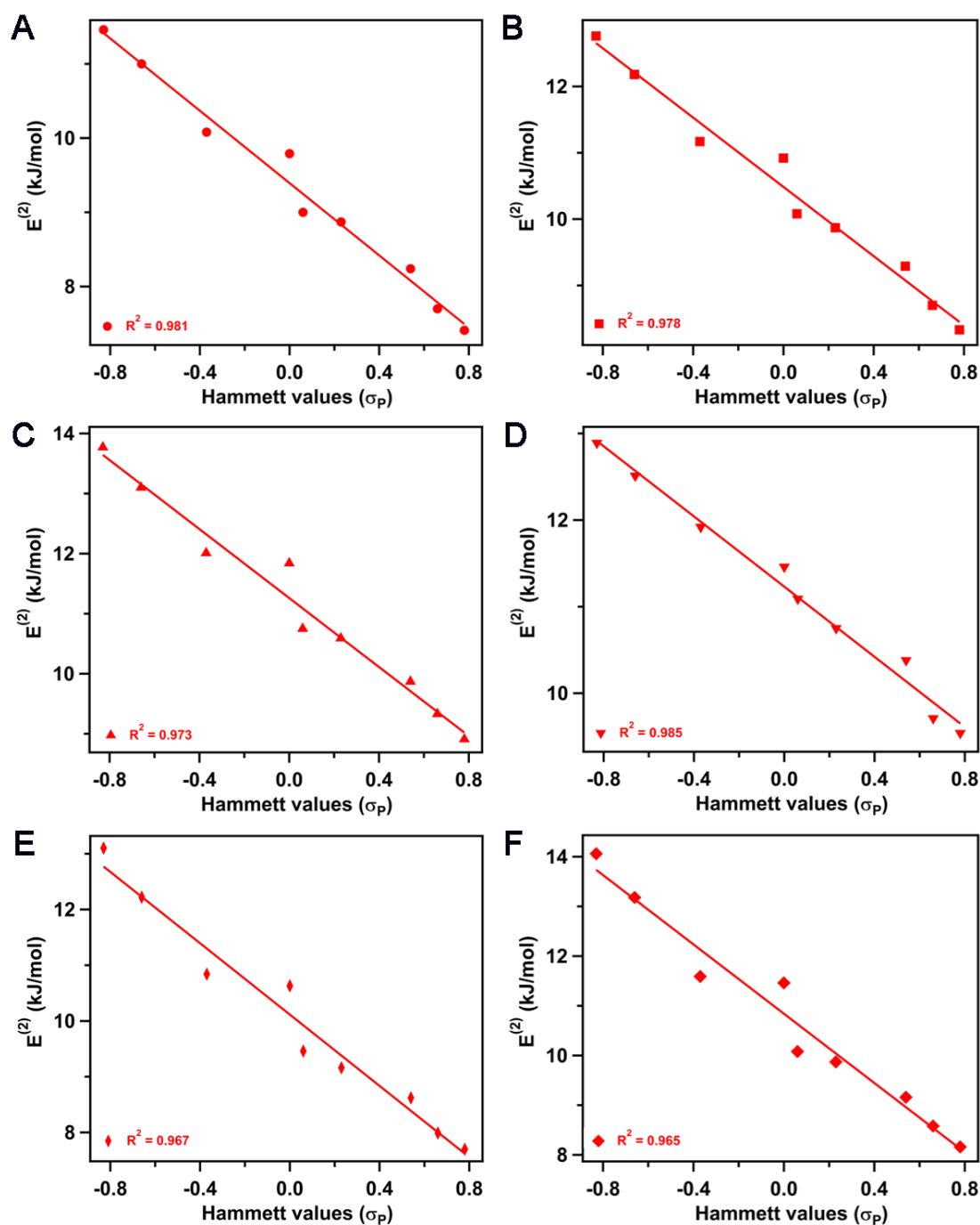


Figure 7.7c. Plots of $E^{(2)}$ values in kJ/mol of $n \rightarrow \pi^*$ interaction in various p -R-Py $\cdots$ CH₃CHO complexes (gas-phase) versus Hammett values of the substituents calculated at the **A**) B3LYP-D3/def2-TZVP; **B**) B3LYP-D3/aug-cc-pVTZ; **C**) B3LYP-D3/6-311++G(d,p); **D**) ω B97X-D/def2-TZVP; **E**) B97-D3/aug-cc-pVTZ; and **F**) B97-D3/6-311++G(d,p) levels.

Furthermore, a linear fit is obtained when the binding energies (ΔE_0) and $\Delta \nu_{C=O}$ of the p -R-Py $\cdots$ HCHO, p -R-Py $\cdots$ HCOC1, and p -R-Py $\cdots$ CH₃CHO complexes are plotted as a function of their $E^{(2)}$ values calculated at the B3LYP-D3/def2-TZVP level (Figure 7.8).

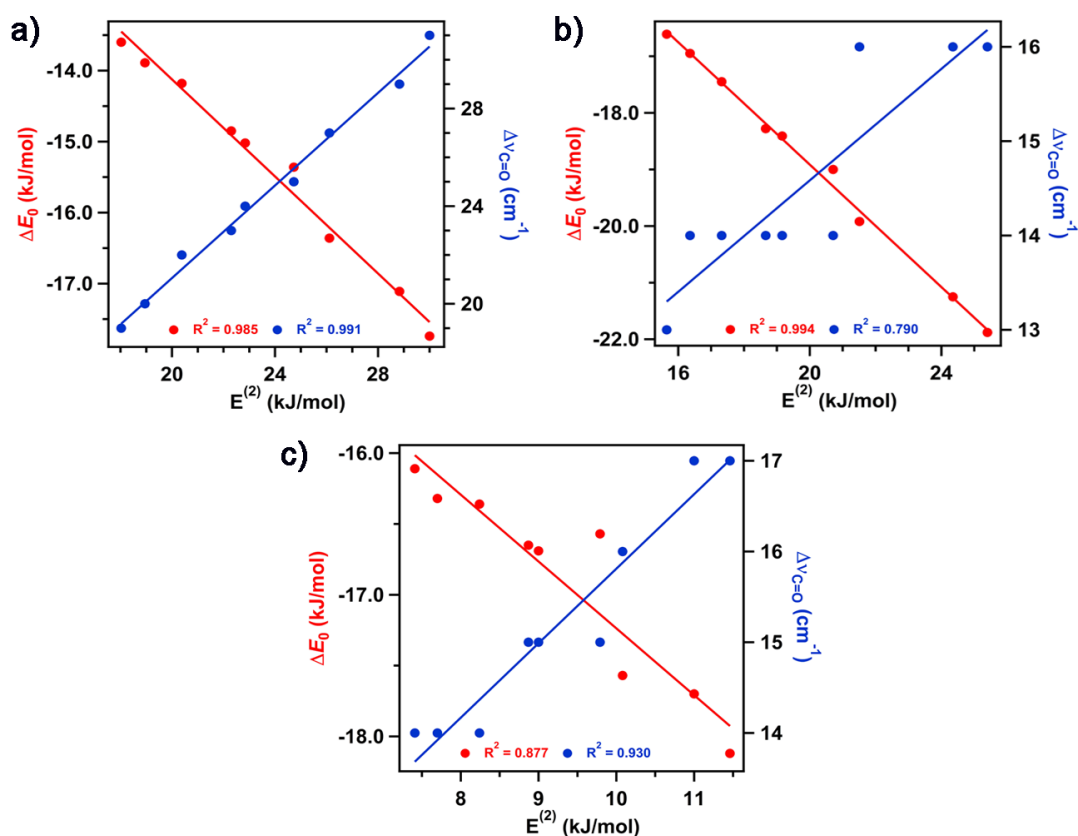


Figure 7.8. Plots of ΔE_0 (kJ/mol) values (red trace) and $\Delta \nu_{C=O}$ (blue trace) of a) *p*-R-Py...HCHO; b) *p*-R-Py...HCOCl; and c) *p*-R-Py...CH₃CHO complexes (gas-phase) versus $E^{(2)}$ (kJ/mol) values of $n \rightarrow \pi^*$ interaction calculated at the B3LYP-D3/def2-TZVP level.

Linear plots of the $\Delta \nu_{C=O}$ values, as well as the $E^{(2)}$ values of *p*-R-Py...HCHO, *p*-R-Py...HCOCl, and *p*-R-Py...CH₃CHO complexes with respect to the occupancy of the $\pi^*_{C=O}$ orbital calculated at the B3LYP-D3/def2-TZVP level, also point out a clear correlation between the strength of the $n \rightarrow \pi^*$ interaction and the redshift of the carbonyl stretching frequency (Figure 7.9). Thus, the $n \rightarrow \pi^*$ interaction is found to have an undeniable role in the stability of various *p*-R-Py...S complexes. The NBO deletion analysis also confirms the presence of the $n \rightarrow \pi^*$ interaction in the *p*-R-Py...S complexes. It is found that the occupancy of the $\pi^*_{C=O}$ orbital decreases after the deletion of $n \rightarrow \pi^*$ interaction. Moreover, the occupancy of the $\pi^*_{C=O}$ orbital after the deletion of the $n \rightarrow \pi^*$ interaction ($\pi^*_{C=O, d}$ occupancy) matches with that of the aldehyde monomer. Figure 7.10 shows that the $\pi^*_{C=O, d}$ occupancy in the *p*-R-Py...HCHO, *p*-R-Py...HCOCl, and *p*-R-Py...CH₃CHO complexes calculated at the B3LYP-D3/def2-TZVP level remains same with the change in the substituents on the pyridine ring. This finding reconfirms that the change in occupancy of the $\pi^*_{C=O}$ orbital in these complexes is only due to the $n \rightarrow \pi^*$ interaction.

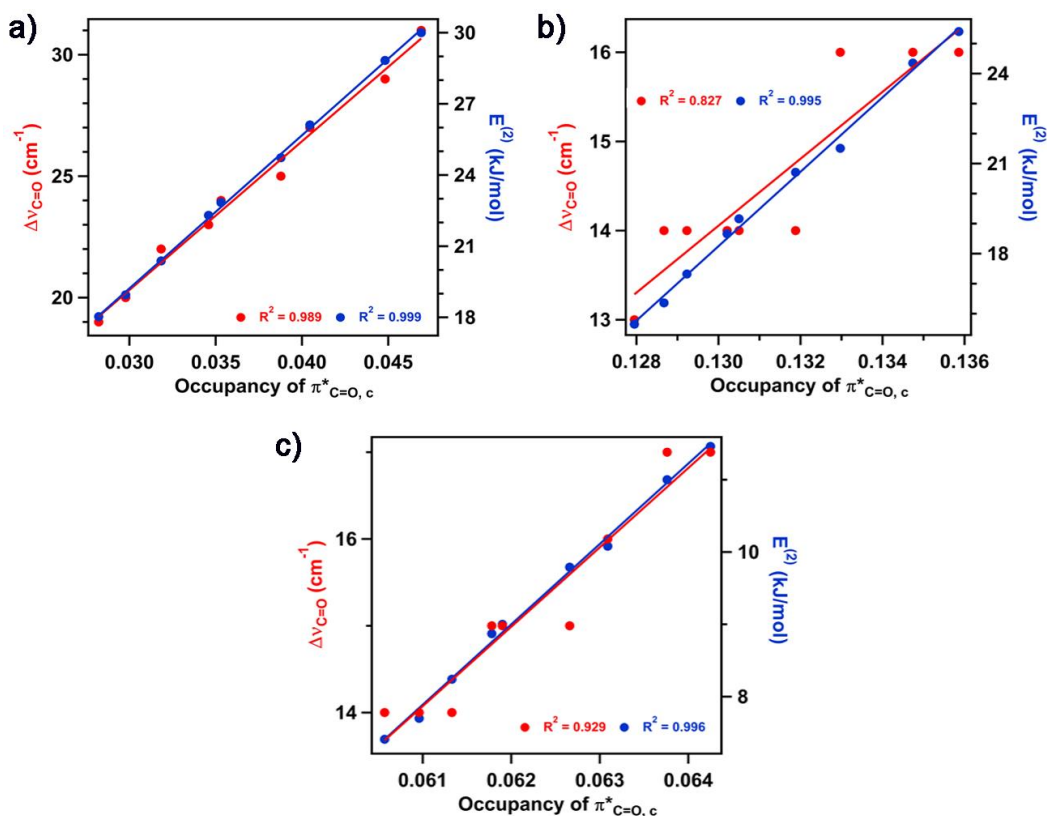


Figure 7.9. Plots of $\Delta\nu_{C=O}$ (red trace) and $E^{(2)}$ (kJ/mol) values of $n \rightarrow \pi^*$ interaction (blue trace) versus occupancy of π^* orbital of the carbonyl bond of a) p -R-Py $\cdots$ HCHO; b) p -R-Py $\cdots$ HCOC1; and c) p -R-Py $\cdots$ CH₃CHO complexes (gas-phase) calculated at the B3LYP-D3/def2-TZVP level.

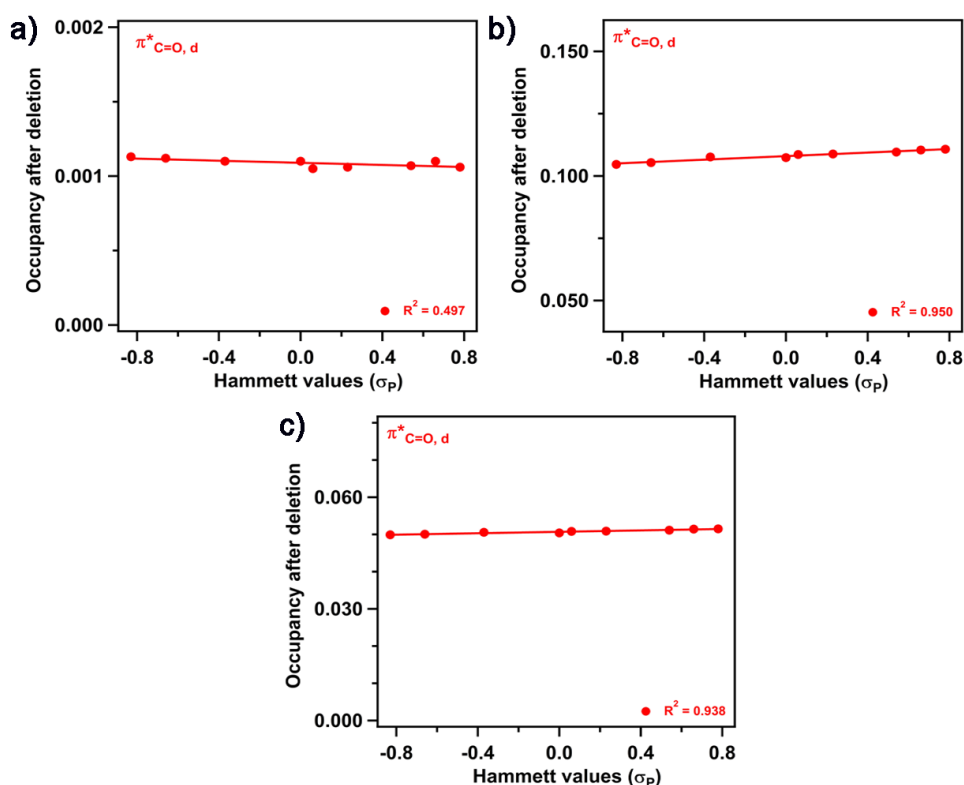


Figure 7.10. Plots of the occupancy of π^* orbital of the carbonyl bond of a) p -R-Py $\cdots$ HCHO; b) p -R-Py $\cdots$ HCOCl; and c) p -R-Py $\cdots$ CH₃CHO complexes (gas-phase) after deletion of the $n \rightarrow \pi^*$ interaction from these complexes versus Hammett values of the substituents calculated at the B3LYP-D3/def2-TZVP level.

QTAIM analysis generates the BCPs for the $n \rightarrow \pi^*$ interactions present in p -R-Py $\cdots$ S complexes. As the interaction becomes weaker with the change of the substitution from the EDGs to the EWGs on the pyridine ring of p -R-Py $\cdots$ HCHO, p -R-Py $\cdots$ HCOCl, and p -R-Py $\cdots$ CH₃CHO complexes, the $\rho(r)$ and $\nabla^2\rho(r)$ values decrease at the BCP of the $n \rightarrow \pi^*$ interaction (Figure 7.11) calculated at the B3LYP-D3/def2-TZVP level. QTAIM molecular graphs of p -R-Py $\cdots$ S complexes calculated at the B3LYP-D3/def2-TZVP level depicting the BCP of $n \rightarrow \pi^*$ interaction are shown in Figure 7.12. NCI RDG versus $\text{Sign}(\lambda_2)\rho(r)$ plot (Figure 7.13) and NCI isosurface plot (Figure 7.14) calculated at the B3LYP-D3/def2-TZVP level also reveal the strength of $n \rightarrow \pi^*$ interaction for different substituents in the p -R-Py $\cdots$ S complexes.

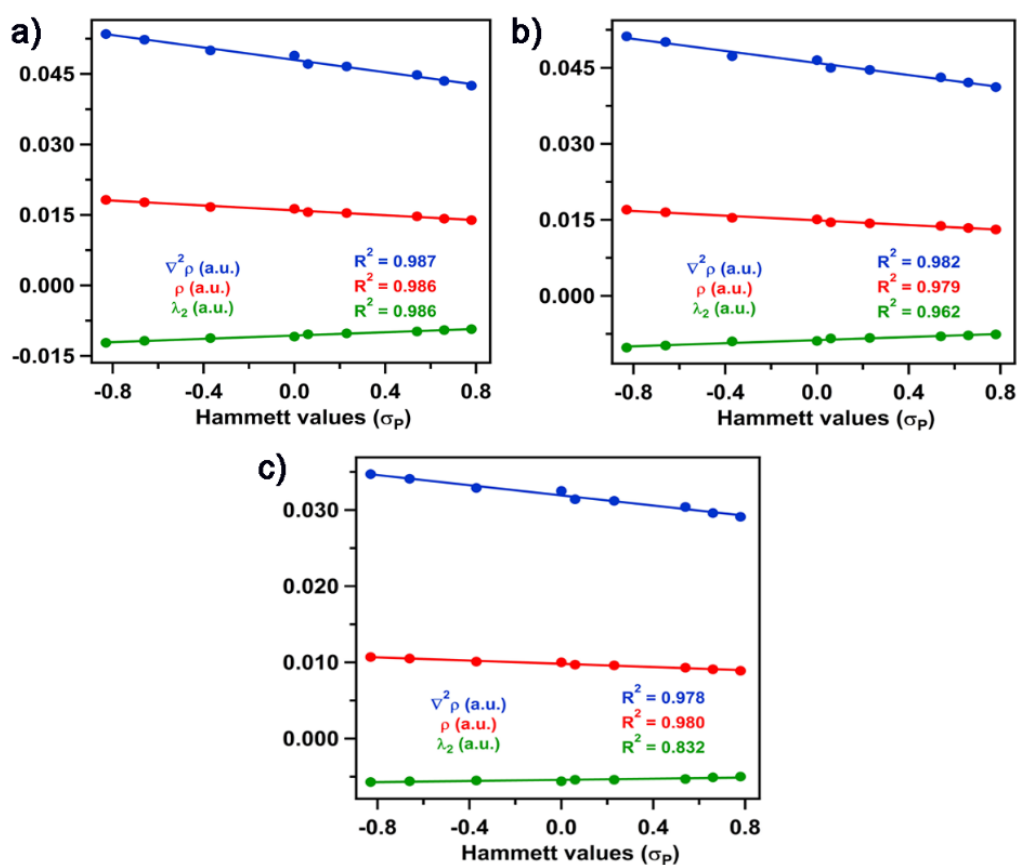


Figure 7.11. Plots of AIM parameters of various a) p -R-Py $\cdots$ HCHO; b) p -R-Py $\cdots$ HCOCl; and c) p -R-Py $\cdots$ CH₃CHO complexes (gas-phase) at the BCP of $n \rightarrow \pi^*$ interaction versus Hammett values of the substituents calculated at the B3LYP-D3/def2-TZVP level.

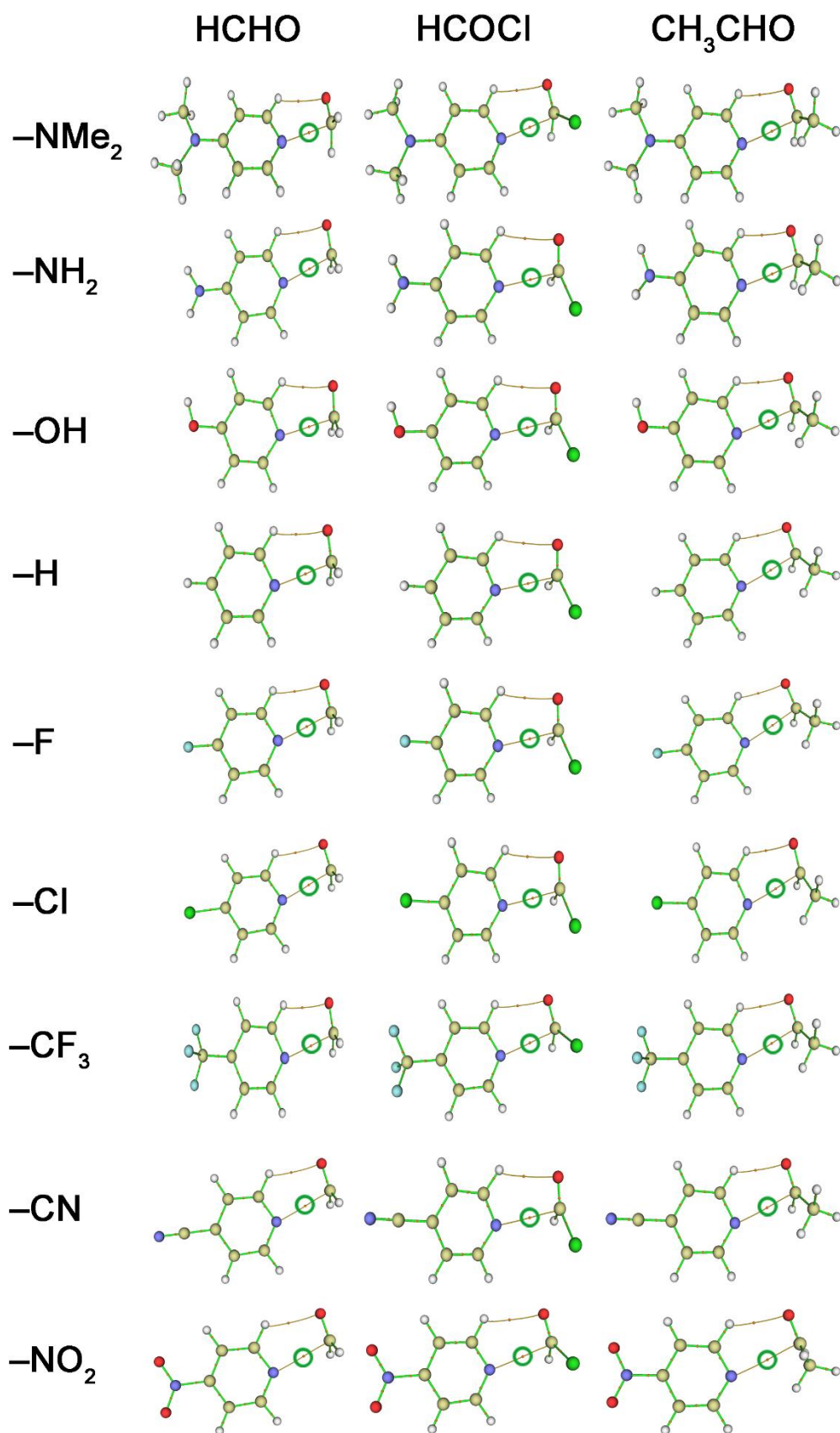


Figure 7.12. AIM molecular graphs of various *p*-R-Py...S complexes (gas-phase), representing BCPs for N...C=O $n \rightarrow \pi^*$ interaction marked with green circles calculated at the B3LYP-D3/def2-TZVP level.

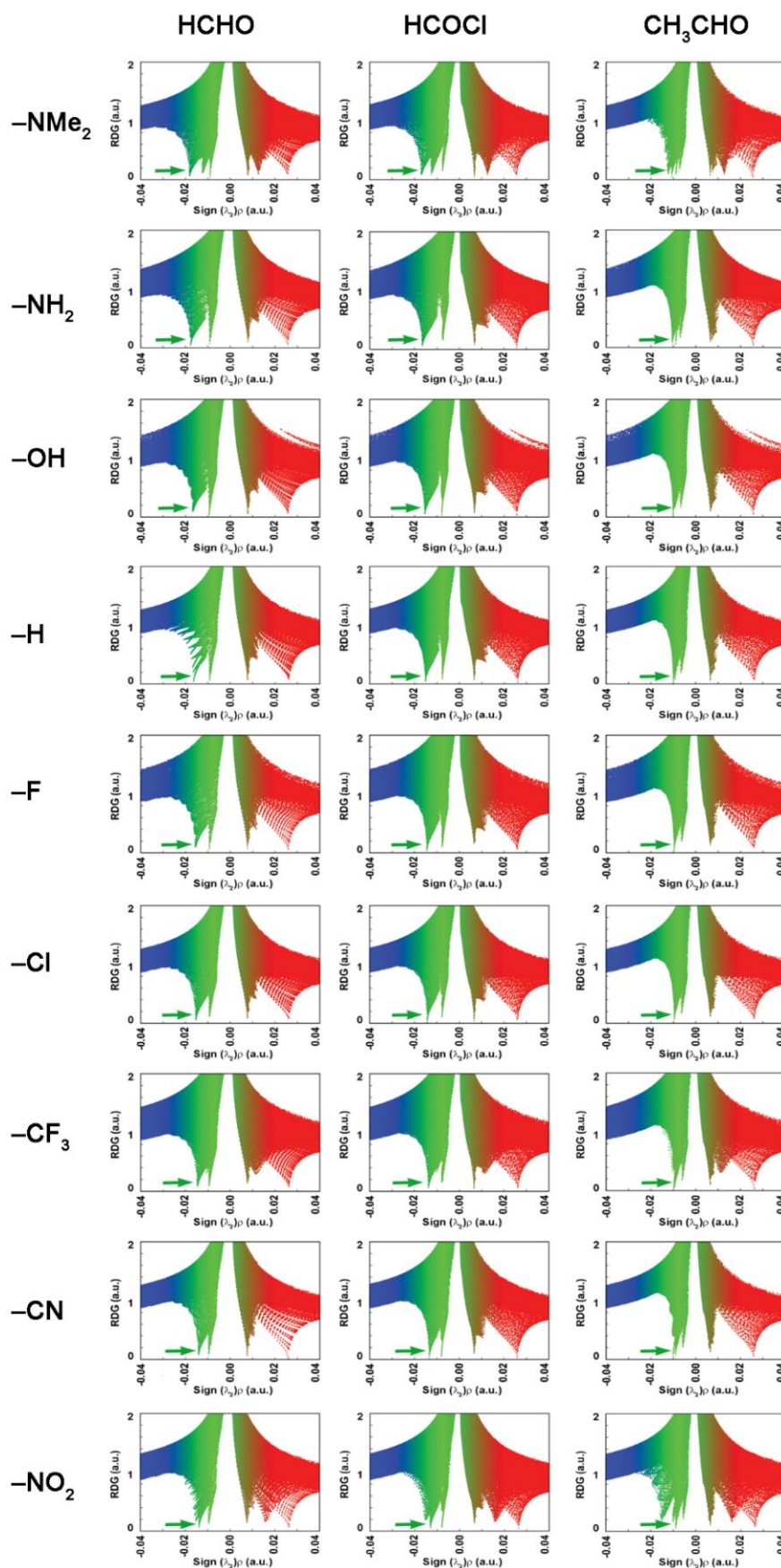


Figure 7.13. NCI RDG plots of various *p*-R-Py...S complexes (gas-phase) with minima corresponding to $n \rightarrow \pi^*$ interaction shown by the green arrow calculated at the B3LYP-

D3/def2-TZVP level. The RDG follows a blue-green-red color scheme over the $-0.04 < \text{Sign}(\lambda_2)\rho < 0.04$, where blue, green, and red colors denote very strong attraction, weak attraction, and strong repulsion, respectively.

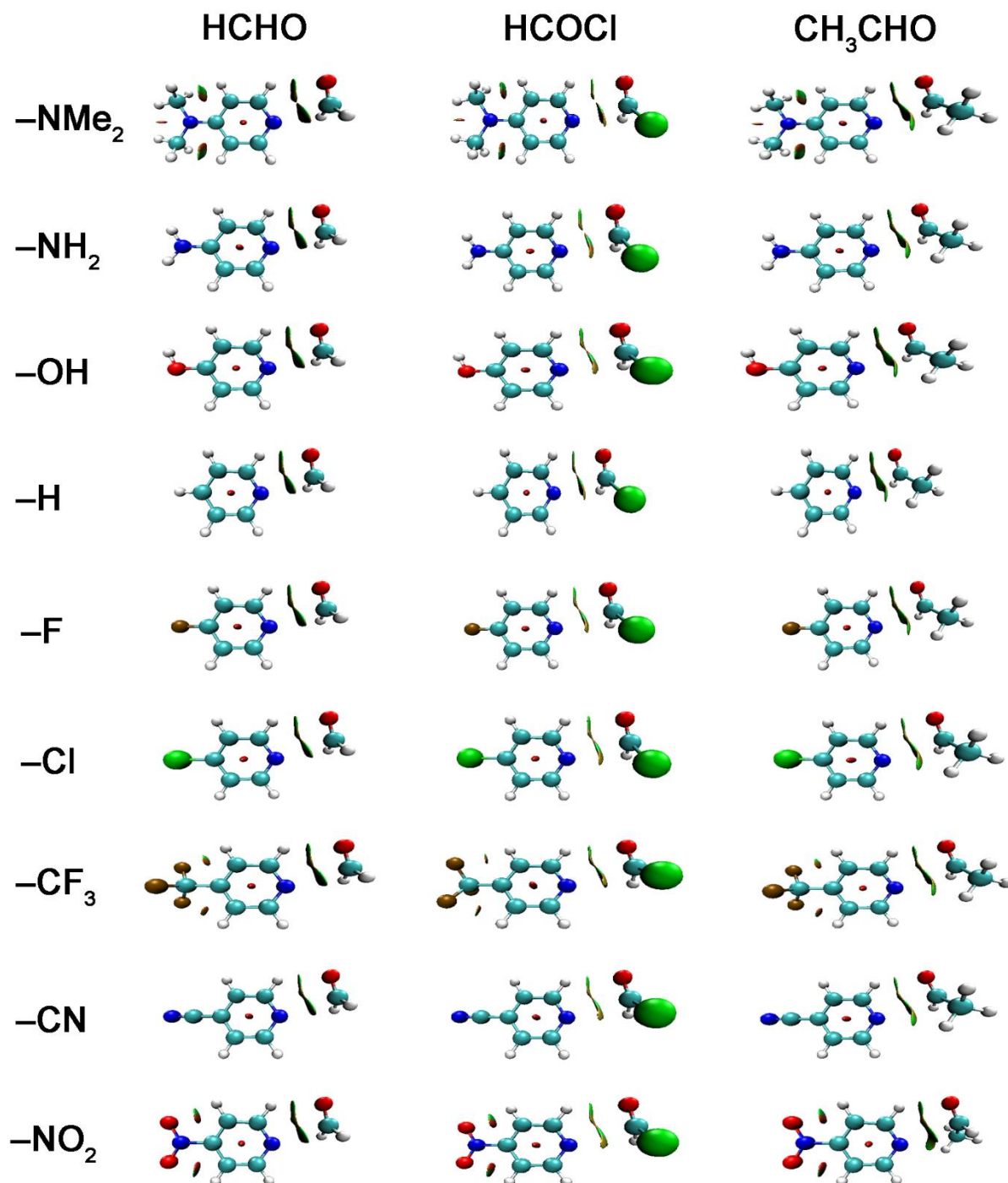


Figure 7.14. NCI isosurface plots of various *p*-R-Py...S complexes (gas-phase) calculated at the B3LYP-D3/def2-TZVP level. The gradient isosurface follows a blue-green-red color scheme over the $-0.04 < \text{Sign}(\lambda_2)\rho < 0.04$, where blue, green, and red colors denote strong attraction, weak attraction, and strong repulsion, respectively.

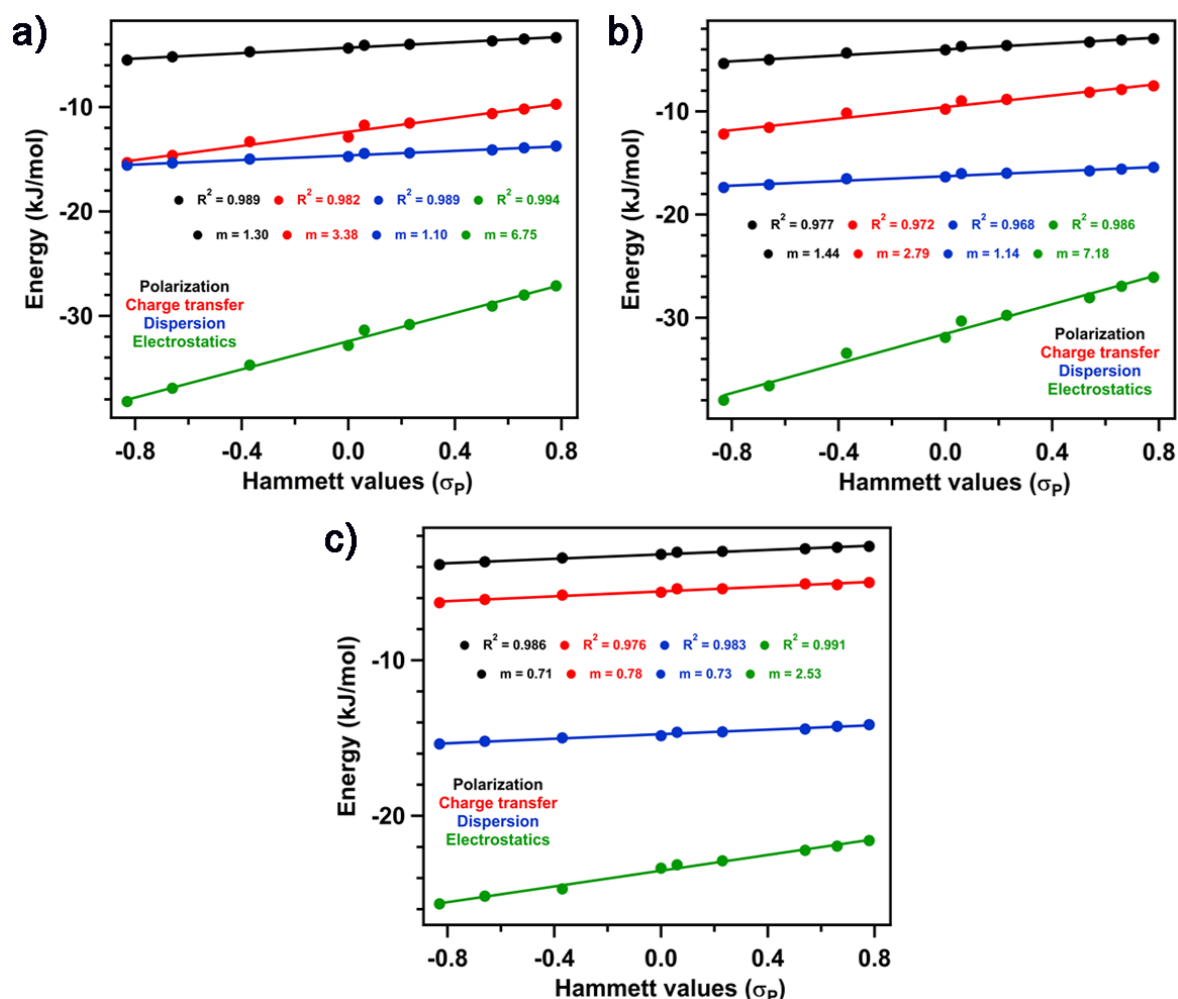


Figure 7.15. Plots of polarization (black trace), charge transfer (red trace), dispersion (blue trace), and electrostatics (green trace) components (kJ/mol) of total interaction energy with the slopes (m) of linear plots of various a) p -R-Py $\cdots$ HCHO; b) p -R-Py $\cdots$ HCOCl; and c) p -R-Py $\cdots$ CH₃CHO complexes (gas-phase) obtained from ALMO-EDA analysis versus Hammett values of the substituents calculated at the B3LYP-D3/def2-TZVP level.

ALMO-EDA calculation has been performed to determine the different components of the interaction energies contributing to stabilizing the p -R-Py $\cdots$ S complexes. This EDA method fragments the binding energy into several components, such as electrostatics (ES), Pauli repulsion (REP), dispersion (DISP), polarization (POL), and charge transfer (CT). Figure 7.15 shows the plots of ES, DISP, POL, and CT components of the binding energies of the p -R-Py $\cdots$ HCHO, p -R-Py $\cdots$ HCOCl, and p -R-Py $\cdots$ CH₃CHO complexes calculated at the B3LYP-D3/def2-TZVP level as a function of the σ_p values of the substituents. It is found that the ES is the major component of the binding energies of these complexes. However, the contribution of the CT and DISP interactions to stabilizing these complexes cannot be ignored.

Although the POL component is much smaller than the other components, it varies systematically with the σ_p of the substituents. It is intriguing to note that the slopes (m) of the four linear plots are in the order of $ES > CT > POL > DISP$. Thus, ES is not only the major component of the binding energies of these complexes but also is decreasing steeply for moving from the EDGs to the EWGs. However, the decrease in the CT and DISP components with the change in the substituents is very slow.

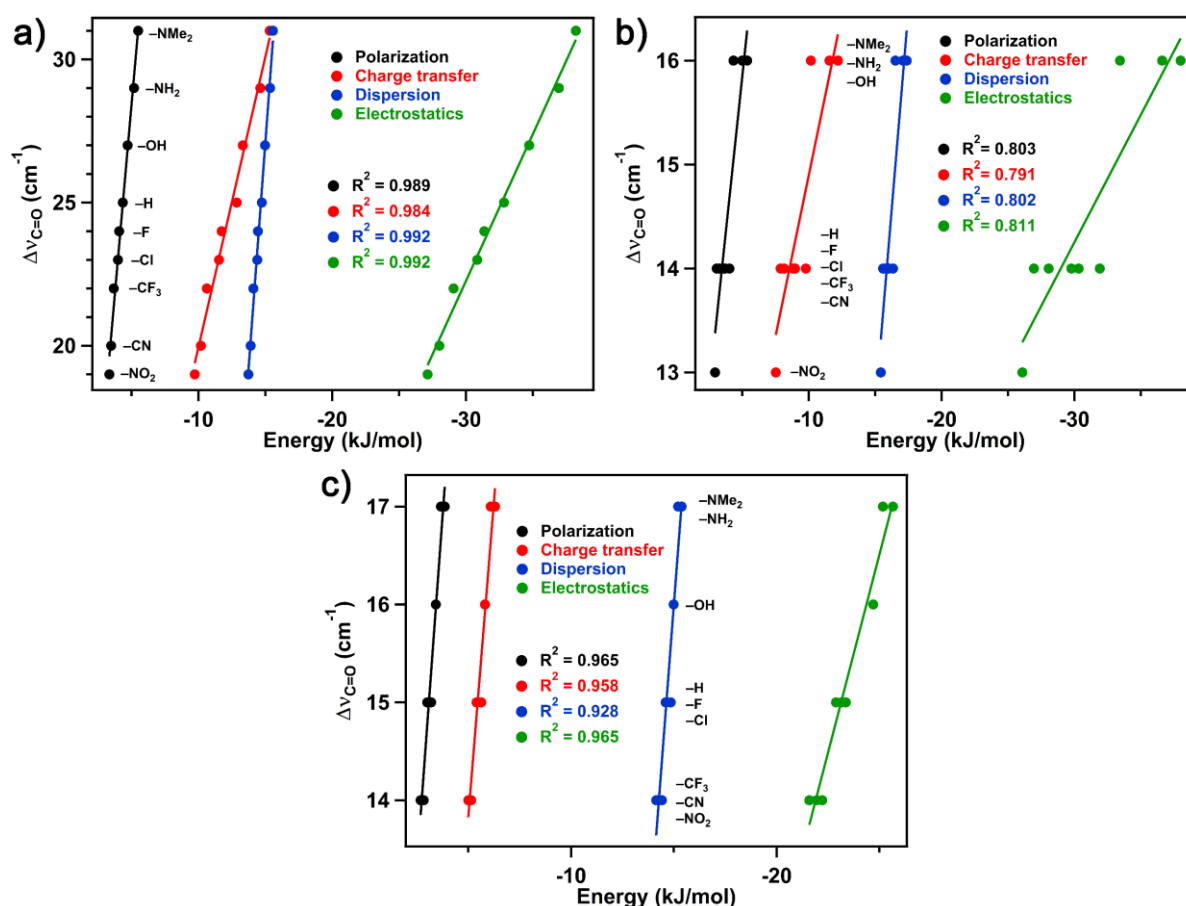


Figure 7.16. Plots of the $\Delta\nu_{C=O}$ values of various a) $p\text{-R-Py}\cdots\text{HCHO}$; b) $p\text{-R-Py}\cdots\text{HCOCl}$; and c) $p\text{-R-Py}\cdots\text{CH}_3\text{CHO}$ complexes versus polarization (black trace), charge transfer (red trace), dispersion (blue trace), and electrostatics (green trace) components of the total interaction energies (kJ/mol) obtained from the ALMO-EDA analysis at the B3LYP-D3/def2-TZVP level.

Figure 7.16 shows the linearly correlated plots of $\Delta\nu_{C=O}$ values as a function of the ES, DISP, POL, and CT components of the binding energies of the $p\text{-R-Py}\cdots\text{HCHO}$, $p\text{-R-Py}\cdots\text{HCOCl}$, and $p\text{-R-Py}\cdots\text{CH}_3\text{CHO}$ complexes calculated at the B3LYP-D3/def2-TZVP level. It is noteworthy that the change in the $\Delta\nu_{C=O}$ values has a significant correlation with the change in the ES and CT components of the binding energies of the $p\text{-R-Py}\cdots\text{S}$

complexes. On the contrary, the correlation of the change in the $\Delta\nu_{\text{C=O}}$ values with the change in the DISP and POL components of the binding energies is much less. Hence, the ES and CT components of the binding energies have a major role in regulating the redshift in the carbonyl stretching frequency in the $p\text{-R-Py}\cdots\text{S}$ complexes bound by the $\text{N}\cdots\text{C=O}$ $n\rightarrow\pi^*$ interaction, although the ES component dominates over the CT. Patwari and co-workers have reported that the redshift in the C–H stretching frequencies of $\text{C-H}\cdots\text{Y}$ ($\text{Y}=\text{O/N}$) hydrogen-bonded complexes are linearly correlated with the ES components of the total energy.²³² On the contrary, the DISP component does not correlate with the IR redshift but modulates the overall energies of complexes. In the case of the hydrogen bond, it is the $n\rightarrow\sigma^*$ interaction component, which is the orbital interaction counterpart of $n\rightarrow\pi^*$ interaction. The $n\rightarrow\sigma^*$ interaction in the hydrogen bond ($\text{C-H}\cdots\text{Y}$) arises due to charge transfer or delocalization of the electrons (n) on the lone pair orbitals of the hydrogen bond acceptor atom (Y) to the σ^* orbital of the hydrogen bond donor (C-H). The CT component of the binding energies of hydrogen-bonded complexes is due to the $n\rightarrow\sigma^*$ orbital interaction. Similarly, the CT component of the binding energies of the $\text{N}\cdots\text{C=O}$ bound complexes ($p\text{-R-Py}\cdots\text{S}$) studied here represents the $n\rightarrow\pi^*$ interaction between the lone pair electrons on the nitrogen atom and π^* orbital of the carbonyl group.

Overall studies on the $p\text{-R-Py}\cdots\text{S}$ complexes suggest that the strength of the $n\rightarrow\pi^*$ interaction can be modulated by varying the substituents at the donor site, and the modulation can be probed by theoretical approaches, including IR studies. The geometries of $p\text{-R-Py}\cdots\text{S}$ complexes are optimized in the solution-phase using various solvents, such as H_2O , CH_2Cl_2 , and CCl_4 , to study the effect of solvents of different polarity on the $n\rightarrow\pi^*$ interaction using the IEFPCM at the B3LYP-D3/def2-TZVP level. It should be noted that there is no significant change in the geometry of $p\text{-R-Py}\cdots\text{S}$ complexes optimized using the PCM model. However, there are changes in geometrical parameters (Table 7.1-7.4), such as distance (d , Å) and angle (θ , °), and in the electronic parameters pertinent to the $n\rightarrow\pi^*$ interaction, such as redshift in carbonyl stretching frequency and $E^{(2)}$ values. It can be noticed that the trend of the results obtained in various solvents is similar to the gas-phase. Moreover, the polarity of solvents is found to have a significant role in the strength of $n\rightarrow\pi^*$ interaction and is found to be decreasing with a decrease in the polarity of the solvents, and this follows the trend $\text{H}_2\text{O} > \text{CH}_2\text{Cl}_2 > \text{CCl}_4 > \text{gas-phase}$.

Table 7.1. Comparison of distance (d , Å) of $p\text{-R-Py}\cdots\text{S}$ complexes in different solvents with the gas-phase calculated at the B3LYP-D3/def2-TZVP level ($\text{S}=\text{R}_1\text{CHO}$; $\text{R}_1 = \text{H}$, Cl , and CH_3)

	H ₂ O			CH ₂ Cl ₂			CCl ₄			Gas-phase		
	H	Cl	CH ₃	H	Cl	CH ₃	H	Cl	CH ₃	H	Cl	CH ₃
–NMe ₂	2.533	2.595	2.884	2.560	2.616	2.889	2.612	2.665	2.905	2.656	2.711	2.916
–NH ₂	2.549	2.614	2.889	2.571	2.635	2.898	2.622	2.680	2.914	2.668	2.723	2.924
–OH	2.589	2.675	2.914	2.610	2.694	2.921	2.656	2.724	2.934	2.694	2.755	2.942
–H	2.603	2.688	2.914	2.622	2.706	2.913	2.668	2.735	2.931	2.707	2.764	2.948
–F	2.631	2.720	2.941	2.653	2.734	2.941	2.695	2.760	2.958	2.727	2.783	2.964
–Cl	2.641	2.725	2.941	2.661	2.738	2.942	2.699	2.764	2.957	2.732	2.787	2.967
–CF ₃	2.656	2.741	2.944	2.676	2.755	2.949	2.718	2.782	2.967	2.754	2.803	2.981
–CN	2.673	2.755	2.951	2.692	2.770	2.956	2.734	2.795	2.979	2.770	2.815	2.994
–NO ₂	2.686	2.770	2.971	2.705	2.783	2.966	2.748	2.807	2.986	2.782	2.823	3.002

Table 7.2. Comparison of angle (θ , °) of *p*-R–Py $\cdots$ S complexes in different solvents with the gas-phase calculated at the B3LYP-D3/def2-TZVP level (S=R₁CHO; R₁ = H, Cl, and CH₃)

	H ₂ O			CH ₂ Cl ₂			CCl ₄			Gas-phase		
	H	Cl	CH ₃	H	Cl	CH ₃	H	Cl	CH ₃	H	Cl	CH ₃
–NMe ₂	104.6	100.4	98.2	104.5	100.4	98.4	104.1	100.0	98.7	103.2	99.5	98.2
–NH ₂	104.4	100.2	98.0	104.3	100.1	98.2	103.8	99.7	98.3	102.8	99.2	97.7
–OH	103.8	99.4	97.4	103.7	99.4	97.5	103.1	99.1	97.5	102.0	98.4	96.6
–H	104.0	99.4	97.3	103.7	99.3	97.5	103.1	99.1	97.3	102.0	98.4	96.5
–F	103.5	99.0	96.7	103.3	98.9	96.8	102.5	98.6	96.6	101.3	97.9	95.5
–Cl	103.4	99.0	96.6	103.2	98.9	96.6	102.5	98.5	96.4	101.1	97.7	95.4
–CF ₃	103.2	98.8	96.3	103.0	98.6	96.2	102.0	98.1	95.7	100.5	97.2	94.5
–CN	103.0	98.6	95.9	102.7	98.4	95.8	101.5	97.7	95.0	99.8	96.7	93.7
–NO ₂	102.9	98.4	95.7	102.6	98.1	95.5	101.3	97.5	94.7	99.6	96.6	93.4

Table 7.3. Comparison of the redshift in the carbonyl stretching frequency ($\Delta\nu_{\text{C=O}}$, cm^{–1}) of *p*-R–Py $\cdots$ S complexes with respect to the aldehyde monomer in different solvents with the gas-phase calculated at the B3LYP-D3/def2-TZVP level (S=R₁CHO; R₁ = H, Cl, and CH₃)

	H ₂ O			CH ₂ Cl ₂			CCl ₄			Gas-phase		
	H	Cl	CH ₃	H	Cl	CH ₃	H	Cl	CH ₃	H	Cl	CH ₃
–NMe ₂	46	19	13	42	17	13	35	17	14	31	16	17
–NH ₂	43	18	13	40	16	13	34	16	14	29	16	17
–OH	37	13	11	34	12	11	30	14	13	27	16	16
–H	35	12	11	33	11	11	28	13	12	25	14	15
–F	31	11	10	29	10	10	25	12	12	24	14	15
–Cl	29	10	10	28	9	10	25	12	12	23	14	15
–CF ₃	27	9	9	26	8	9	23	12	11	22	14	14
–CN	26	9	9	25	7	9	21	11	11	20	14	14
–NO ₂	24	8	8	23	8	9	20	11	10	19	13	14

Table 7.4. Comparison of the $E^{(2)}$ values (kJmol) of $n \rightarrow \pi^*$ interaction of p -R-Py...S complexes in different solvents with the gas-phase calculated at the B3LYP-D3/def2-TZVP level (S=R₁CHO; R₁ = H, Cl, and CH₃)

	H ₂ O			CH ₂ Cl ₂			CCl ₄			Gas-phase		
	H	Cl	CH ₃	H	Cl	CH ₃	H	Cl	CH ₃	H	Cl	CH ₃
–NMe ₂	46.28	40.12	14.06	42.17	37.03	13.72	35.23	30.71	12.51	30.00	25.40	11.46
–NH ₂	44.18	37.70	13.68	40.96	34.85	13.18	34.23	29.12	11.97	28.83	24.35	11.00
–OH	38.12	29.75	12.18	35.56	27.82	11.80	30.33	24.52	10.84	26.11	21.51	10.08
–H	35.56	28.37	12.01	33.39	26.57	12.01	28.66	23.51	10.88	24.73	20.71	9.79
–F	32.72	25.19	10.63	30.54	23.81	10.59	26.23	21.38	9.62	22.84	19.16	9.00
–Cl	31.25	24.43	10.54	29.33	23.26	10.42	25.56	20.84	9.58	22.30	18.66	8.87
–CF ₃	29.25	22.80	10.25	27.49	21.63	10.00	23.60	19.20	9.04	20.38	17.32	8.24
–CN	27.66	21.46	9.79	25.94	20.25	9.67	22.13	18.12	8.49	18.95	16.36	7.70
–NO ₂	26.23	20.21	8.91	24.64	19.20	9.08	21.00	17.24	8.20	18.03	15.65	7.41

7.3.2 Substitution near carbonyl group ($n \rightarrow \pi^*$ acceptor site)

The first part of this chapter deals with modulating the strength of $n \rightarrow \pi^*$ interaction by tuning the substitutions at the *para* position of the pyridine ring. Further, its strength can be modulated by replacing the hydrogen atom of the HCHO with the methyl and chloro groups for a given donor moiety. Thus, tweaking the electronic properties of the carbonyl group can modulate its strength. The methyl group, which acts as an EDG, pushes the electron density towards the carbonyl group, making it electron-rich and less susceptible to accept the delocalized electron density in the π^* orbital from a lone pair donor. In contrast, the role of the chloro group is exciting due to its both -I and +I effects. Hence, the strength of $n \rightarrow \pi^*$ interaction will decrease while going from HCHO to CH₃CHO, whereas, in the case of HCOCl, the fate of the strength of $n \rightarrow \pi^*$ interaction will be determined by a subtle balance between the -I and +I effect of the Cl group.

7.3.2.1 Comparison of the methyl and chloro groups as the electron donor

The carbonyl group of $n \rightarrow \pi^*$ acceptors discussed in this work has two neighboring covalent bonds, i.e., C–H bonds (HCHO), C–H and C–Cl (HCOCl), and C–H and C–CH₃ (CH₃CHO). Two types of hyperconjugative interaction, namely *push* and *pull* effects, are present in the aldehydes or related compounds. The *push* effect involves delocalizing the σ electron density of neighboring covalent bonds to the σ^*/π^* orbitals of the carbonyl group. In contrast, the *pull* effect delocalizes the lone pair electron density of the carbonyl oxygen to the nearby σ^* orbital of the C–H, C–Cl, and C–CH₃ bonds. These effects are calculated for the *p*-R–Py $\cdots$ S complexes to compare the donor properties of the methyl and chloro groups and determine the dominance of the -I and +I effects of the chloro group. Table 7.5 shows the $E^{(2)}$ values for the *push* and *pull* effects for all the *p*-R–Py $\cdots$ S complexes calculated at the B3LYP-D3/def2-TZVP level. It can be noticed that the total energies (calculated by subtracting the *push* effect from the *pull* effect) for the HCHO and HCOCl complexes are almost similar. In contrast, the total energies for the CH₃CHO complexes are ~60 kJ/mol less than those for the other complexes. Thus, the methyl group is a better electron donor than the chloro group. The expected trend of the strength of the $n \rightarrow \pi^*$ interaction in the complexes is HCHO > HCOCl > CH₃CHO.

Table 7.5. $E^{(2)}$ (kJ/mol) values of the push and pull effects for the *p*-R–Py $\cdots$ S complexes (gas-phase) calculated at the B3LYP-D3/def2-TZVP level

	HCHO	HCOCl	CH ₃ CHO
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	Push	Pull	Δ	Push	Pull	Δ	Push	Pull	Δ
Monomer	0.00	205.43	205.43	114.64	311.08	196.44	61.09	210.58	149.49
–NMe ₂	0.00	201.50	201.50	104.60	314.26	209.66	62.76	205.35	142.59
–NH ₂	0.00	201.33	201.33	105.86	313.55	207.69	62.76	205.23	142.47
–OH	0.00	201.08	201.08	107.95	311.16	203.22	63.18	204.93	141.75
–H	0.00	201.50	201.50	107.95	311.71	203.76	63.18	205.39	142.21
–F	0.00	201.33	201.33	109.20	310.62	201.42	63.18	205.10	141.92
–Cl	0.00	201.33	201.33	109.20	310.45	201.25	63.18	203.26	140.08
–CF ₃	0.00	201.33	201.33	110.46	309.87	199.41	63.60	205.23	141.63
–CN	0.00	201.17	201.17	110.88	309.07	198.20	63.60	204.97	141.38
–NO ₂	0.00	201.17	201.17	111.29	308.95	197.65	63.60	205.02	141.42

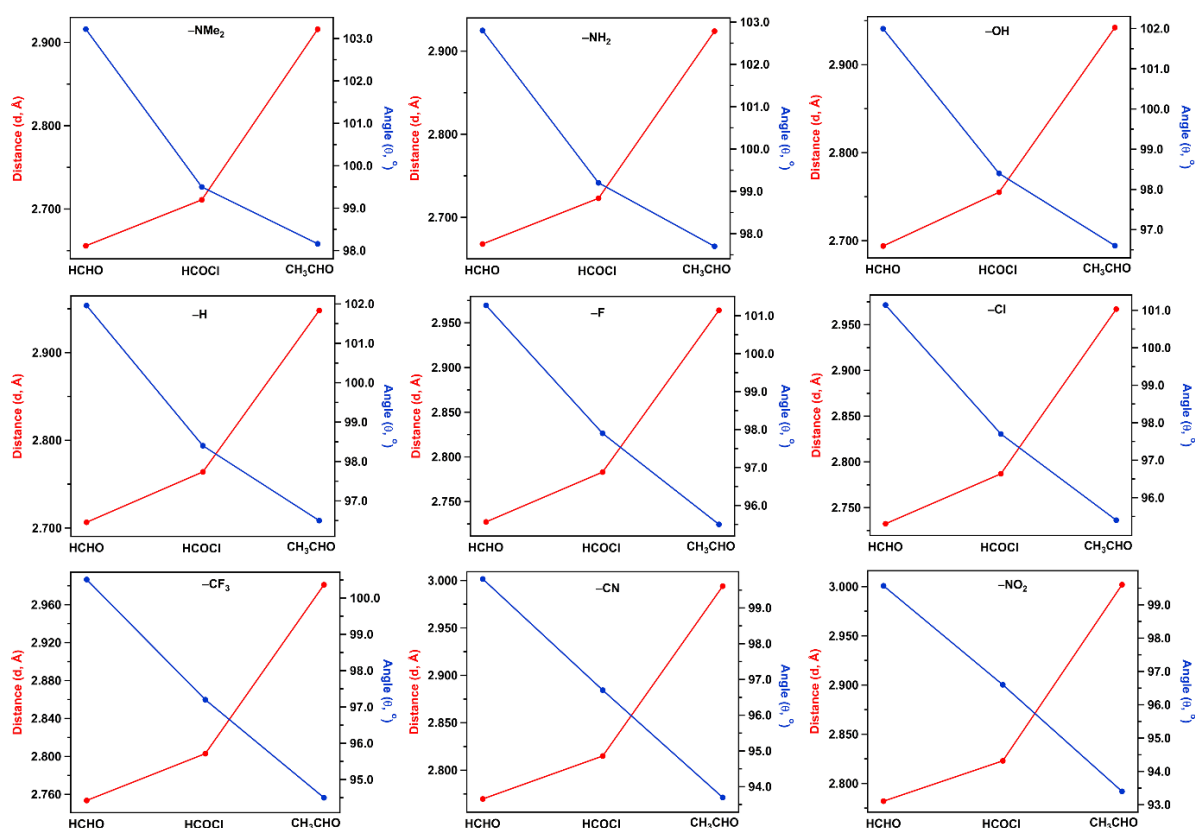


Figure 7.17. Plots of distance (red trace) and $\angle\text{N-C-O}$ (blue trace) for the $p\text{-R-Py}\cdots\text{S}$ complexes (gas-phase) calculated at the B3LYP-D3/def2-TZVP level. The lines connecting the data points are not fitted but are provided to guide the eyes.

As discussed earlier, the geometrical parameters give a rough idea of the strength of the $n \rightarrow \pi^*$ interaction. Figure 7.17 shows that the B3LYP-D3/def2-TZVP level calculated distance for the p -R-Py $\cdots$ S complexes (red trace) is the least in HCHO and maximum for CH₃CHO. The $\angle$ N-C-O deviates from the Bürgi-Dunitz trajectory (blue trace) as we move from HCHO to CH₃CHO. It implies that the $n \rightarrow \pi^*$ interaction periodically weakens as the hydrogen atom of HCHO is replaced by the Cl and CH₃ groups. It should be noticed that the +I effect of the Cl group dominates over its -I effect, and thus, the strength of the interaction with HCOCl lies in between the HCHO and CH₃CHO complexes.

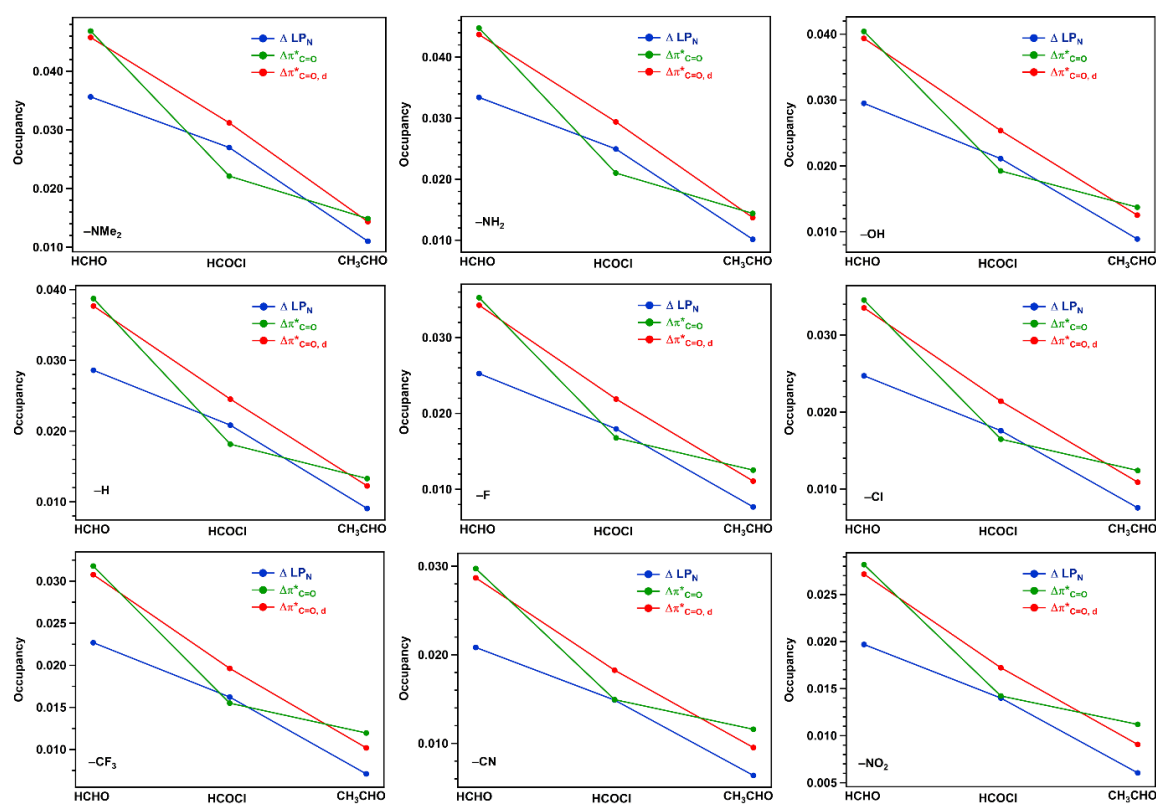


Figure 7.18. Plots of change in occupancy of the nitrogen atom (ΔLP_N) after the formation of the complex with respect to the p -R-Py monomer (blue trace) and change in occupancy of π^* orbital of carbonyl bond ($\Delta \pi^*_{C=O}$) (green trace) of the complexes (gas-phase) with respect to aldehydes, and change in occupancy of π^* orbital of carbonyl bond after deletion of $n \rightarrow \pi^*$ interaction for the p -R-Py $\cdots$ S complexes (gas-phase) calculated at B3LYP-D3/def2-TZVP level. The lines connecting the data points are not fitted but are provided to guide the eyes.

The presence or the relative strength of the $n \rightarrow \pi^*$ interaction in the complexes can be monitored by checking the difference in the π^* orbital occupancy of the carbonyl group and the lone pair orbital occupancy of the nitrogen atom in the complexes and monomer. The blue

trace in Figure 7.18 shows that the B3LYP-D3/def2-TZVP level calculated difference in the occupancy of the lone pair orbital of the nitrogen atom of the complexes with respect to that in the *p*-R-Py monomer (ΔLP_N) is maximum for HCHO complexes while the same is minimum for CH₃CHO complexes. Similarly, the difference in the occupancy of the π^* orbital of the carbonyl group of complexes with respect to the aldehyde monomer ($\Delta \pi^*_{C=O}$) is more in the case of HCHO complexes than the CH₃CHO complexes (green trace in Figure 7.18). These orbital occupancies reveal that the $n \rightarrow \pi^*$ interaction decreases with the substitution of the hydrogen atom of HCHO by the Cl or CH₃ groups. NBO deletion analysis performed at the B3LYP-D3/def2-TZVP level, i.e., the difference in the occupancy of the $\pi^*_{C=O, d}$ of the complexes (before and after deletion of the $n \rightarrow \pi^*$ interaction) follows a similar trend (red trace in Figure 7.18).

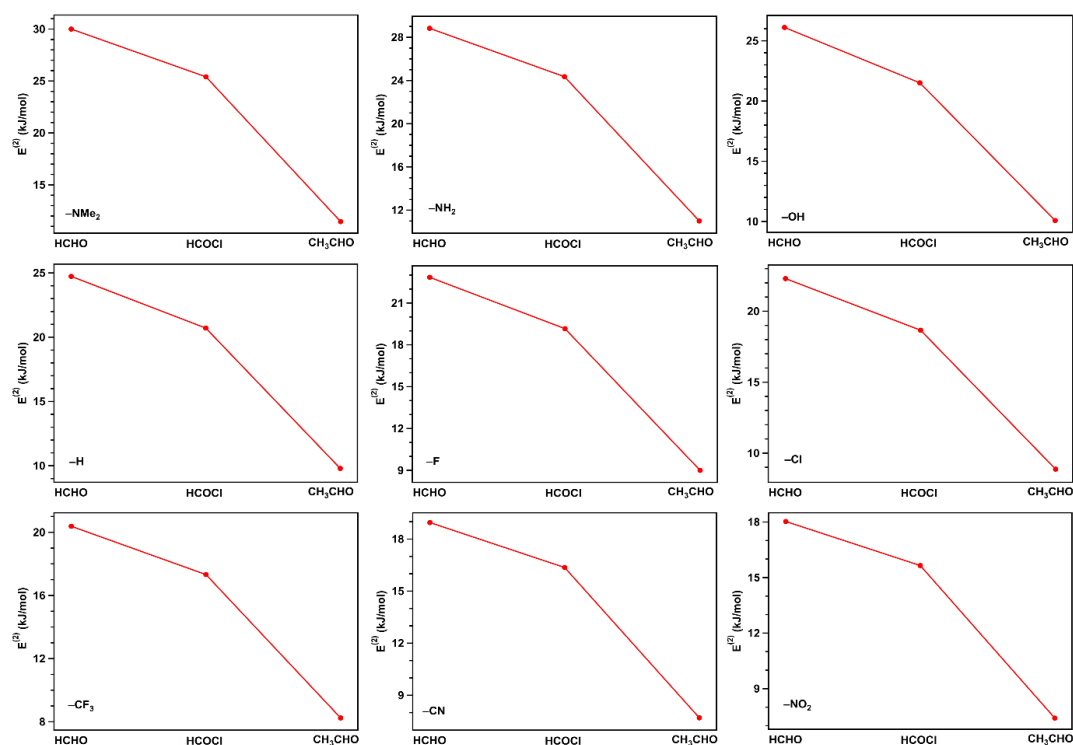


Figure 7.19. Plot of $E^{(2)}$ (kJ/mol) values of $n \rightarrow \pi^*$ interaction for the *p*-R-Py $\cdots$ S complexes (gas-phase) calculated at B3LYP-D3/def2-TZVP level. The lines connecting the data points are not fitted but are provided to guide the eyes.

It is found from the NBO analysis performed at the B3LYP-D3/def2-TZVP level that the $E^{(2)}$ values for the $n \rightarrow \pi^*$ interaction decrease as the acceptor moiety is changed from HCHO to CH₃CHO (Figure 7.19). The NBO results reconfirm that the delocalization of electron density in the CH₃CHO complex is much less than in the HCHO complex.

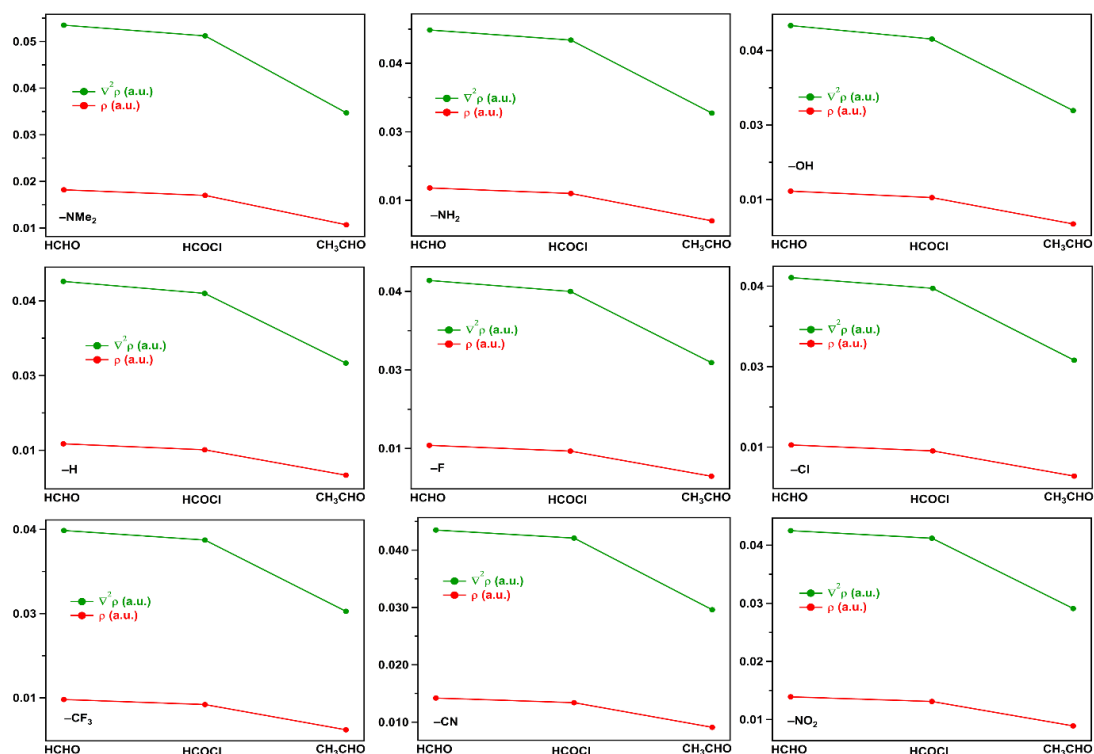


Figure 7.20. Plots of AIM parameters of the p -R-Py $\cdots$ S complexes (gas-phase) at the BCP of the $n \rightarrow \pi^*$ interaction calculated at B3LYP-D3/def2-TZVP level. The lines connecting the data points are not fitted but are provided to guide the eyes.

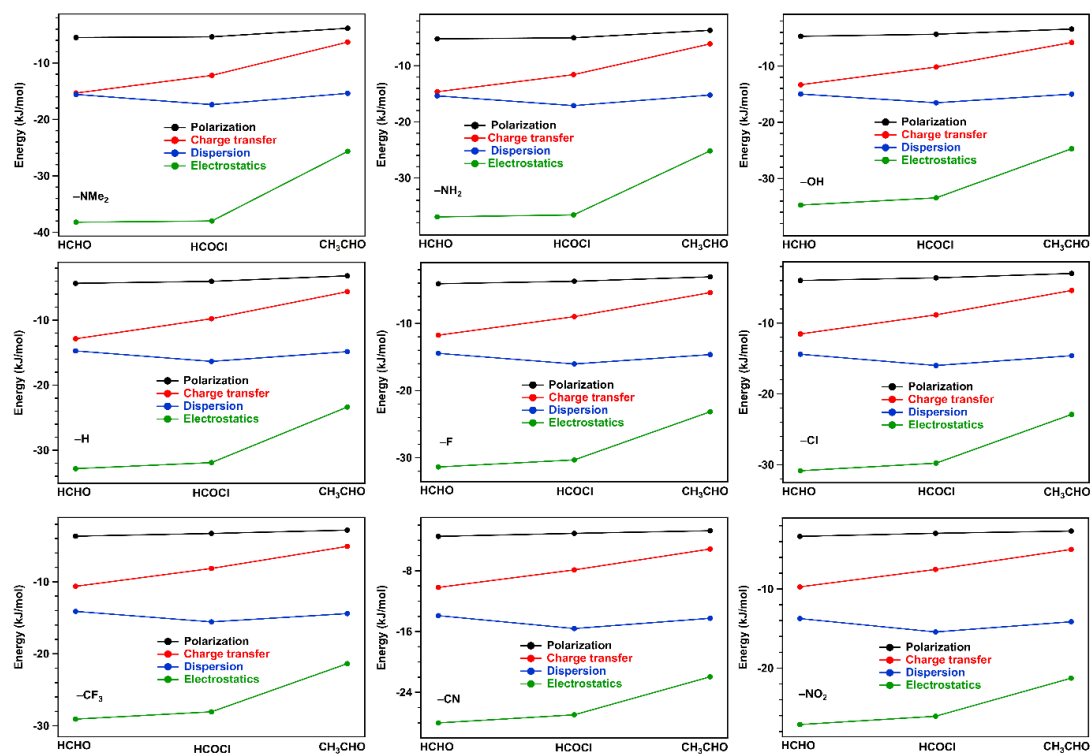


Figure 7.21. Plots of POL (black trace), CT (red trace), DISP (blue trace), and ES (green trace) components (kJ/mol) of total interaction energy of the p -R-Py $\cdots$ S complexes (gas-phase)

obtained from ALMO-EDA analysis calculated at B3LYP-D3/def2-TZVP level. The lines connecting the data points are not fitted but are provided to guide the eyes.

The AIM parameters (Figure 7.20) calculated at the BCP for the $n \rightarrow \pi^*$ interaction in these complexes calculated at the B3LYP-D3/def2-TZVP level suggest that the HCHO complexes have stronger interaction. ALMO-EDA analysis performed at the B3LYP-D3/def2-TZVP level shows that the ES, compared to the CT, contributes more strongly to stabilizing these complexes (Figure 7.21). It is also found that both ES and CT decrease when the $n \rightarrow \pi^*$ acceptor moiety is changed from HCHO to CH_3CHO .

7.4 Conclusions

Herein, we have demonstrated the modulation of the strength of the $n \rightarrow \pi^*$ interaction in the complexes of *p*-substituted pyridines with formaldehyde, formyl chloride, and acetaldehyde using the solution and gas-phase quantum chemistry calculations. The electronic substitution has been varied from electron-donating to electron-withdrawing groups at the $n \rightarrow \pi^*$ donor (*p*-substitution on the pyridine ring) and $n \rightarrow \pi^*$ acceptor sites (chloro and methyl substitutions at the place of hydrogen of the formaldehyde). As the $n \rightarrow \pi^*$ interaction is about the delocalization of the lone pair (*n*) electrons to the π^* orbital, the substituents at both donor and acceptor sites can systematically tune the occupancy of the lone pair orbital of the nitrogen atom as well as the π^* orbital of the carbonyl group to achieve the desired variation in the strength of this interaction. The geometrical parameters relevant to the $n \rightarrow \pi^*$ interaction, binding energies, and IR redshift in the carbonyl stretching frequency of the complexes show a linear relationship with the Hammett values of the substituents. Interestingly, the BCP for this weak intermolecular $n \rightarrow \pi^*$ interaction has been found for all the complexes using QTAIM analysis. Various other theoretical approaches, such as the NCI index and NBO analyses, exhibit a linear correlation between the strength of the $n \rightarrow \pi^*$ interaction and the Hammett values of the substituents. The ALMO-EDA analysis shows that electrostatics is the major contribution to the binding energies of these complexes. However, the charge transfer component, which represents the $n \rightarrow \pi^*$ orbital interaction, also significantly stabilizes these complexes. It is found that the IR redshift in the carbonyl stretching frequency of the $n \rightarrow \pi^*$ interaction bonded *p*-R-Py $\cdots$ S complexes is regulated by the electrostatics as well as charge transfer interaction. This work may help in designing materials and drugs by optimizing the $n \rightarrow \pi^*$ interaction.

Chapter 8: Summary of the Thesis and Future Directions

8.1 Summary of the thesis

We have successfully explored $\text{C}=\text{O}\cdots\text{aromatic n}\rightarrow\pi^*$ interaction in phenyl acetate and phenyl formate $\cdots$ water complex, and $\text{N}\cdots\text{C}=\text{O n}\rightarrow\pi^*$ interaction in various molecular systems, such as ethyl 2-(2-(dimethylamino) phenyl) acetate, 3-[2-(dimethylamino) phenyl] propanal, and complexes of *p*-substituted pyridines with aldehydes (formaldehyde, methanoyl chloride, and acetaldehyde), using gas-phase electronic and vibrational spectroscopy with the help of state-of-art quantum chemistry calculations. Two primary goals of this thesis were to tune the strength of the $\text{n}\rightarrow\pi^*$ interaction and to determine its role/contribution in the redshift of carbonyl stretching frequency in the absence of any hyperconjugative interaction otherwise present in the ester/amides, which was successfully investigated and reported in this thesis.

We have investigated the effect of the methyl group substitution near the $\text{n}\rightarrow\pi^*$ donor in phenyl formate on the $\text{n}\rightarrow\pi^*$ interaction. It was shown that due to the electron-donation from this methyl group, electron density at the $\text{n}\rightarrow\pi^*$ donor, i.e., carbonyl group, increases, and thus, the strength of the $\text{C}=\text{O}\cdots\text{aromatic n}\rightarrow\pi^*$ interaction increases. Moreover, methyl substitution near the carbonyl group also increases the steric repulsion in the other conformer, making it less stable. Thus, an increase in the strength of the $\text{C}=\text{O}\cdots\text{aromatic n}\rightarrow\pi^*$ interaction in one conformer and an increase in the steric repulsion in another conformer induces the conformational heterogeneity in the molecular system, as a result of which, the conformer lacking the $\text{n}\rightarrow\pi^*$ interaction was not observed in the experiment.

Further, we tried to mask the strength of the $\text{C}=\text{O}\cdots\text{aromatic n}\rightarrow\pi^*$ interaction in phenyl formate by making hydrogen bonds with the same carbonyl group, which is involved in the $\text{n}\rightarrow\pi^*$ interaction. It was found that the strength of the $\text{n}\rightarrow\pi^*$ interaction indeed decreases in the presence of a hydrogen bond in the phenyl formate $\cdots$ water complex. Moreover, the strength of the hydrogen bonding also decreases in the presence of the $\text{n}\rightarrow\pi^*$ interaction in this complex.

We have also tried to observe the $\text{N}\cdots\text{C}=\text{O n}\rightarrow\pi^*$ interaction in the gas-phase in ethyl 2-(2-(dimethylamino) phenyl) acetate. A single conformation having $\text{n}\rightarrow\pi^*$ interaction was observed in the experiment, along with the stabilization of all the six low-energy conformers by the $\text{n}\rightarrow\pi^*$ interaction. Variable temperature ^{13}C NMR spectroscopy was also performed to confirm the presence of the $\text{n}\rightarrow\pi^*$ interaction in solution-phase.

Later on, we tried to modulate the strength of the $\text{N}\cdots\text{C}=\text{O n}\rightarrow\pi^*$ interaction using quantum chemistry calculations in 3-[2-(dimethylamino) phenyl] propanal by tuning the

electron density at the *para* position of the $n \rightarrow \pi^*$ donor, i.e., $-\text{NMe}_2$ group. We found that the strength of the $n \rightarrow \pi^*$ interaction increases as the *para* position is substituted with the electron-donating groups, and its strength decreases with the substitution of electron-withdrawing groups. Moreover, it was also found that flexible propanal side-chain in 3-[2-(dimethylamino) phenyl] propanal folds due to the presence of the $n \rightarrow \pi^*$ interaction. It was shown that the folding propensity decreases as the strength of the $n \rightarrow \pi^*$ interaction decreases with the tuning of *para* position with electron-withdrawing groups.

Further to this, we have shown that the strength of the intermolecular $\text{N} \cdots \text{C}=\text{O}$ $n \rightarrow \pi^*$ interaction can be modulated in the complexes of *p*-substituted pyridines with aldehydes using quantum chemistry calculations. It was found that the primary force in stabilizing these complexes was the $n \rightarrow \pi^*$ interaction, and the stability of these complexes decreases as the strength of the $n \rightarrow \pi^*$ interaction decreases with the substitution of electron-withdrawing groups at the *para* position of the nitrogen atom of the pyridine ring.

The contribution of the $n \rightarrow \pi^*$ interaction to the redshift of the carbonyl stretching frequency in the absence of any hyperconjugative interaction was found in 3-[2-(dimethylamino) phenyl] propanal and complexes of *p*-substituted pyridines with aldehydes. In the above-mentioned molecular systems, the carbonyl group ($n \rightarrow \pi^*$ acceptor) belongs to the aldehydes free from hyperconjugation. Thus, the redshift observed in the carbonyl stretching frequency is purely due to the $n \rightarrow \pi^*$ interaction without any perturbation arising from hyperconjugation.

8.2 Future Directions

The last two chapters of this thesis involved the molecular systems, where the carbonyl group is free from hyperconjugation and has been studied using quantum chemistry calculations. The contribution of the $n \rightarrow \pi^*$ interaction to the theoretical redshift of carbonyl stretching frequency without hyperconjugation has been determined from the theoretical calculations. However, it will be interesting to seek the gas-phase IR spectroscopic evidence of such findings in the future. Also, gas-phase experiments could be performed for some of the substituents at the *para* position of the $n \rightarrow \pi^*$ donor in order to understand the impact of the $n \rightarrow \pi^*$ interaction on the experimental redshift in the carbonyl stretching frequency.

While working on Chapters 5 and 6, attempts were made to synthesize the 1-(2-(dimethylamino)phenyl)propan-2-one using the reported synthetic procedure,^{233, 234} but could not succeed. This compound can be synthesized in the future to obtain experimental evidence of the $n \rightarrow \pi^*$ interaction. The redshift in the carbonyl stretching frequency of this compound

will be solely due to the $n \rightarrow \pi^*$ interaction without any perturbation from the hyperconjugative interaction. DFT results, including NBO analysis performed at the B3LYP-D3/def2-TZVP level (shown in Figure 8.1), confirm the presence of the $n \rightarrow \pi^*$ interaction in this compound. Furthermore, experiments could be performed by substituting some *para* substituent from EWG and EDG to explore the modulation of the $n \rightarrow \pi^*$ interaction.

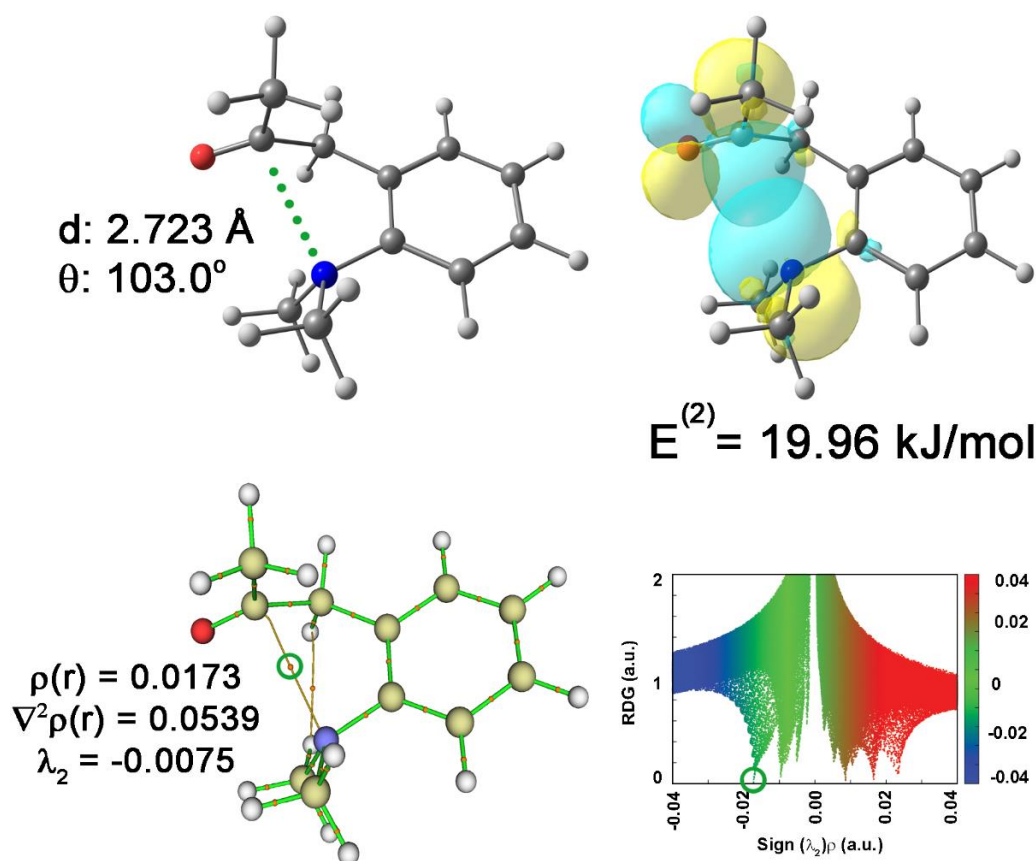


Figure 8.1. S_0 state optimized geometry of 1-(2-(dimethylamino)phenyl)propan-2-one with relevant geometrical parameters, such as distance (d , Å) and angle (θ , °), NBO orbital overlaps with $E^{(2)}$ values of $n \rightarrow \pi^*$ interaction, molecular graphs with AIM parameters showing BCP for $n \rightarrow \pi^*$ interaction marked with green circle, and NCI RDG plots showing RDG minima corresponding to the $n \rightarrow \pi^*$ interaction marked with a green circle.

In this thesis, we have discussed that the strength of the $N \cdots C=O$ $n \rightarrow \pi^*$ interaction can be modulated intramolecularly and intermolecularly by varying the electronic substituents at the *para* position of $n \rightarrow \pi^*$ donor. In the future, gas-phase spectroscopic studies in combination with theoretical analyses could be performed for a systematic understanding of the tuning of the $n \rightarrow \pi^*$ interaction by varying the electron density at the $n \rightarrow \pi^*$ acceptor site. In this regard, we have explored the *ortho*-substituted biphenyl derivatives theoretically, where either of the benzene rings has $n \rightarrow \pi^*$ donor ($-NMe_2$) and $n \rightarrow \pi^*$ acceptor ($-CHO$) attached to the *ortho*

position of the ring. Herein, the *para* position of the $n \rightarrow \pi^*$ acceptor can be tuned from the EDGs to EWGs in order to study the effect of these substituents on the $n \rightarrow \pi^*$ interaction.

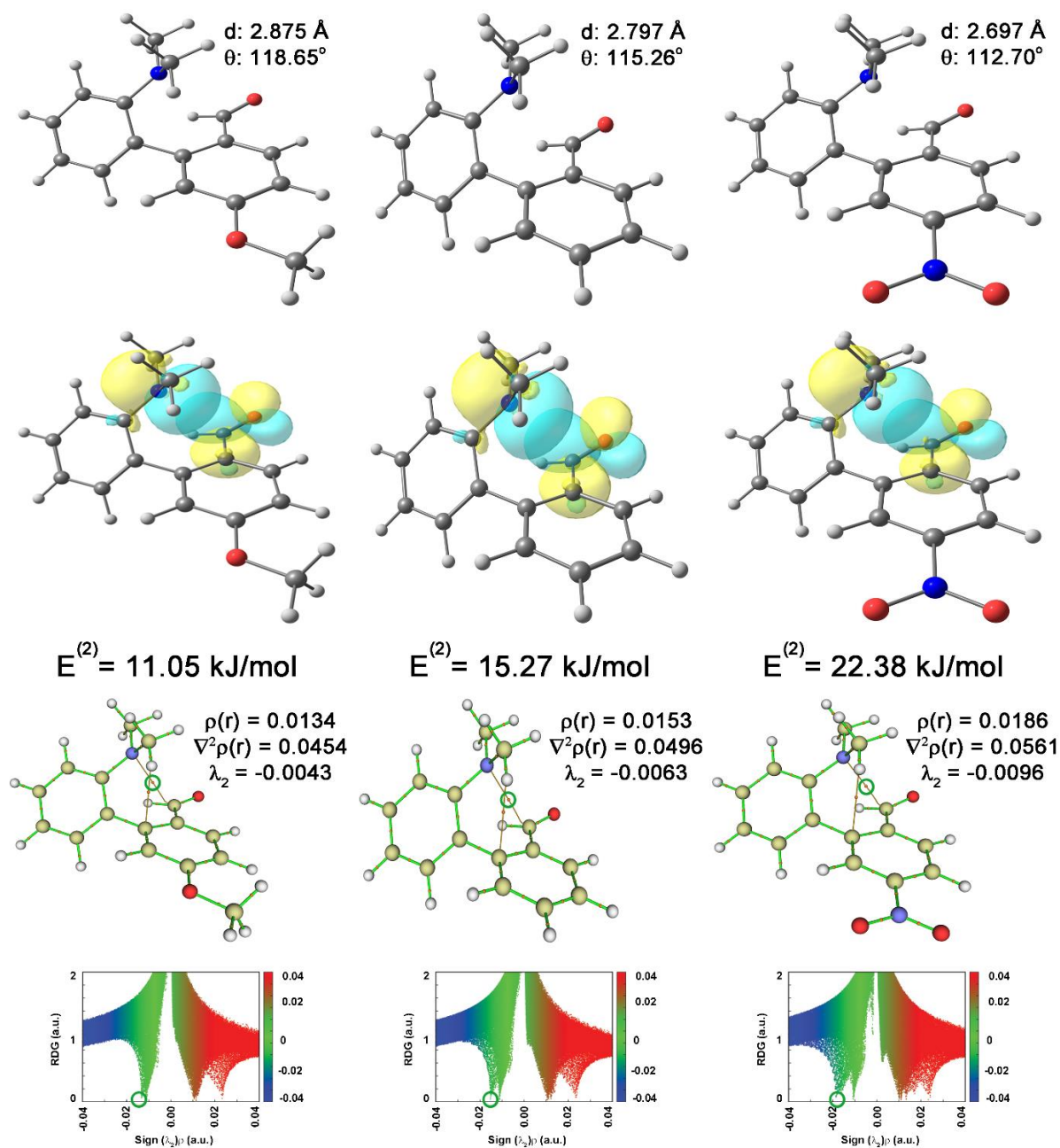


Figure 8.2. S_0 state optimized geometries with relevant geometrical parameters, such as distance (d , Å) and angle (θ , °), NBO orbital overlaps with $E^{(2)}$ values of $n \rightarrow \pi^*$ interaction, molecular graphs with AIM parameters showing BCP for $n \rightarrow \pi^*$ interaction marked with green circle, and NCI RDG plots showing RDG minima corresponding to the $n \rightarrow \pi^*$ interaction marked with green circle for various biphenyl derivatives with the -OMe, -H, and -NO₂ substituents at the *para* position of the CHO group ($n \rightarrow \pi^*$ acceptor).

Preliminary DFT results (shown in Figure 8.2), including the geometrical parameters obtained from the ground state optimized geometries of the biphenyl derivatives with the –NO₂, –H, and –OMe substituents at the *para* position calculated at the B3LYP-D3/def2-TZVP level, such as distance and angle shows the close contact between nitrogen and carbonyl carbon atoms, suggesting the n→π* interaction. NBO analysis performed on these optimized geometries confirms the presence of the n→π* interaction in these biphenyl derivatives. It is clear from the geometrical parameters and E⁽²⁾ values that the strength of the n→π* interaction can be increased by varying the electronic substituents from the EDG to EWG. Further, electron density calculations, such as QTAIM and NCI index analyses, corroborate the results obtained from the NBO analysis. It can be noticed from the AIM parameters that the electron density and second eigenvalue at the BCP of the n→π* interaction increase as we move to the EWG. Moreover, the RDG minima corresponding to the n→π* interaction move towards a more negative value with the EWG, confirming the strengthening of the n→π* interaction. These results confirm that the EWG at the *para* position makes the carbonyl group (n→π* acceptor) much more susceptible to the formation of the n→π* interaction, and the reverse was observed with the EDG at the *para* position.

Further, the nature of the n→π* interaction could be studied, and a concrete understanding of the n→π* interaction could be developed by performing gas-phase spectroscopic experiments. It will help to modulate the n→π* interaction and understand its critical phenomenon. In turn, the understanding of the n→π* interaction will help in biological phenomena like drug delivery, where non-covalent interaction plays a significant role, and the stabilization of the proteins due to the presence of the n→π* interaction.

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P. Panwaria and A. Das, *Phys. Chem. Chem. Phys.*, 2022, **24**, 22371 DOI: 10.1039/D2CP02070J

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Effect of Substituents on the Intramolecular $n \rightarrow \pi^*$ Interaction in 3-[2-(Dimethylamino) phenyl] propanal: A Computational Study

Author: Prakash Panwaria, Aloke Das
 Publication: The Journal of Physical Chemistry A
 Publisher: American Chemical Society
 Date: Apr 1, 2023

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Modulation of $n \rightarrow \pi^*$ Interaction in the Complexes of *p*-Substituted Pyridines with Aldehydes: A Theoretical Study

Author: Prakash Panwaria, Aloke Das
 Publication: The Journal of Physical Chemistry A
 Publisher: American Chemical Society
 Date: Jul 1, 2023

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