

Design and Syntheses of Chiral Phosphorus- Based Assemblies for Effective Enantioselective Applications

विद्या वाचस्पति की

उपाधि की अपेक्षाओं की आंशिक पूर्ति में प्रस्तुत शोध प्रबंध

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**INDIAN INSTITUTE OF SCIENCE EDUCATION AND
RESEARCH PUNE**

2025

Dedicated to
My family and friends



भारतीय विज्ञान शिक्षा एवं अनुसंधान संस्थान, पुणे

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Certificate

I certify that the work incorporated in the thesis entitled “*Design and Syntheses of Chiral Phosphorus-Based Assemblies for Effective Enantioselective Applications*” submitted by *Cavya Jose* has been carried out by the candidate at the Indian Institute of Science Education and Research (IISER), Pune, 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. I further certify that the above statements made by him/her in regard to his/her thesis are correct to the best of my knowledge.

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I declare that this written submission represents my idea in my own words and where others' ideas have been included; I have adequately cited and referenced the original sources. 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 for 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. R. Boomi Shankar.

Date: 10/03/2025

Cavya Jose

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This thesis is more than just the culmination of my research in the lab or at my desk, it marks a significant personal milestone in my journey. While the pursuit of a Ph.D. is often described as a solitary endeavour, it would not have been possible without the guidance, encouragement, and unwavering support of many invaluable individuals. I am deeply grateful to everyone who has inspired, motivated and stood by me throughout this journey, helping me reach this important moment in my life.

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Synopsis

In this thesis, we explore the design, synthesis, and structural characterization of a series of chiral phosphorus-nitrogen (P-N) based systems featuring diverse topologies, including acyclic, cyclic, and polyhedral cage architectures. Furthermore, it investigates their chiral recognition properties, shedding light on their potential applications in enantioselective processes and molecular discrimination. Through these studies, this work aims to contribute to the broader understanding of supramolecular chirality and its implications in advanced functional materials.

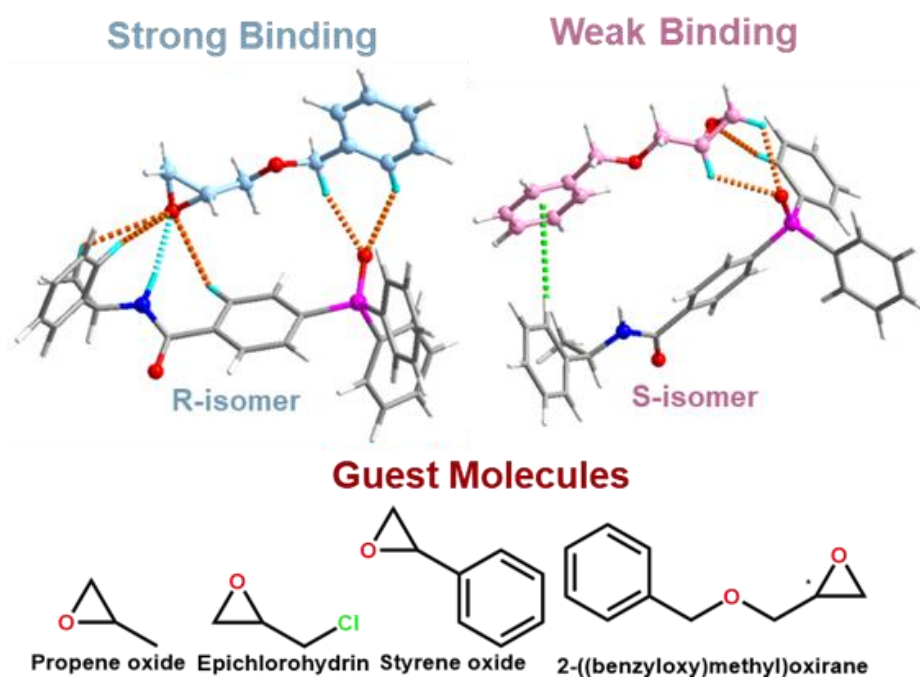
Chapter 1: Introduction

Chirality, a fundamental molecular property, plays a crucial role in various scientific fields, from chemistry and pharmacology to biology and materials science. This chapter explores the concept of chirality at different hierarchical levels, from molecular to supramolecular structures, highlighting its significance in biological and synthetic systems. The discussion includes molecular chirality, where asymmetric spatial arrangements define enantiomeric forms, and supramolecular chirality, which emerges from non-covalent interactions in self-assembled systems. The chapter also delves into the importance of chiral recognition and separation, emphasizing their applications in pharmaceuticals, asymmetric catalysis, and biological interactions. Furthermore, various supramolecular systems, including host-guest complexes, macrocyclic compounds, self-assembled structures, and metal-organic cages, are introduced as promising candidates for enantioselective applications. The adaptability and reversibility of supramolecular chirality under different environmental conditions make these systems highly valuable in sensing, separation, and catalysis. The chapter sets the foundation for the thesis by discussing advanced tools and techniques for chiral recognition and separation, providing insights into the dynamic nature and potential applications of chiral supramolecular architectures.

Chapter 2: A Chiral Phosphine Oxide for Enantioselective Recognition of Epoxides

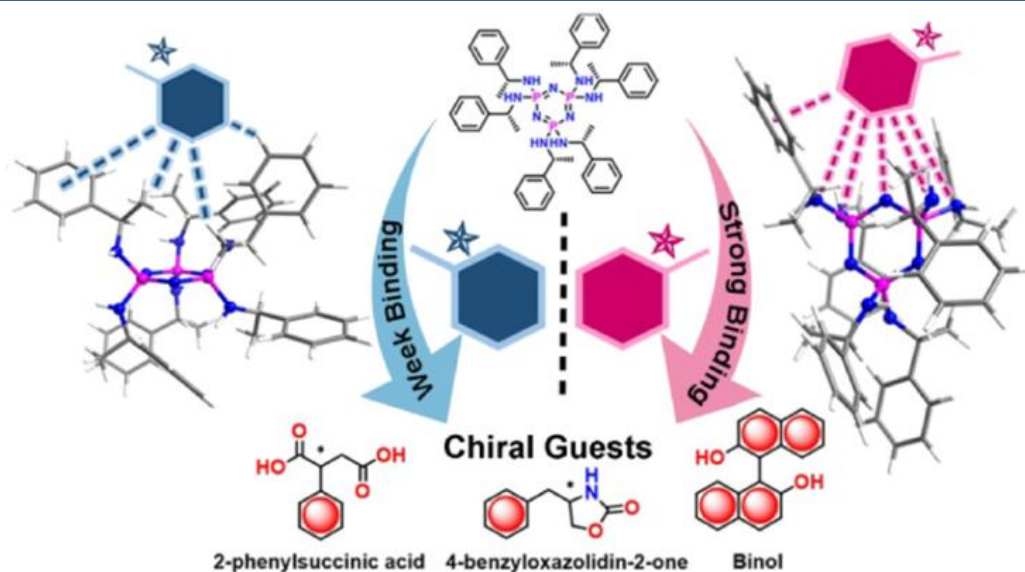
Chirality plays a vital role in clinical, chemical, and biological research, as the majority of bioactive compounds found in nature exhibit chiral properties. Thus, chiral sensors exhibiting exceptional selectivity, sensitivity, and stability are crucial due to their significant applications in asymmetric catalysis and substrate recognition in biological systems. The chiral recognition efficiency is primarily influenced by subtle variations in non-covalent interactions between host and enantiomeric guest molecules. Thus, we have designed a chiral phosphine oxide that can serve as both hydrogen bond donor and acceptor, making it a versatile platform for host-guest chemistry. In this study, we present an enantiopure phosphine oxide, 1-R [POPh₂(R*)], where R* corresponds to an amide substituent (R)-((C₆H₄)(CO)(NH)(CH(CH₃)Ph)), featuring chiral α -methylbenzyl unit. The chiral recognition ability of the chiral phosphine oxide was explored for a family of epoxide guest molecules. Notably, an

exceptional guest selectivity (ξ) value of 3214 was observed for 2-((benzyloxy)methyl)oxirane (BO), selective for its *R*-enantiomer. DFT-optimized structures of the host-guest complexes indicate that the difference in the multiple non-covalent interactions at the two distinct binding sites of the phosphine oxide plays a key role in achieving the observed high binding selectivity. It has been observed that the binding affinity and selectivity of this phosphine oxide increase as the number of interaction sites and the steric bulk of the guest molecules increase within this family of epoxide guests.

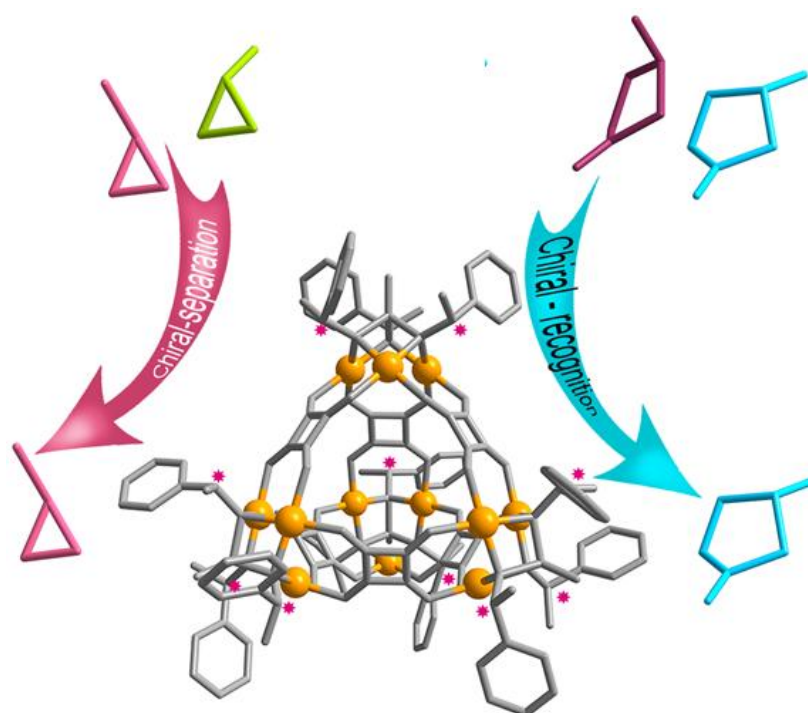


Chapter 3: A Chiral Hexa-amino Cyclotriphosphazene for Enantioselective Recognition of Small Organic Compounds

Chiral recognition and separation studies are of paramount importance in research in view of their applications in asymmetric catalysis and substrate recognition in biological processes. The efficiencies of these processes are governed by the subtle differences in non-covalent interactions between the host and guest molecules. Hexakis(alkylamino)phosphazenes are versatile building blocks for host-guest chemistry for their ability to act as both the donor and acceptor of H-bonds. Herein, we report an enantiomeric pair of cyclotriphosphazenes $[P_3N_3(NHR^*)_6]$, $[R^* = (R)\text{-(CH(CH}_3\text{)Ph)]}$ (1-*R*) and $[(S)\text{-(CH(CH}_3\text{)Ph)]}$ (1-*S*), with chiral α -methylbenzylamino substituents. The chiral recognition capabilities of its *R*-enantiomer were further probed for several chiral organic compounds containing a range of functional groups. Among these, a remarkable guest selectivity (ξ) value of 2506 was observed for binol (BOL) in favour of its *R*-enantiomer. DFT-optimized structures of the host-guest pairs suggest that the multiple non-covalent interactions between the molecules in the two unique types of binding sites at the phosphazenes play a crucial role in the observed high binding selectivities.



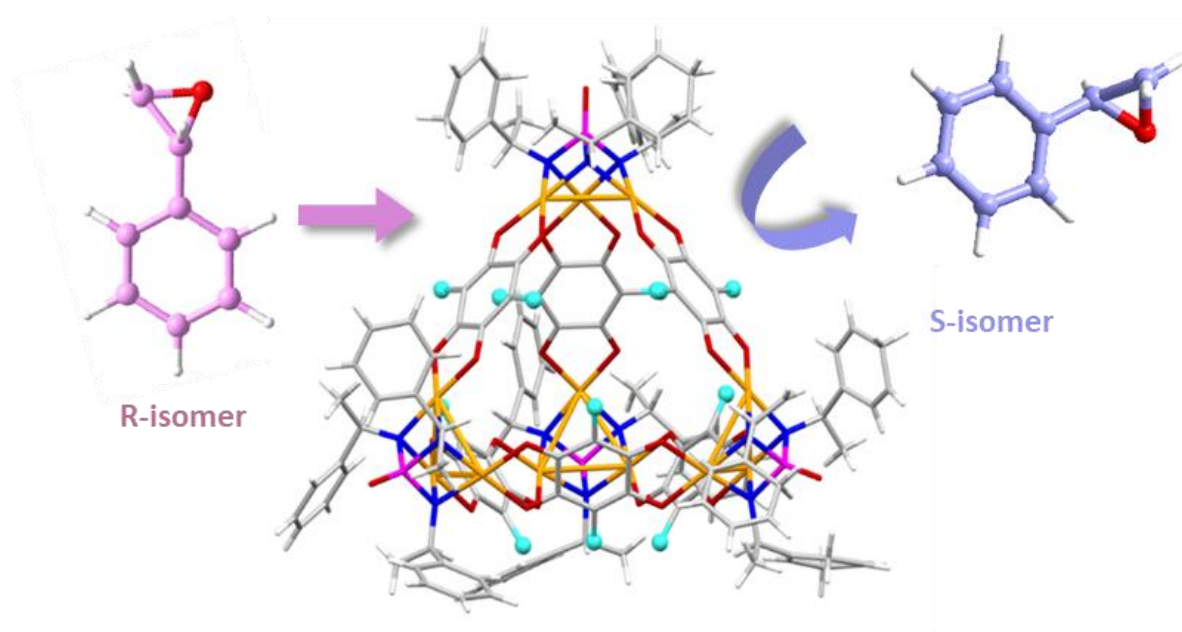
Chapter 4: Squarate-Tethered Enantiomeric Imido-Pd(II) Cages for Recognition and Separation of Chiral Organic Molecules



Chiral coordination cages have emerged as an efficient platform for the enantioselective processes via host-guest interactions. Here, we report an enantiomeric pair of tetrahedral cages of formula $[(\text{Pd}_3[\text{PO}(\text{N}^*(\text{CH}(\text{CH}_3)\text{Ph})_3])_4(\text{C}_4\text{O}_4)_6]$ supported by chiral tris(imido)phosphate trianions and squarate ($\text{C}_4\text{O}_4^{2-}$) linkers. These cages exhibit unusual coordination isomerism for Pd(II)-linker bonds compared to the other Pd(II) cages of this family. Further, they were employed for the recognition and separation of small chiral molecules containing various functionalities. High enantioselectivities of 67

and 41 were found in the case of *R*-4-hydroxydihydrofuran-2(3H)-one and *S*-epichlorohydrin recognized by the *R*-isomer of the cage. Chiral separation studies showed remarkable enantiomeric excess values of 93 and 85% for the *S*-epichlorohydrin and *R*-4-benzyl-2-oxazolidinone, respectively, from their racemic mixtures. These studies showcase the potential of coordination cages for enantioselective applications.

Chapter 5: Fine-tuning of Window Size of Enantiomeric Imido-Pd(II) Cages for Effective Enantio Separation of Organic Molecules



Chiral sensing and separation of enantiomers are crucial for the synthesis of biologically relevant compounds, as well as for applications in catalysis and pharmaceutical development. Chiral coordination cages have gained significant attention as effective platforms for enantioselective processes through their well-defined, tunable cavities that facilitate host-guest interactions. In this study, we systematically explored the enantioselective binding and separation properties of two tetrahedral Pd(II) cages, 1-R and 2-R, with the molecular formula $[(\text{Pd}_3[\text{PO}(\text{N}(\text{*CH}(\text{CH}_3)\text{Ph})_3])_4(\text{C}_6\text{O}_4\text{X}_2)_6]$, where $\text{X} = \text{Cl}$ or F . Their enantioselective abilities were investigated for small chiral molecules with diverse functional groups separately. Notably, the *R*-isomer of the 2-R cage demonstrated high enantioselectivity value of 88 for *R*-styrene oxide. Chiral separation experiments further revealed impressive enantiomeric excess values of 98% for *R*-styrene oxide when separated from their racemic mixtures by 2-R. The enhanced selectivity and separation efficiency were attributed to an optimal guest-to-cavity fit and the presence of multiple interaction sites within the host framework. Remarkably, fluorine substitution in 2-R led to a 16-fold enhancement in enantioselective separation efficiency compared to its chlorine-substituted counterpart, primarily due to improved portal dimensions, tighter molecular packing, and increased hydrogen

bonding interactions. These findings highlight the potential of coordination cages for various enantioselective applications.

Abbreviations

Anal.	Analysis
Calcd.	Calculated
CCDC	Cambridge Crystallographic Data Centre
DFT	Density Functional Theory
DMSO	Dimethyl Sulphoxide
DCM	Dichloromethane
MeOH	Methanol
Ph	Phenyl
ESI	Electron Spray Ionisation
FT-IR	Fourier Transform Infrared Spectroscopy
MALDI-TOF	Matrix Assisted Laser Desorption Ionization-Time Of Flight
MS	Mass Spectrometry
NMR	Nuclear Magnetic Resonance
RT	Room Temperature
SCXRD	Single Crystal X-Ray Diffraction
TGA	Thermogravimetric Analysis
DOSY	Diffusion Ordered Spectroscopy
NOESY	Nuclear Overhauser Effect Spectroscopy
ROESY	Rotating-frame nuclear Overhauser Effect Spectroscopy
mg	Milligram
mmol	Millimole
mm	Millimetre

ml	Millilitre
μl	Microlitre
ppm	Parts Per Million
min	Minute
hr	Hour
Å	Angstrom
°	Degree

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Chapter 3

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Chapter 4

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List of Publications

❖ Contributions Included in the Thesis

1. Squarate-Tethered Enantiomeric Imido-Pd (II) Cages for Recognition and Separation of Chiral Organic Molecules

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2. A Chiral Hexa-amino Cyclotriphosphazene for Enantioselective Recognition of Small Organic Compounds.

C. Jose, Sradha, N., & R. Boomishankar*

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3. Portal Substituent Modulations in Chiral Imido-Pd(II) Cages for the Enhanced Separation of Styrene Oxide Enantiomers.

C. Jose, A. Sarkar, K. V. Khopade, & R. Boomishankar*

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4. A Chiral Phosphine Oxide for Enantio Recognition of Epoxides

C. Jose, & R. Boomishankar*

(*Manuscript under Preparation*)

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5. Effective Enantioselective Recognition by Chiral Amino-Phosphonium Salts

P. Rajasekar, C. Jose, M. Sarkar, R. Boomishankar*

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6. Polyanionic Imido-P(V) Ligands: From Transition Metal Complexes to Coordination Driven Self-Assemblies

M. Sarkar, P. Rajasekar, C. Jose, R. Boomishankar*

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Chapter -1

Introduction

1.1. Basic concepts of chirality

The term "chirality" originates from the Greek word "cheir," meaning "hand". Although the left and right hands lack internal symmetry, they are a pair of 'left-handed' and 'right-handed' mirror images that are non-superimposable. Chirality refers to objects that can exist as two non-superimposable mirror images.¹ This intriguing phenomenon is widely observed in nature and spans across various hierarchical levels, from subatomic to galactic scales (Figure 1.1).² At the subatomic level, chirality can be observed in particle spin. At molecular level, it is found in numerous natural chiral molecules, for example amino acids, sugars, and terpenes, as well as in many synthetic compounds. Moreover, chirality is prevalent in supramolecular systems like DNA, RNA, and proteins, along with several synthetic macromolecules. On the microscopic scale, certain microorganisms, such as rabies and influenza viruses, exhibit chirality through helical symmetry in their viral morphology. Moreover, organisms like snails demonstrate chiral structures on their outer skins. Remarkably, even our galaxy exhibits chirality, illustrating that this phenomenon exists at all levels involving natural and synthetic systems from the subatomic to the cosmic scale.

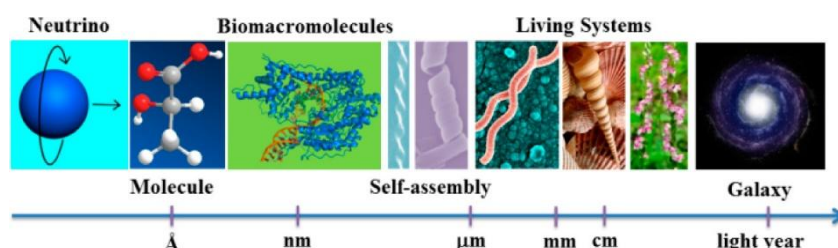


Figure 1.1. Chirality in nature at different scales, chiral structures ranging from the galactic helical structures to the neutrino unit. Reprinted with permission from Liu, M.; Zhang, L.; Wang, T. Supramolecular chirality in self-assembled systems. *Chem. Rev.* **2015**, *115*, 7304–7397. Copyright © 2015, American Chemical Society.

Since Pasteur's groundbreaking work on chiral resolution, involving the separation of enantiomeric crystals of the sodium-ammonium salt of tartaric acid,³ research on chirality has expanded significantly, addressing the challenges and potential of selective chemical synthesis and catalysis. The importance of chiral products obtained from these efforts is well-recognized, particularly in biologically relevant applications, including pharmaceuticals, drug development, sensing, diagnostics, bio-imaging, biomolecular

recognition, and disease treatment.⁴⁻⁸ Beyond their biological relevance, chiral compounds are also integral in industries focused on flavor and fragrance development, optical and electronic devices, asymmetric catalysis, liquid crystal technology, and spin control.⁹⁻¹³

1.1.1. Molecular Chirality

In molecular systems, chirality emerges when atoms are arranged in a specific spatial configuration, often exhibiting asymmetric orientation around a center, axis, or plane that leads to point, axial, or planar chirality (Figure 1.2). Among these, point chirality is the most fundamental form, resulting from the presence of distinct substituents that are attached to a central atom, imparting C_1 symmetry to the entire molecule. A classic example of point chirality is an asymmetric carbon atom or a sp^3 -hybridized carbon atom that is bonded to four different substituents.

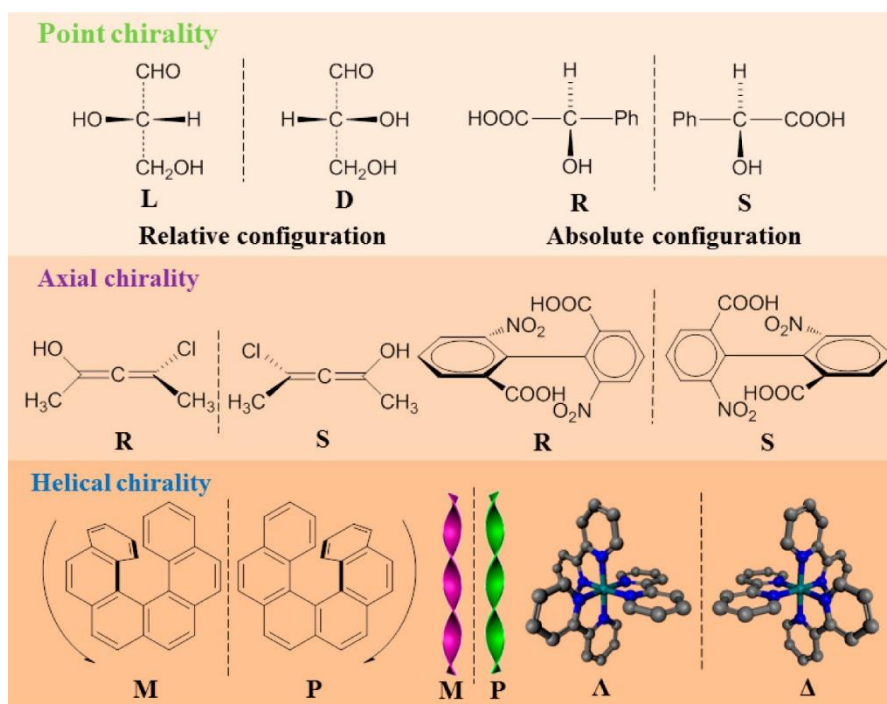


Figure 1.2. Different types of molecular chirality. Reprinted with permission from Liu, M.; Zhang, L.; Wang, T. Supramolecular chirality in self-assembled systems. *Chem. Rev.* **2015**, *115*, 7304–7397. Copyright © 2015, American Chemical Society.

Molecular chirality can also originate from compounds that do not contain an asymmetric carbon atom, but due to the presence of planar chirality and axial chirality. Planar chirality arises from the presence of two inherently achiral, non-coplanar rings that exhibit dissymmetry relative to one another or contain more than two distinct substituents arranged

in an unsymmetrical fashion. These rings should be interconnected by a rotational barrier that hinders free rotation. An example of a compound exhibiting planar chirality is BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl). Additionally, iron complexes that coordinate with an unsymmetrical η^4 -diene also display planar chirality.¹⁴ Axial chirality represents a common stereochemical behavior found in three-dimensional molecules. A chiral axis is established when the spatial arrangement of substituents connected by rotationally restricted bond results in the formation of non-superimposable mirror images. Typical examples of axial chirality include highly substituted biaryl scaffolds and dissymmetrically substituted allenes.^{15, 16}

More broadly, molecules containing chiral centers are classified as stereoisomers, which are further divided into enantiomers, which are non-superimposable mirror images, and diastereomers, which enclose at least two asymmetric centers and are not mirror images of one another. These enantiomeric forms are generally indistinguishable based on their basic physical properties; their chirality becomes apparent only upon interaction with plane-polarized light and or interaction with another chiral entity. The interaction between a given chiral molecule and another chiral molecule is highly dependent on the stereochemistry of each interacting component. Interestingly, although the probability of forming both enantiomers is more or less equal in a symmetric environment, natural compounds primarily appear in a single enantiomeric form. For instance, amino acids in living organisms typically exist in the L-form and saccharides in the D-form. Such homochiral characteristics are essential for sustaining various physiological activities of living organisms. For example, an enantiomer of carvone, specifically the (*R*)-enantiomer has the scent of spearmint, while the opposing (*S*)-enantiomer gives off the aroma of caraway seeds, which indicates the chiral recognition abilities of human olfactory receptors.

1.1.2. Supramolecular Chirality

Supramolecular chirality emerges from the non-symmetric, three-dimensional arrangement of components in non-covalently interacting assemblies.¹⁷ Unlike purely covalent molecules with defined configurations and conformations, supramolecular assemblies can adopt chiral structures based on both the intrinsic chirality and spatial arrangement of components held together by hydrogen bonding, π - π stacking, solvophobic interactions, metal coordination, halogen bonds, van der Waals forces, and host-guest complexation among the constituent building units.¹⁸

Importantly, not all components in these assemblies need to be chiral; asymmetry may arise

if one or more components are chiral or even if entirely achiral components associate to form an overall structure devoid of symmetry elements. Consequently, both chiral and achiral molecules can assemble into supramolecular chiral architectures. In such supramolecular structures, chirality could be generated through self-assembly of chiral building units or by inducing non-symmetric organization of achiral components using chiral external stimuli, for example circularly chiral solvents, polarized light, and chiral dopants.¹⁷ This non-covalent synthesis enables the synthesis of supramolecules in either diastereomeric or enantiomeric forms, expanding the potential for chiral supramolecular design. In systems composed entirely of achiral components, the supramolecular outcome is generally racemic. However, the supramolecular chirality of the system is often determined by and may align with the chirality of the building blocks of the systems. The inherently dynamic nature of supramolecular chirality enables it to respond to external stimuli and environmental conditions. Since this chirality is driven by noncovalent interactions, It demonstrates reversibility and adaptability to various environmental factors, including temperature, pH, ultrasound, and solvent polarity, along with chiral memory effects.¹⁹⁻²¹ This enables fine-tuning, including reversal of supramolecular chirality, and allows precise control of hierarchical supramolecular architectures. Notably, these chiral supramolecules, whether synthesized from chiral or achiral building units, often exhibit increased chiroptical properties and other fascinating chirality behaviors.²² These amplifications arises from the cooperative assembly or arrangement of components at the supramolecular level via the synergy of multiple noncovalent forces resulting in a nonlinear enhancement in the chiroptical signals with respect to the proportion of chiral structure or the enantiomeric surplus of chiral components. Such self assemblies characterized by robust and reversible supramolecular chirality, along with distinctive electrical, magnetic, optical, optical, and spintronic properties, have enabled a wide range of applications, including recognition, separation, sensing, catalysis, optical technologies, spintronics, information storage, and biomedical fields.²³⁻²⁹

Chiral supramolecules are closely associated with the field of biology, as demonstrated by numerous biomolecules, including amino acids, sugars, and peptides, which possess the capability to self-assemble together, forming complex supramolecular structures through different noncovalent interactions in natural systems (Figure 1.3). The chirality of these macromolecules serves as fundamental motifs in biological systems, playing critical roles in various physiological processes of living organisms by enabling stereospecific interactions with biological components, a distinctive property not found in achiral supramolecules.³⁰⁻³²

These interactions are vital for numerous biological functions, including drug delivery, cell adhesion, and tumor suppression. Moreover, these supramolecular assemblies with specifically engineered, intricate architectures can function as platforms, facilitating the development of novel bottom-up approaches for synthesizing chiral molecules.

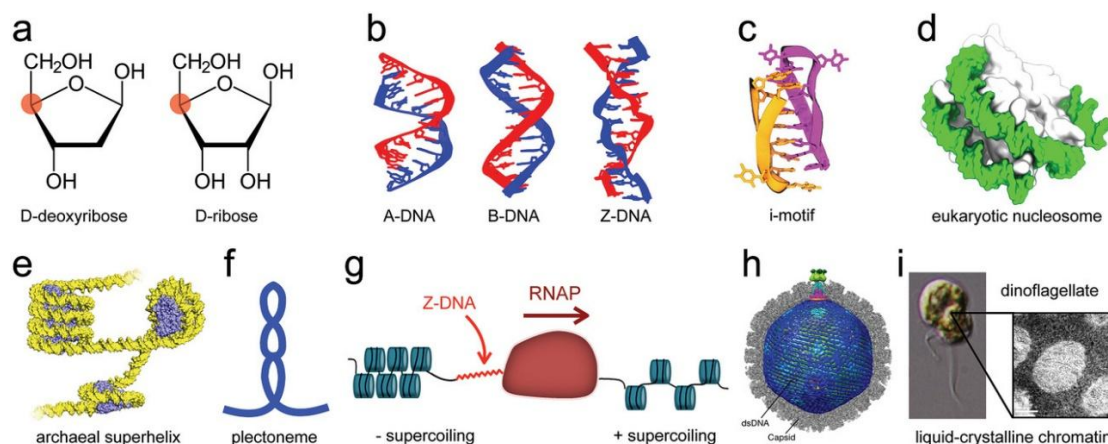


Figure 1.3. Chirality in biological nucleic acid systems. Reprinted with permission from Winogradoff, D.; Li, P.-Y.; Joshi, H.; Quednau, L.; Maffeo, C.; Aksimentiev, A. Chiral Systems Made from DNA. *Adv. Sci.* **2021**, *8*, 2003113. Copyright © 2021 Advanced Science published by Wiley-VCH GmbH

1.2. Chiral recognition and separation

1.2.1. Chiral recognition

Chiral recognition is a fundamental concept in nature, indicating the capability of a chiral host material to differentiate between a pair of enantiomeric guest molecules. Generally, the interactions of the two homochiral molecules of an enantiomer with another chiral molecule result in distinct outcomes due to differences in the relative orientations of interacting groups. When a chiral host interacts with a pair of enantiomers, the intermolecular non-covalent interactions vary, leading to the formation of diastereomeric complexes. Thus these complexes exhibit different physical and chemical properties, which can be easily examined by conventional spectroscopic techniques such as UV-Vis and fluorescence spectroscopy, binding constant measurements, enthalpy and entropy evaluations, and NMR spectral shifts, and crystal structure determination.

The sensing and recognition of enantiomers and other diastereomers is an essential process as chirality plays a important role in biological systems and chemical processes. In

biological systems, the enzymes are often chiral in nature, and they interact specifically with one enantiomer of a substrate and do not interact with the other enantiomer leading to different products that might be ineffective or toxic in biological systems. For example, the enzyme alcohol dehydrogenase selectively converts the *S*- 2-butanol to 2-butanone.³³ Moreover, most drugs are chiral, and often only one enantiomer is biologically active, while the other may have no effect or be toxic. For instance, the drug L-dopamine is used to treat Parkinson's disease, whereas the other enantiomer, D-dopamine, causes mitochondrial deficiency and weight loss.³⁴ Similarly, in agrochemicals like mecoprop, only one enantiomer is biologically active, which reduces efficacy and increases environmental hazards if the enantiomers are not effectively separated.³⁵ Thus, the capability to sense, recognize, and separate the enantiomers is essential for drug development and chemical synthesis, enhancing safety, efficacy, and environmental impacts.³⁶

Despite its importance, the enantioselective abilities of enantiomers remain a significant challenge in developing chemical sensors. This difficulty is particularly pronounced in real-life applications, such as the development of drugs and agrochemicals. In this context, chiral macromolecules and supramolecular assemblies have emerged as promising candidates for such applications.²⁵ Chiral supramolecular systems exhibit dynamic behavior, making them extremely responsive to the addition of non-racemic molecules. This dynamic behavior with respect to their chemical environment makes them a stronger candidate for various types of chiral sensors, as these systems may undergo changes in their morphology upon interaction with non-racemic analytes, such as solubility, chiroptical properties (e.g., circular dichroism (CD) and circularly polarized luminescence (CPL)), or conductivity. Such changes can be detected either visually or via spectroscopic measurements.³⁷ Supramolecular architectures with well-defined internal cavities and functional sites also hold the potential for enantioselective applications owing to their distinct chiral environments and the confinement effects due to the presence of central cavities.³⁸ This selective recognition is driven by a combination of specific non-covalent interactions between the host and the guest.

1.2.1.1. Enantio-discriminating Host–Guest Systems

Chiral recognition using host-guest chemistry involves a chiral host molecule that can selectively bind to one enantiomer of guest molecules over the other. This is achieved by the asymmetric 3D- spatial arrangement of interacting groups via noncovalent interactions such as hydrogen bonding, dipole-dipole, π - π stacking, hydrophobic, and steric interactions

between the chiral host and the enantiomeric guests, which result in the formation of diastereomeric complexes. In host-guest enantio-discrimination systems, it is widely understood that a minimum of three-point non-covalent intermolecular interactions within the host and guest systems is necessary for effective enantio-discrimination.²⁵

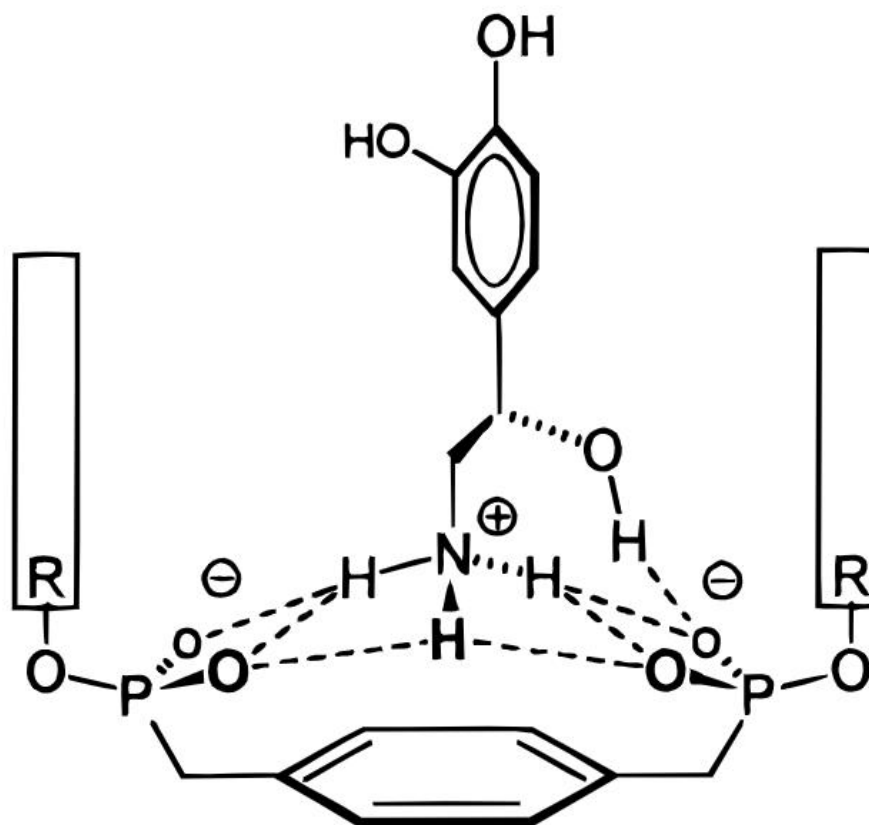


Figure 1.4. The complex of *p*-xylylene bisphosphonates with nor-adrenaline.⁴⁰

Reprinted with permission from Schrader, T. Toward synthetic adrenaline receptors: strong, selective, and biomimetic recognition of biologically active amino alcohols by bisphosphonate receptor molecules. *J. Org. Chem.* **1998**, 63, 264–272. Copyright © 1998, American Chemical Society

However, determining the ideal number of interaction sites remains an open question. This guest-binding with a chiral host is a complex process influenced by both enthalpic and entropic factors, including the encapsulation of guest molecules and the displacement of any solvent molecules that are already coordinated with the host.³⁸ The solubility and stability of the host in solution are also essential for efficient binding.³⁹ A notable example of an enantio-discriminating host-guest system was reported by Schrader and co-workers,

which displayed functionalized hosts featuring cleft-like structures and bisphosphonate esters as primary binding sites for diammonium guests and amino alcohols (Figure 1.4).⁴⁰ One such host allowed unhindered access for the cationic groups of the guest molecules to interact with the phosphonate binding sites, demonstrating an effective and rational approach to enantio-discrimination.

1.2.1.2. Advanced Tools and Techniques for Chiral Recognition and Sensing

Circular dichroism (CD) spectroscopy has been extensively used for the recognition of chiral molecules. Enantiomeric or diastereomeric chiral complexes are formed upon binding with enantio-pure guest molecules, leading to characteristic induced CD (ICD) signals in the absorption region of the chromophoric receptors present within chiral macromolecules. These signals help in the determination of the enantiomeric excess and absolute configurations of chiral guests based on the sign and intensity of the Cotton effects.⁴¹

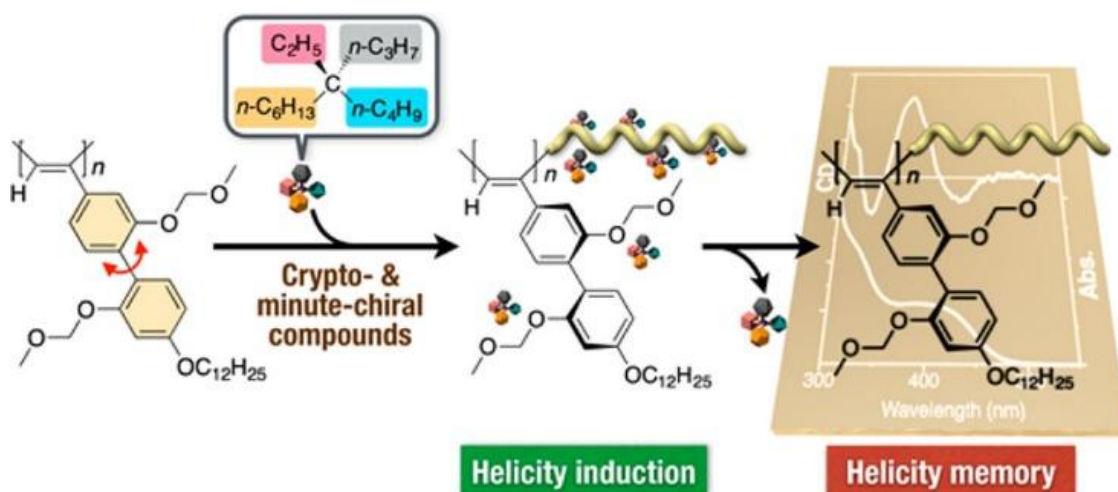


Figure 1.5. Schematic illustration of a sequential induction of axial chirality at the biphenyl pendants of poly-1 and its macromolecular helicity accompanied by chiral amplification through noncovalent interactions with chiral hydrocarbons and subsequent memory of the induced axial chirality and helicity of poly-1 after complete removal of chiral hydrocarbons and isotopomers.⁴² Reprinted with permission from Maeda, K.; Hirose, D.; Okoshi, N.; Shimomura, K.; Wada, Y.; Ikai, T.; Kanoh, S.; Yashima, E. Direct detection of hardly detectable hidden chirality of hydrocarbons and deuterated isotopomers by a helical polyacetylene through chiral amplification and memory. *J. Am. Chem. Soc.* **2018**, *140*, 3270–3276. Copyright © 2018, American Chemical Society

For instance, a helical polyacetylene (poly-1) polymer with 4-biphenyl pendant groups with methoxymethoxy substitutions at the 2,2 positions (Figure 1.5), which is optically inactive but adopts a one-handed helical conformation in the presence of chiral analytes.⁴² The chirality transfer from the analyte to the helical polymer backbone is facilitated by interactions between the two adjacent pendant groups bearing alkoxymethoxy functionalities. Moreover, this polymer exhibits non-covalent helicity induction and a chiral memory effect that persists even after the analyte is removed, which results in a strong and characteristic ICD response. This enables the polymer to detect the enantiomers even at extremely low concentrations.

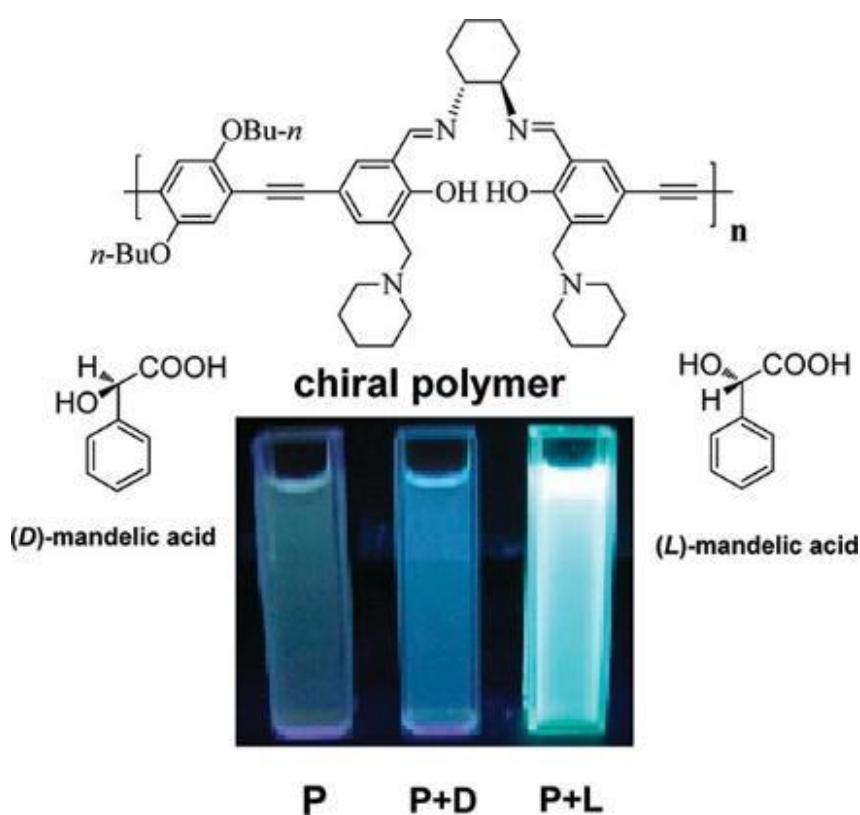


Figure 1.6. (*R,R*)-salen-based chiral polymer exhibiting a greater fluorescence “turn-on” response toward (L) mandelic acids and appear bright blue fluorescence.⁴⁵ Reprinted with permission from Song, F.; Wei, G.; Wang, L.; Jiao, J.; Cheng, Y.; Zhu, C. Salen-based chiral fluorescence polymer sensor for enantioselective recognition of α -hydroxyl carboxylic acids. *J. Org. Chem.* **2012**, 77, 4759–4764. Copyright © 2012, American Chemical Society

Recently, significant strides have been performed for developing highly enantioselective

fluorescent sensors employing various photo-luminescent probes for the recognition of chiral compounds. Shao, Xu and coworkers designed a fluorescence-based chiral sensor for differentiating the enantiomers of tetrahydropalmatine (L- and D-THP) as model analytes.⁴³ This was achieved by introducing an apurinic/apyrimidinic (AP) site into the structure of a DNA duplex, serving as an enantioselective discrimination probe. The binding specificity of the AP site was determined through the intrinsic fluorescence of L-THP and D-THP. The sensing mechanism involves the selective identification of THP at the AP site that efficiently displaces the pre-bound fluorophore enhancing the fluorescence. It is perceived that only L-THP could substitute the fluorophore, while D-THP showed no such effect. The ability to distinguish L-THP from D-THP was visibly apparent in the solution, as L-THP generated a brighter blue fluorescence under UV light. Other examples of fluorescence-based chiral sensors include the detection of α -hydroxy carboxylic acids using Salen-based chiral polymers (Figure 1.6),⁴⁴ amino acids using BINOL-based perfluoroalkyl ketones,⁴⁵ amino alcohols with perfluoroalkyl BINOL-based chiral diketones,³⁷ and chiral functional amines via 1,10-bi-2-naphthol (BINOL)-based bis(naphthylimine) compounds.⁴⁶

Nuclear Magnetic Resonance (NMR) spectroscopy is another highly effective technique for studying chirality sensing, especially with the use of chiral derivatizing agents (CDAs) and chiral solvating agents (CSAs). Compared to the CDA method, the CSA approach has several advantages, such as eliminating labor-intensive derivatization steps and enabling straightforward NMR analysis by simply mixing a CSA with the sample. Song and co-workers developed a bis thiourea-based proton NMR sensor capable of recognizing a wide variety of chiral compounds, including alcohols, sulfoxides, lactones, epoxides, amino alcohols, amides, β -chiral carboxylic acids, and chiral carboxylic acids.⁴⁷ Furthermore, Bian, Song and co-workers established a method for determining the configurations of α -amino acids by comparing ^1H NMR chemical shift values in the presence of chiral target guest molecules.⁴⁸ This method displays highly resolved NMR spectra with well-distinguishable proton signals, for the mixed solutions of chiral solvating agents. Moreover, Huang and co-workers fabricated an efficient chiral sensor for recognizing various acids using multiple NMR techniques.⁴⁹

1.1.1. Chiral separation

As highlighted, chirality is important in biological systems due to the homochirality of nucleic acids, sugars, and peptides, which serve as the building blocks of several biomolecules. Thus separation of these enantiopure biomolecules is of great importance in

pharmaceuticals. It is also observed that the demand for non-racemic chiral molecules is progressively increasing in fields such as chemistry, food technology, agriculture, information technology, and nanotechnology. As a result, the development of enantiomerically pure compounds and drugs is of primary importance to maximize their efficacy and minimize potential toxicity.

1.1.1.1. Advanced Tools and Techniques for Chiral Separation and Sensing

Over the past years, significant progress has been achieved in enantio-separation, using separation techniques namely chromatography, membrane separation, and electrophoresis. The major focus in these fields has been the development of novel chiral stationary phases (CSPs) and chiral selectors. The noted advancements in derivatization and complexation reagents and specially engineered MS instruments have further improved the enantiomer discrimination.

Chiral chromatography, like gas chromatography, high-performance liquid chromatography, and supercritical fluid chromatography, is one of the frequently applied techniques for enantio-separation. While these chromatographic techniques have been well established over the years, they still offer significant opportunities for innovation in CSP development. Beyond traditional CSPs like cyclodextrins, macrocyclic antibiotics, and polysaccharides,⁵⁰⁻⁵² new classes of crystalline porous materials like covalent-organic frameworks (COFs), metal-organic frameworks (MOFs), and porous organic cages (POCs) are proving useful for enantiomeric separation (Figure 1.7).⁵³⁻⁵⁶ POCs are defined as soluble porous materials made from monomers carrying defined internal cavities,⁵⁷ and their cavities promote the host-guest interactions, helping in the chirality discrimination. For example, Xie and Zhang and coworkers have synthesized a 3,3',5,5'-tetraformyl-4,4'-biphenyldiol and (1*R*,2*R*)-cyclohexanediamine derived chiral cage (NC1-*R*) immobilized on uniform silica particles to form NC1-*R*@silica CSPs.⁵⁷ This was shown to outperform the commercial Chiralcel OD-H columns and Chiralpak AD-H columns in HPLC enantioseparation, signifying the ability of POCs in this chiral HPLC chromatography. Additionally, the solubility of POCs enables them to be coated onto capillaries for gas chromatography. Homochiral NC1-*R*, for example, was dissolved in DCM and polysiloxane OV-1701 to yield NC1-*R*-coated capillaries that achieved the separation of alcohols, esters, and ethers, which are not separable by commercial β -DEX 120 columns.⁵⁸

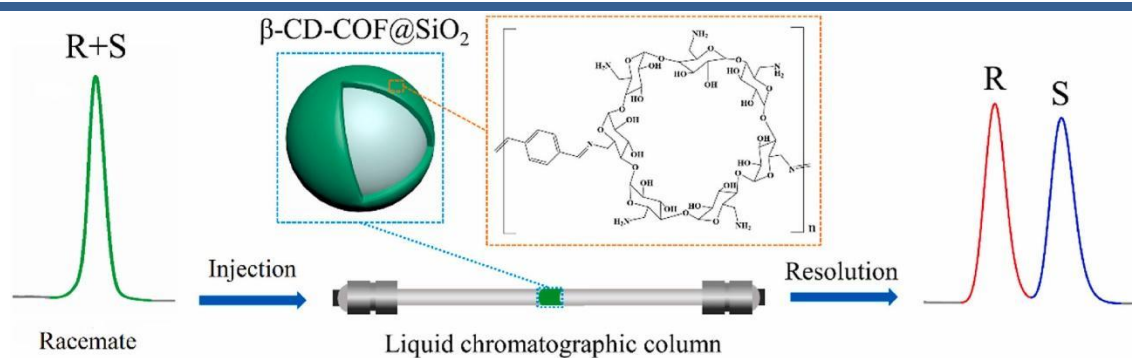


Figure 1.7. The fabricated β -CD-COF@SiO₂-packed column exhibiting high excellent separation performance with various types of racemic alcohols, ketones, organic acids, and amines.⁵⁴ Reprinted with permission from Xu, N.-Y.; Guo, P.; Chen, J.-K.; Zhang, J.-H.; Wang, B.-J.; Xie, S.-M.; Yuan, L.-M. Chiral core-shell microspheres β -CD-COF@SiO₂ used for HPLC enantioseparation. *Talanta* **2021**, 235, 122754. Copyright © 2021 Elsevier B.V. All rights reserved.

Capillary electrophoresis (CE) is predominantly utilized for the enantioseparation of biologically relevant compounds. Most of the studies about chiral CE comprise the use of cyclodextrins (CD) as chiral sensors. Additionally, along with the commercially available CDs such as CM- β -CD and native β -CD, other innovative functional CDs are also studied for the chiral CE analysis. For example, hydroxypropyl- β -cyclodextrin has been employed in a CE-MS method for the enantioseparation of herbal drugs such as tetrahydropalmatine and canadine enantiomers directly from complex *Corydalis Rhizoma* samples.⁵⁹ Chiral ionic liquids constitute an additional class of effective chiral selectors for capillary electrophoresis, featuring excellent stability, volatility, and water solubility. A series of new tetraalkylammonium-L-tartrate ionic liquids were synthesized, demonstrating superior enantioseparation of model enantiomers compared to tartrate ester-based chiral selectors.⁶⁰ Furthermore, integrating different chiral selectors has also enhanced the chiral separation in CE. An example of this combination would be a dual chiral–achiral sensor system, using HP- β -CD and 5,10,15,20-tetrakis(4-hydroxyphenyl) porphyrin-for the CE analysis of chiral aminoalkanol derivatives used as anticancer agents (Figure 1.8).⁶¹

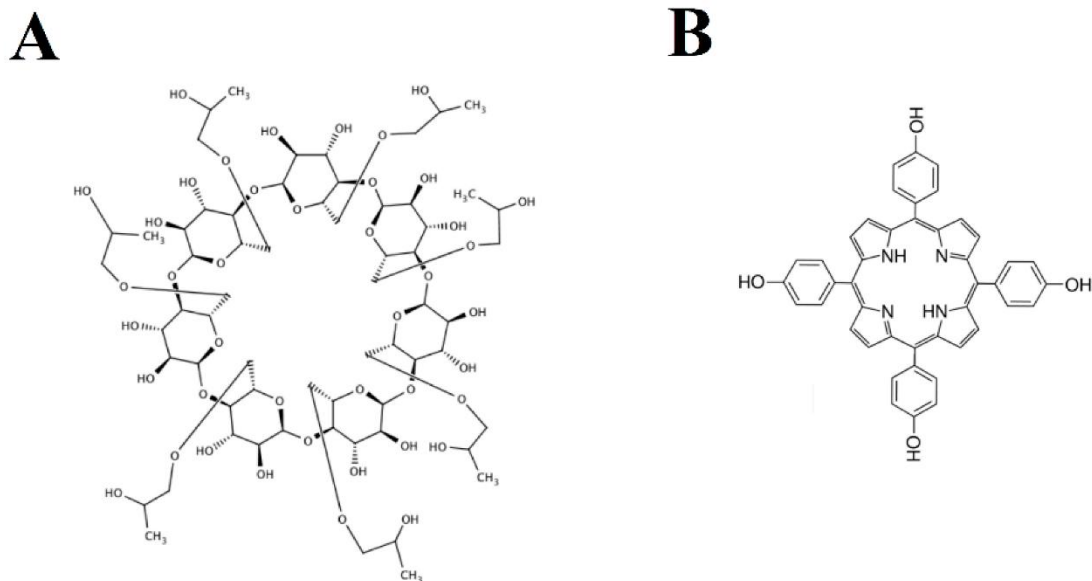


Figure 1.8. Chemical structures of (A) 2-hydroxypropyl-β-cyclodextrin (B), 5,10,15,20-tetrakis (4-hydroxyphenyl) porphyrin.⁶¹ Reprinted from Grodner, B.; Napiórkowska, M.

Dual 2-Hydroxypropyl-β-Cyclodextrin and 5,10,15,20-Tetrakis(4-Hydroxyphenyl) Porphyrin System as a Novel Chiral-Achiral Selector Complex for Enantioseparation of Aminoalkanol Derivatives with Anticancer Activity in Capillary Electrophoresis. *Molecules* **2021**, *26*, 993.

Capillary electrochromatography (CEC) is a rapid and efficient method of separating and analyzing chiral compounds, primarily due to the incorporation of a stationary phase (SP) made within the capillary system, which provides an advantage over conventional CE. Recent developments in chiral CEC have focused on developing chiral open-tubular or monolithic columns alongside new CSPs. CD derivatives are still the most commonly used CSPs of CEC. HP-γ-CD, β-CD, ethanediamine-β-CD, CE-β-CD, and SBE-β-CD have been used for enantioseparation of a various chiral drugs and dansyl-amino acids.⁶²⁻⁶⁴ In addition to this, covalent organic frameworks, enzymes, and antibiotic-based chiral stationary phases look auspicious for chiral separations.⁶⁵⁻⁶⁷ For example, β-CD and L-phenylalanine were combined with zeolite silicate nanoparticles to generate CSPs for open-tubular capillary columns in CEC for the separation of enantiomers of catechu herbs and salbutamol in complex sample matrices (Figure 1.9).⁶⁸ Enantioselective permeability membranes were broadly used in large-scale chiral separation in the pharmaceutical and chemical industry compared to chromatographic techniques used more on an analytical scale.⁶⁹

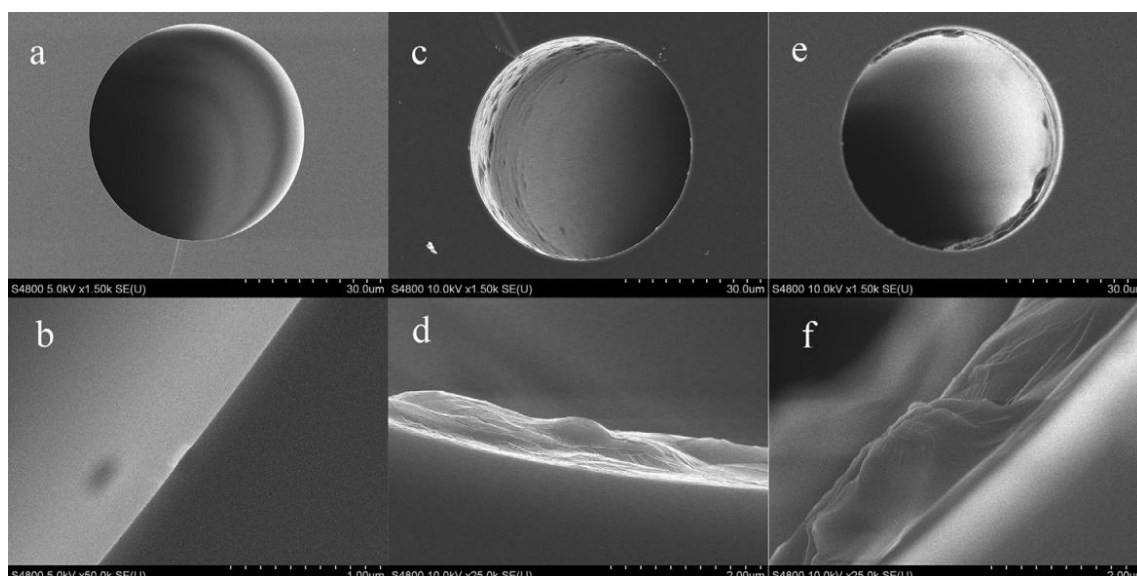


Figure 1.9. SEM images of (a, b) bare capillary, (c, d) β -CD@SiO₂NPs/PDA-OT column, (e, f) β -CD/L-Phe@SiO₂NPs/PDA-OT column.⁶⁸ Reprinted with permission from Yang, L.; Zhao, X.; Chai, Y.; Li, C.; Zhang, Y.; Chen, L.; Ye, J.; Chu, Q. Preparation and evaluation of chiral open-tubular columns supported with zeolite silica nanoparticles and single/dual chiral selectors using capillary electrochromatography with amperometric detection. *J. Chromatogr. A* **2021**, 1651, 462298. Copyright © 2021 Elsevier B.V. All rights reserved.

Conventional chiral membranes have been produced mostly with polysaccharides, i.e., cellulose, lipids, sodium alginate, poly-acetylene, and peptides.⁷⁰ For example, Zang and Aoki and coworkers have developed chiral graft co-polymers with enantiomeric oligomethylpinanylsiloxane grafts that are flexible, and a rigid poly(phenylacetylene) backbone, which exhibited a remarkable separation of racemic mandelic acid.⁷¹ In addition, Otsuka and coworkers synthesized cellulose tris(3,5-dimethylphenylcarbamate) to produce textiles composed of nanofibers for the enantio separation of (*R,S*)-1-(1-naphthyl)ethanol via rapid vacuum filtration.⁷² Membranes modified with ethylenediamine- β -CD demonstrated remarkable enantioselectivity with %ee values of 100.0% for tryptophan and 75.34% for propranolol (Figure 1.10).⁷³ Mixed matrix membranes (MMMs), including CD-based materials like CD-MOF and CD-COF, have shown vast potential. A membrane with an active phase of 20 wt% CD-MOF displayed high enantioselectivity and stability for separating the enantiopure 1-phenylethanol.⁷⁴

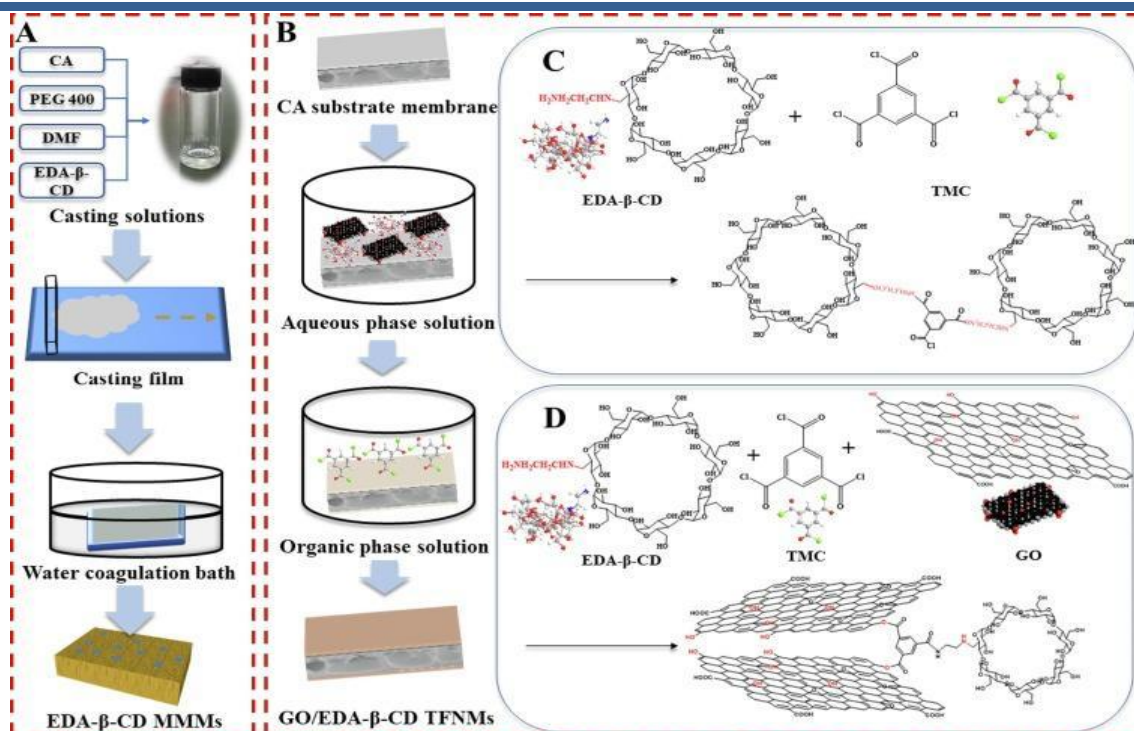


Figure 1.10. (A) Schematic representation for the synthesis of EDA-β-CD MMMs, (B) EDA-β-CD TFNMs and GO/EDA-β-CD TFNMs; (C) Chemical modification of EDA-β-CD TFNMs (D) and GO/EDA-β-CD TFNMs.⁷³ Reprinted with permission from Bai, X.; Ke, J.; Qiu, X.; Liu, H.; Ji, Y.; Chen, J. Ethylenediamine-β-cyclodextrin modified graphene oxide nanocomposite membranes for highly efficient chiral separation of tryptophan and propranolol enantiomers. *Sep. Purif. Technol.* **2022**, 290, 120833. Copyright © 2022

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1.1.2. Chiral recognition by small molecular host

Schrader developed bisphosphonate esters as key interacting units for amino alcohols and diammonium guests for their enantio discrimination.⁴⁰ The bisphosphonate esters are incorporated into a spirobisindane framework to create two distinct hosts. The first host is a cleft-like structure that allows unhindered access to the phosphonate groups by cationic groups of the guest. The second host incorporates a mesitylene spacer that blocks the cleft, thus imposing steric hindrance, distinguishing the enantiomers using sterically driven chemoselectivity by preventing the rotation within the cleft. This design of a host provides further discrimination towards the enantiomers, with the most effective binding resulting from the alignment of guest ammonium groups with host phosphonate groups. However,

the mesitylene spacer plays a key role by providing a third interaction site for the guest molecule, along with other interactions like the C-H $\cdots\pi$ interactions.

Another example demonstrated by Xie and coworkers, involved tuning the flexibility, size, strength and number of interaction sites in imidazole-containing cyclophane receptors to enantiomerically discriminate different methyl ester derivatives of amino acids.⁷⁵ Similarly, Fuji and co-workers created different supramolecular hosts fused with multiple functional elements for enantiomeric color readouts like phenolphthalein unit that normally provides a visible color change on binding of diamines of suitable size with multiple crown ethers (Figure 1.11).⁷⁶

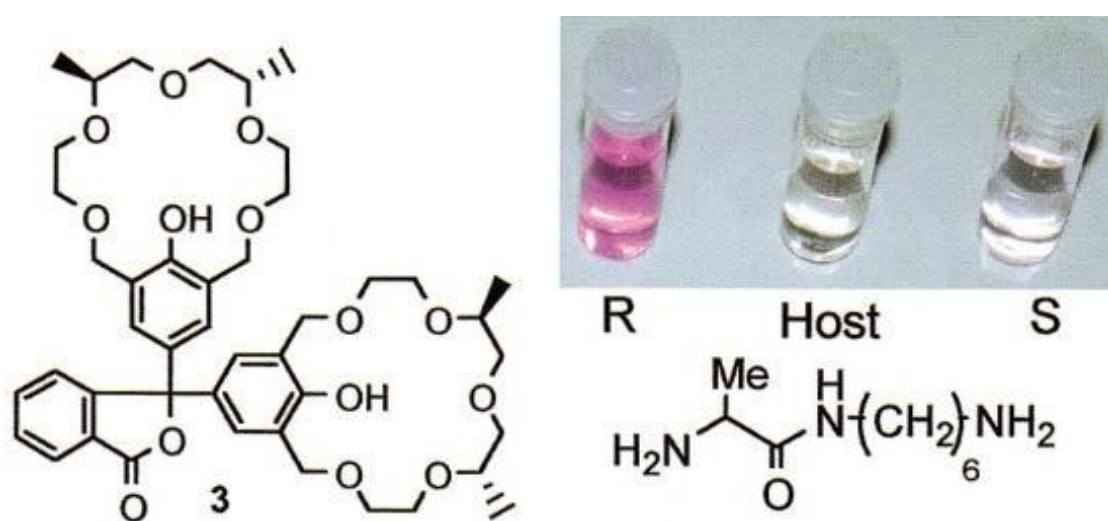


Figure 1.11. Optically active supramolecular host molecule based on a phenolphthalein skeleton for displaying visible color change during the enantiomeric recognition of alanine derivatives.⁷⁶ Reprinted with permission from Tsubaki, K.; Nuruzzaman, M.; Kusumoto, T.;

Hayashi, N.; Bin-Gui, W.; Fuji, K. Visual enantiomeric recognition using chiral phenolphthalein derivatives. *Org. Lett.* **2001**, 3, 4071–4073. Copyright © 2001, American Chemical Society.

Ahn and coworkers demonstrated the synergy between intermolecular interactions and steric effects in an chiral-discriminating system.⁷⁷ This study emphasized the pivotal role of π - π and hydrogen-bonding interactions in the chiral sensing abilities of most of the host-guest systems. They utilized an unconventional host molecule where the phenyl-substituted oxazoline pendant arms in the host molecule afford a C_3 -symmetric cavity to facilitate effective enantio-discrimination for R-chiral primary organoammonium guests.

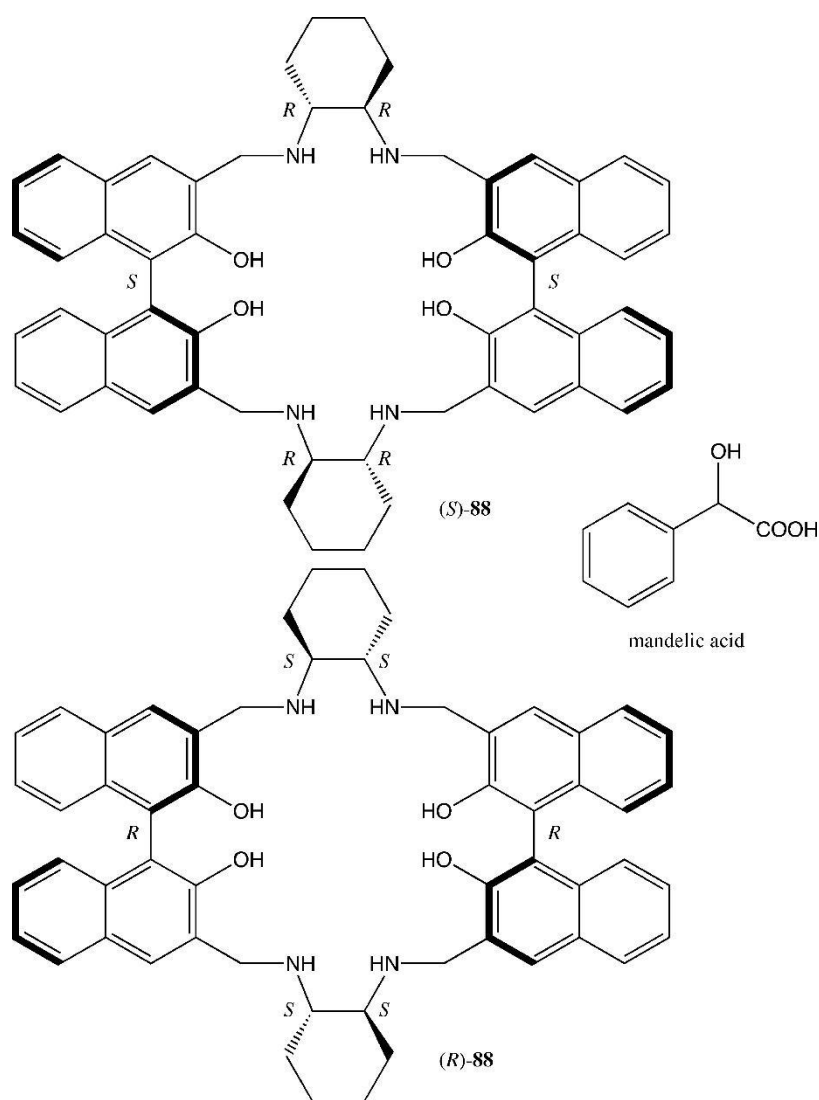


Figure 1.12. Optically active artificial host macrocycles derived from binaphthyl groups for enantiomeric recognition of mandelic acid.⁷⁹ Reprinted with permission from Li, Z. B.; Lin,

J.; Pu, L. A cyclohexyl-1,2-diamine-derived bis(binaphthyl) macrocycle: enhanced sensitivity and enantioselectivity in the fluorescent recognition of mandelic acid. *Angew. Chem., Int. Ed.* **2005**, *117*, 1718–1721. Copyright © 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Slaven and coworkers synthesized a BINOL-based chiral selector with p-phenylenebis(2-ethynyl) which acts as a spacer and displayed the enantioselective recognition of α -methylbenzylamine and methyl ester of valine.⁷⁸ Further, Li and co-workers attempted to utilize fluorescence spectroscopy as a viable tool for enantiodiscrimination of mandelic acid. The fluorescence emission exhibited by the excimer complex served as a probe to the chiral

recognition.⁷⁹ In macrocycles derived from binaphthyl groups which act as a chiral source as well as a fluorophore, and alcohol as well as amine functional groups assist with intermolecular interactions (Figure 1.12). For the (*S*)-host, there was negligible fluorescence from (*R*)-mandelic acid, while (*S*)-mandelic acid gave rise to a very strong fluorescence signal that was ~ 20 times greater than that of the free host. The enantioselectivity of the system was further verified with the (*R*)-host, which showed no fluorescence for the case of (*S*)-mandelic acid and a very strong emission resulting from (*R*)-mandelic acid.

In 1978, Irie and co-workers demonstrated fluorescence quenching of 1,1'-binaphthyl by the two enantiomers of *N,N*-dimethyl- α -phenethylamine.⁸⁰ Notably, using a (*R*)-host with optical purity of 77.5%, they found a substantial difference in quenching of the fluorescence between (*R*)- and (*S*)-enantiomers of *N,N*-dimethyl- α -phenethylamine. The ratio of fluorescence quenching rates (*R-guest/S-guest*) was observed to be 1.90, suggesting that the quenching mechanism was affected by the molecular interaction with a certain orientation of the chiral analyte leading to enantio discriminations. Further studies on 1,1'-binaphthyl for the chiral discrimination of chiral amines *N,N*-dimethyl-1-phenyl-2-methylpropylamines and *N,N*-dimethyl-1-phenyl-2,2-dimethylpropylamines, both having bulkier alkyl substituents in comparison to *N,N*-dimethyl- α -phenethylamine, displayed increased enantioselectivity.⁸¹

Raut and Tottertf investigated the enantio-discriminating abilities of hexahelicene for the chiral amine, *N*-methyl-4-(2-methylbutyl)aniline (Figure 1.13).⁸² Separation of the optically active hexahelicene from the racemic mixture was accomplished via flash chromatography on silica preloaded with (*S*)-2-(2,4,5, 7-tetranitro-9-fluorenylideneaminoxy)propionic acid [(+)-TAPA]. Aromatic amines quenched the fluorescence of the host in acetonitrile with marked efficiency. In contrast, aliphatic amines did not quench it, possibly due to strong π - π interactions among the host and aromatic amine units in a polar solvent. The highest enantioselectivity was perceived with the amino alcohol *R*-2-amino-1-propanol employing helicene diol as a chiral selector. However, only alkylation of the oxygen atoms of helicene diol results in no chirality discrimination, suggesting the importance of hydrogen bonding interaction between the host and the guest molecule.⁸³

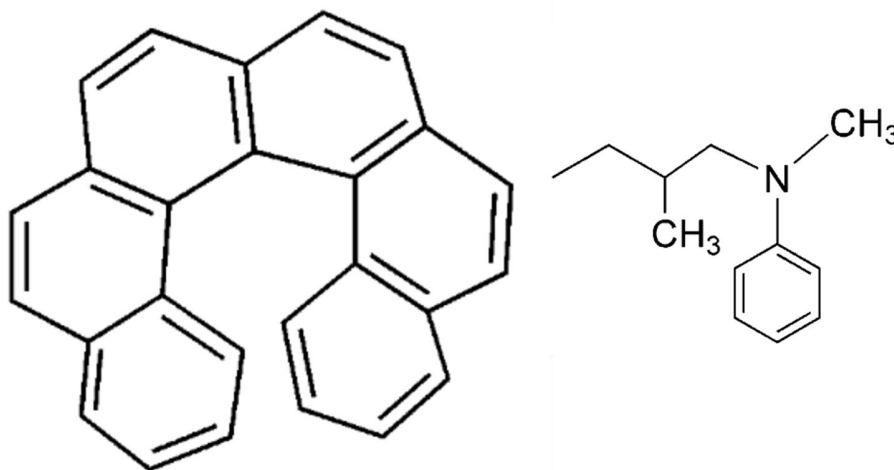


Figure 1.13. Optically active hexahelicene for recognizing chiral amine, N-methyl-4-(2-methylbutyl)aniline.⁸² Reprinted with permission from **Pu, L.** Fluorescence of Organic Molecules in Chiral Recognition. *Chem. Rev.* **2004**, *104*, 1687–1716. Copyright © 2004 American Chemical Society

Diamond and co-workers developed a new fluorescence technique to determine the enantiomeric content of chiral amines against a chiral phase. They synthesized calixarene derivatives with chiral fluorophores such as macrocyclic oligomeric phenols for the fluorescent recognition of compounds such as 1-phenylethylamine and norephedrine.⁸⁴ Further, Prodi and co-workers proved that dimethyl acridino crown ethers displayed enantioselective properties for (*R*)-1-(1-naphthyl)ethylammonium perchlorate and (*R*)-1-phenylethylammonium perchlorate salts bypassing the generation of protonated acridinium ions which was confirmed by UV absorption measurements (Figure 1.14).⁸⁵ The large difference in the K_a of both of the enantiomers with the crown ether, determined by appraising fluorescence intensities at 445 nm and 330 nm, demonstrates the enantioselective abilities of these crown ether-based compounds. During chiral HPLC separation of DNS-amino acids, Marchelli and co-workers found that the addition of the bis(1-phenylalanylamidato)copper(II) complex as an additive with the fluorescence detector had greater peak areas for the D-amino acids than their L-enantiomers clearly suggesting the chiral recognition abilities of these bis(1-phenylalanylamidato)copper(II) complex.⁸⁶

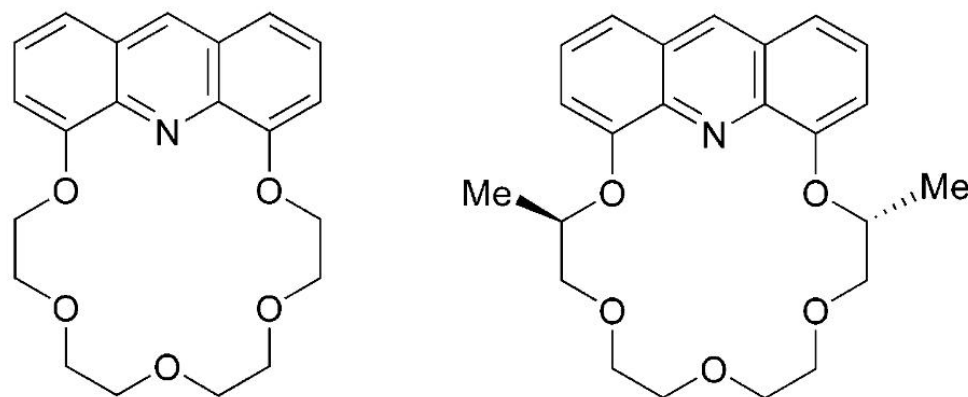


Figure 1.14. Dimethyl acridino crown ethers which are used for the enantio recognition of chiral (1-naphthyl)ethylammonium perchlorate and 1-phenylethylammonium perchlorate salts.⁸⁵ Reprinted with permission from Pu, L. Fluorescence of Organic Molecules in Chiral Recognition. *Chem. Rev.* **2004**, *104*, 1687–1716. Copyright © 2004 American Chemical Society

1.2. Chirality in supramolecular systems

1.2.1. Biomolecular supramolecules

Chiral supramolecular systems are fundamental for biological processes, acting as the basis for most cellular functions involved in life. They consist of multiple components held together by noncovalent interactions such as hydrogen bonding, π - π interactions, van der Waals forces, as well as other hydrophobic effects resulting in a chiral architecture. Since these interactions are weaker than strong covalent bonds, they enable dynamic and reversible assemblies. Supramolecular structures enable the organization and functioning of biomolecules-including proteins, nucleic acids, lipids, and carbohydrates in life forms. For example, the double-helical structure of DNA arises from supramolecular interactions between complementary base pairs. Proteins adopt a unique 3-D conformation induced by the chirality of their amino acids to compile into higher-order chiral structures, such as enzyme complexes or cytoskeletal filaments. Chiral supramolecular systems play key functional roles in molecular recognition and signaling. Enzyme-substrate interactions, antibody-antigen binding, and receptor-ligand recognition all depend on chirality to confer specificity and selectivity. For example, the interaction between chiral neurotransmitters and their cognate receptors in the nervous system employs conformational specificity in

biological signaling.⁸⁷ In photosynthetic light-harvesting complexes, the chiral disposition of pigments increases their efficacies as a channel for energy transfer.⁸⁸ In membranes, chiral lipid arrangements form asymmetric bilayers, vital for different cellular processes such as signaling, vesicle formation, and selective transport.⁸⁹ Another example of a supramolecular system is hemoglobin, which helps provide transportation support of oxygen throughout the blood, as it is essential for cooperative interactions between hemes and globin proteins.⁹⁰ The principles of supramolecular chirality in living systems encompass aspects of the molecular basis of life, opening doors for innovative utilization in medicine, materials science, and many nanotechnology applications. The interplay of chirality, self-assembly, and function illustrates the profound sophistication of nature's architecture at the molecular level.⁹¹

1.2.2. Host-Guest Complexes

Cryptophane, a term introduced by A. Collet in 1985, refers to a category of hollow organic compounds capable of reversibly binding and isolating individual analytes from their surroundings.⁹² They possess a distinctive globular structure, formed by connecting two cyclotribenzylene (CTB) units with a minimum of three linkers, whose length and composition can be modified according to the desired function. In addition to their unique binding properties, most of these host molecules are chiral due to their resultant structure rather than the presence of a stereo center. Enantiopure cryptophane derivatives are known for their molecular recognition abilities and unique chiroptical properties. Enantiopure cyclotribenzylene derivatives are fundamental constituents to equip chiral cryptophane derivatives. Collet and co-workers develop this strategy to prime various optically active cryptophane derivatives for the first time.⁹³

The second strategy, referred to as diastereomer separation, is where a chiral auxiliary interacts with racemic cryptophanes, allowing for subsequent enantio-selective crystallization or chromatography isolation for diastereomer separation. For instance, microcrystals of cryptophane derivatives functionalized with camphanic acid chloride allowed easy recovery of enantiopure forms without loss of optical activity (Figure 1.15).⁹⁴

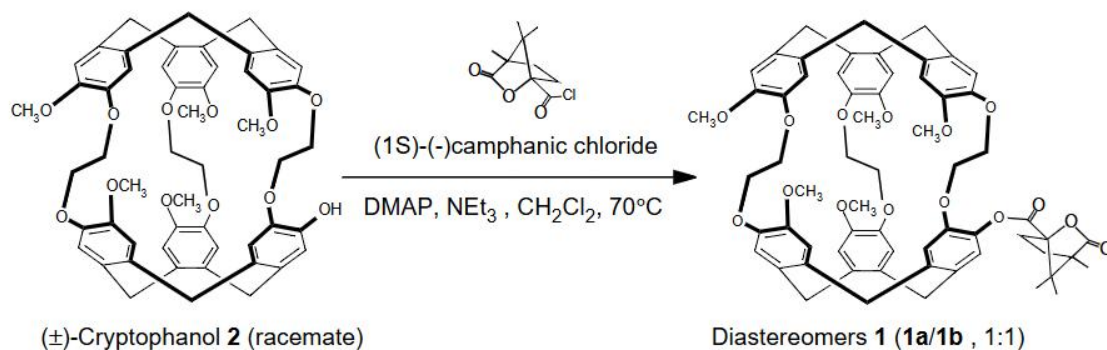


Figure 15. Preparation of chiral cryptophane from racemic cryptophanol-A.⁹⁴ Reprinted with permission from Brotin, T.; Barbe, R.; Darzac, M.; Dutasta, J. P. Novel synthetic approach for optical resolution of cryptophanol-A: a direct access to chiral cryptophanes and their chiroptical properties. *Chem. Eur. J.* **2003**, 9, 5784–5792. Copyright © 2003 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Other synthetical approaches, such as chiral HPLC, afford high levels of enantiomeric purity via optical resolution.⁹⁵ Cryptophanes' ability to separate guest molecules in a chiral environment is one of their most intriguing features. For example, an enantiopure sulfur-containing cryptophane with bigger cavities has been successfully implemented for the enantioselective discrimination of chlorofluoromethane (CHFCII).⁹⁶ As a result, combining chiroptical techniques with quantum calculations provides powerful methods to explore the nature of guest molecules within chiral environments. Additionally, using cryptophane enantiomers to discriminate small chiral guests offers the potential to create stationary chiral phases.

Cyclodextrins (CDs) are cyclic oligosaccharides consisting of (+)-glucopyranose units linked via α -(1,4) bonds, featuring a hydrophobic cavity at the inner surface and a hydrophilic outer surface. The most typical CDs are α -, β -, and γ -CDs, which consist of 6, 7, and 8 glucose units, respectively (Figure 1.16). The hydrophobic cavities allow CDs to fully or partially encapsulate various of guest molecules, forming "host-guest" inclusion complexes through van der Waals forces, hydrophobic interactions, hydrogen bonding, and other forces.⁹⁷ Since the CDs are inherently chiral, the formation of these inclusion complexes is stereoselective, making CDs and their derivatives a promising candidate for chiral recognition and separation.⁹⁸ Thus, CDs are widely used in the chiral resolution of racemic compounds in fields such as pharmaceuticals, agrochemicals, and the food

industry.⁹⁹ They are used either as additives in mobile phases or as chiral stationary phases (CSPs) in chromatographic techniques.¹⁰⁰

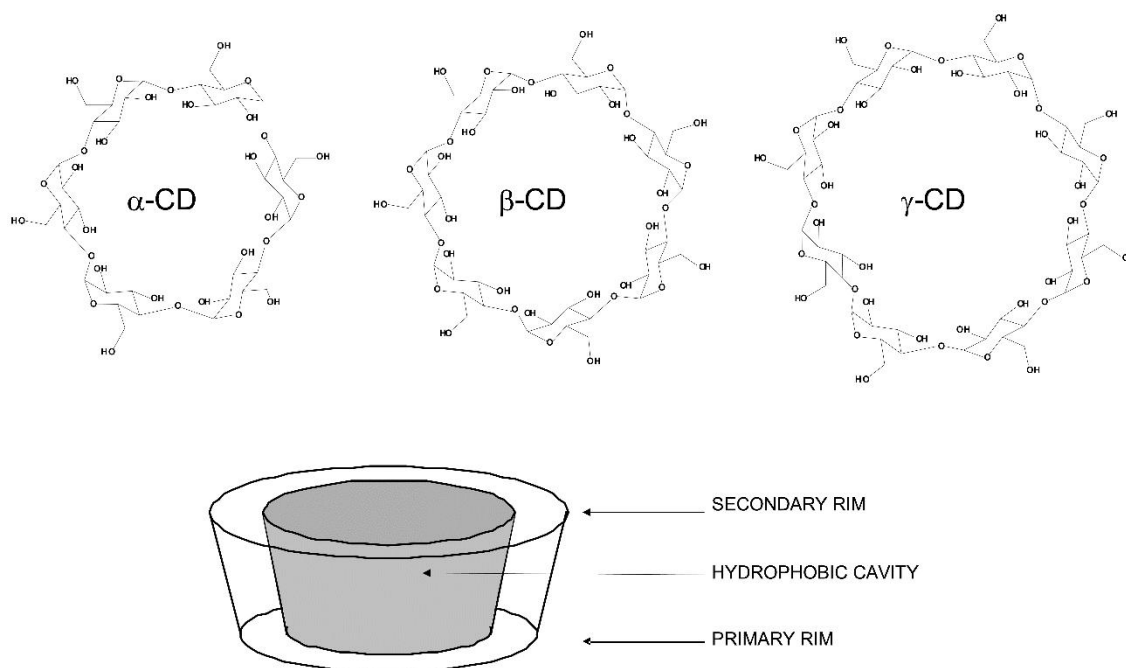


Figure 1.16. Molecular structure of α , β , and γ cyclodextrins (top view) and the schematic representation of the truncated cone shape of cyclodextrins (side view). Reprinted from Shahgaldian, P.; Pielies, U. Cyclodextrin Derivatives as Chiral Supramolecular Receptors for Enantioselective Sensing. *Sensors* **2006**, 6, 593–615.

The typical method is to immobilize derivatized CDs onto solid silica supports via covalent bonding, providing stable CD-CSPs. Chen and colleagues developed a heptakis(2,3,6-tri-O-methoxymethyl)- β -cyclodextrin CSP that was fabricated to a capillary column using a static coating strategy, for the effective resolution of various volatile analytes, such as 2-hydroxypropionates, ethyl 2-hydroxypropionates, and methyl 2-methylsulfonylpropionates.¹⁰¹

Cucurbit[n]urils (Q[n]) are a relatively new class of macrocycles named after their resemblance to the shape of a "gourd" or "pumpkin" from the Cucurbitaceae plant family, as well as to a vessel used by alchemists for distillation.¹⁰² From a molecular and structural perspective, they can be described as open-ended barrels in various sizes. Currently, there are five conventional Q[n] members, with n ranging from 5 to 10.¹⁰³ Their high binding constants and symmetrical cavity structures have led to various applications, including

enantio-recognition, chiral molecular switches, and chiral stationary phases. The first chiral Q[n] synthesized was ($\pm$)-Bis-ns-Q[6] featuring a chiral cavity that demonstrates enantio- and diastereoselective recognition through cavity selection (Figure 1.17).¹⁰⁴ A moderate chiral recognition was observed for (+)-1-phenylethanamine with a resulting diastereomeric mixture in a 72:28 ratio. Since the two bridging methylenes are absent in the ($\pm$)-Bis-ns-Q[6] structure, it results in a slightly bigger cavity compared to classical Q[6] increasing the range of size of guest molecules for encapsulation. Furthermore, Venturi and co-workers reported Q[7 or 8]-mediated chiral molecular switches responding to (*R*)-binaphthalene-bipyridinium guests in an aqueous solution.¹⁰⁵

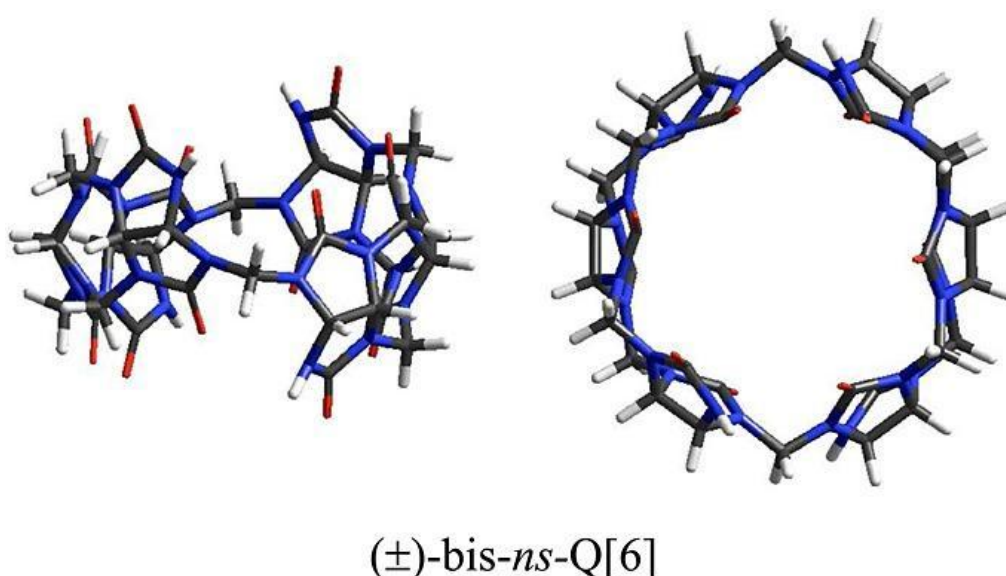


Figure 1.17. Portal and side views of ($\pm$)-bis-nor-seco-cucurbit[6]uril (($\pm$)-bis-ns-Q[6]).

Reprinted with permission from **Mandadapu, V.; Day, A. I.; Ghanem, A.** Cucurbituril: Chiral Applications. *Chirality* **2014**, 26, 712–723. Copyright © 2014 Wiley Periodicals, Inc.

1.2.3. Macrocyclic Compounds

Crown ethers are a well-known class of macrocycles that consist of cyclic polyethers with a cavity-like structure where their inner cavity is composed of electronegative heteroatoms, such as oxygen, sulfur, or nitrogen.¹⁰⁶ In contrast, the outer edge is hydrophobic in nature. Crown ethers are often applied for chiral separation in different techniques, namely HPLC, CE, and supercritical fluid chromatography. Since the crown ethers are inherently achiral, a chirality must be introduced to enable enantioselective applications. The chiral derivatives

include the crown ethers modified with chiral tartaric acid molecules, those incorporating polysaccharides to create a chiral environment, and those synthesized by adding naphthalene monomers to the macrocycle. Chiral crown ethers are a promising candidate for enantioselective applications owing to their proficiency to form diastereomeric complexes with chiral molecules. For example, chiral crown ethers are frequently employed in HPLC as CSPs for enantio- separation. In the late 1970s, Cram and co-workers pioneered chiral crown ethers bound to silica and polymer resins for enantiomer separation (Figure 1.18).¹⁰⁷

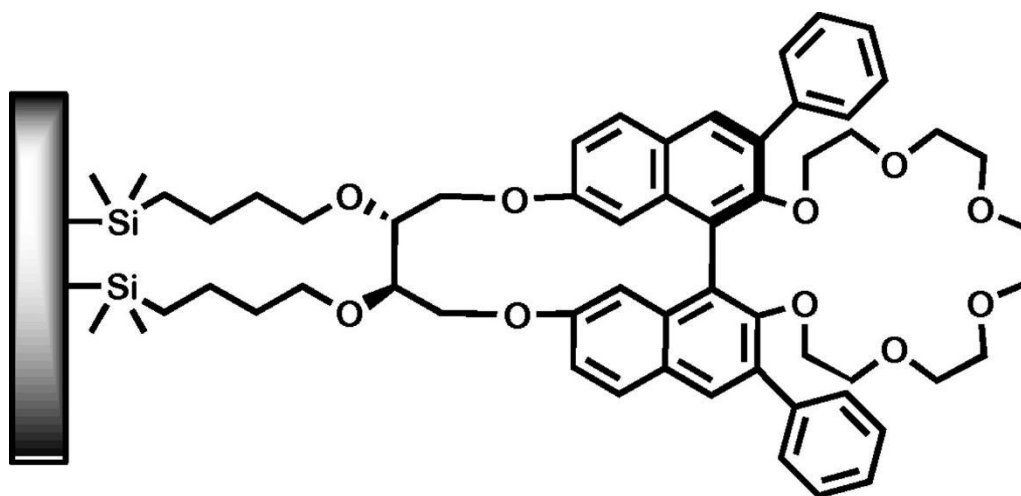


Figure 18. Solid supported crown ethers for chiral separation.¹⁰⁷ Reprinted with permission from **Gokel, G. W.; Leevy, W. M.; Weber, M. E.** Crown Ethers: Sensors for Ions and Molecular Scaffolds for Materials and Biological Models. *Chem. Rev.* **2004**, *104* (5), 2723–2750. Copyright © 2004, American Chemical Society.

Furthermore, Hyun and co-workers demonstrated an effective chiral separation of enantiomeric compounds with primary amino groups, while a diphenyl-substituted 1,1'-binaphthyl crown ether attached to silica gel successfully resolved fluoroquinolone enantiomers.¹⁰⁸ Chiral crown ethers act as selectors in electrochemical systems to identify specific enantiomers. For example, β,β' -dihydroxy- α , and α' -binaphthyl can be incorporated within a macrocycle, producing chiral crown ethers.¹⁰⁹ These chiral crown ethers can form diastereomeric complexes with chiral ammonium salts, in which one configuration will be favored over another due to steric hindrance, displaying enantio recognition. They have been used in several other applications, such as asymmetric synthesis, where they function

as ligands or organocatalysts to improve enantioselectivity during the process. They are also known to contribute significantly in host-guest chemistry by forming complexes with chiral amines, which are used to develop different chiral materials, such as membranes for enantioselective separation.¹¹⁰ These diverse applications make chiral crown ethers essential in analytical chemistry, pharmaceuticals, and material science.¹¹¹

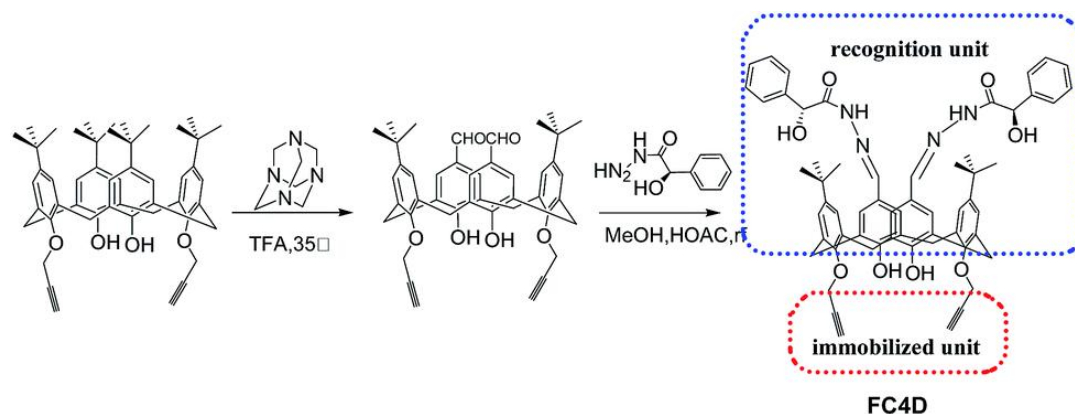


Figure 1.19. The synthesis of chiral FC4D.¹¹² Reprinted with permission from Mao, X.; Zhao, H.; Luo, L.; Tian, D.; Li, H. Highly Sensitive Chiral Recognition of Amino Propanol in Serum with R-Mandelic Acid-Linked Calix[4]arene Modified Graphene. *J. Mater. Chem. C* **2015**, 3, 1325–1329. Copyright © 2015 Royal Society of Chemistry.

Calixarene is a type of macro-cyclic condensation compound formed through the reaction of formaldehyde and p-substituted phenol under alkaline conditions. It also features a cavity structure, where the inner cavity is electron-rich due to the presence of aromatic groups. One edge of calixarene has a small opening, with strong polar hydroxyl groups distributed along its edge, while the opposite edge consists of hydrocarbon groups, making it hydrophobic. Calixarene structure features some fundamental characteristics for developing advanced functional materials, such as the adjustable intrinsic cavity, where the size of the same can be adjusted based on reaction conditions. Second, it can be easily derivatized since the phenolic hydroxyl and p-substituent groups of the benzene ring could be functionalized by introducing different groups for creating selective chiral selectors. Lastly, it exhibits good thermal stability, low toxicity, and flexibility. Li and co-workers produced a novel calixarene derivative and applied it in electrochemical chiral recognition.¹¹² In this study, R-mandelic acid was grafted onto the surface of calix[4]arene (FC4D) (Figure 1.19), which undergoes a click reaction with graphene. Moreover, the R-mandelic acid acts as a

chiral auxiliary which enables chiral recognition through strong hydrogen bonding with the guest molecules. In this particular synthesis, two chiral units are attached to the upper edge of the calixarene, enhancing the recognition of enantiomers through a synergistic effect. Notably, the resulting FC4D-G showed extremely high selectivity in recognizing aminopropanol enantiomers, leveraging the benefits of both the functional calixarene and graphene.

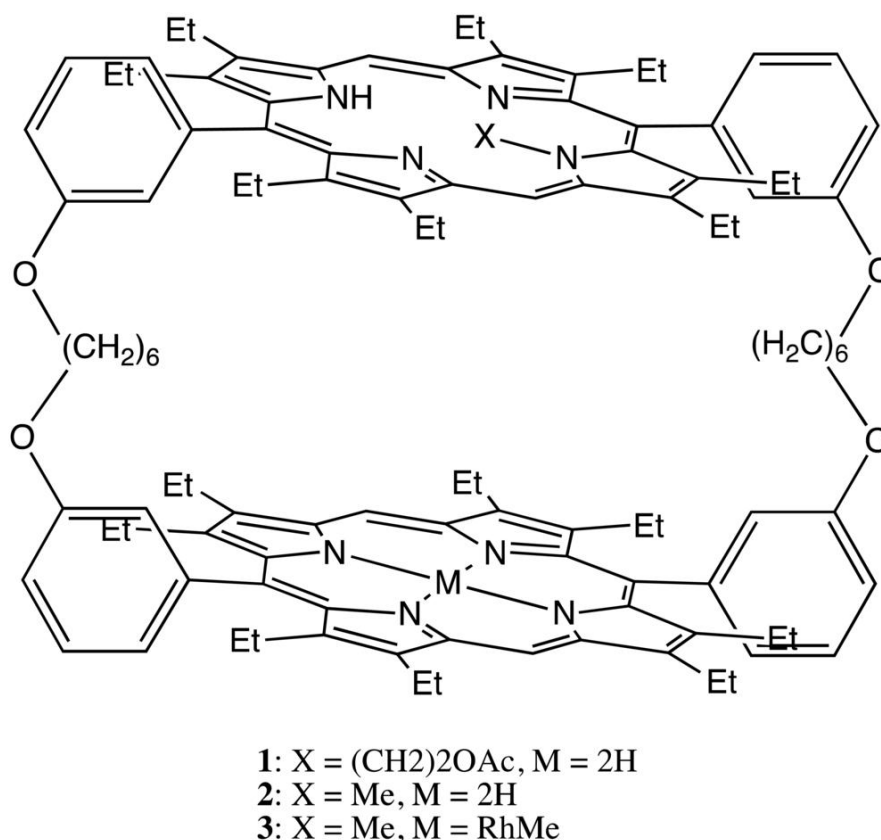


Figure 1.20. Molecular structures of the doubly-strapped bis-porphyrins.¹¹⁵ Reprinted with permission from Shoji, Y.; Tashiro, K.; Aida, T. one-pot enantioselective extraction of chiral fullerene C₇₆ using a cyclic host carrying an asymmetrically distorted, highly π -basic porphyrin module. *J. Am. Chem. Soc.* **2010**, 132, 5928–5929. Copyright © 2010 American Chemical Society.

Porphyrins, namely chlorophyll and hemes, are essential natural macrocycles that play critical roles in biological systems. Their π -conjugated structure, planar configuration, proficiency to coordinate with metal ions, and ease of chemical modification make them highly versatile for several applications.¹¹³ These properties enable porphyrins to assemble

into various hierarchical structures through controlled covalent or noncovalent interactions with chiral and achiral units making the resultant structure chiral. Strategies for synthesizing chiral porphyrins include structural and supramolecular approaches.¹¹⁴ For example, rigidly linked systems, like doubly-strapped bis-porphyrins where the chirality is introduced via alkylation of pyrrole nitrogens, exhibit enantiomeric discrimination of C₇₆ fullerenes (Figure 1.20).¹¹⁵ Another strategy is to use chiral linkages, as seen in the case of leucine-strapped bis-porphyrins, which induce helical configurations.¹¹⁶ These resultant chiral porphyrins facilitate the optical resolution of bidentate oligopeptides. Moreover, flexibly linked architectures, such as ethane-bridged bis-chlorins, depend on supramolecular interactions to stabilize chirality, further enhanced by interaction with chiral guests. Monomeric porphyrins, including cyclodextrin-porphyrin conjugates, generate chiral aggregates in response to environmental factors like pH changes. Additionally, porphyrin stacking can break symmetry, enabling achiral porphyrins to form chiral assemblies. Chiral porphyrins are widely used in various fields due to their robust optical, structural, and catalytic features. For example, binaphthyl-bridged porphyrins enhance stereoselectivity by creating a chiral environment during asymmetric catalysis.¹¹⁷ Biomimetic applications leverage porphyrins to mimic natural systems such as enzymes, as demonstrated by cyclodextrin-porphyrin conjugates that enable cooperative host-guest interactions for chiral recognition.¹¹⁸ Furthermore, ethane-bridged bis-chlorins function as chiroptical sensors, utilizing exciton coupling to identify chirality in guest molecules. These versatile applications make chiral porphyrins invaluable for advancements in medicine, environmental sensing, and material science.¹¹⁹

1.2.4. Self-Assembled Structures

Chiral metal-organic frameworks (CMOFs) are a sub-class of metal-organic frameworks (MOFs), which are crystalline nanoporous materials (2D or 3D) built from inorganic nodes and organic linkers. CMOFs involve the introduction of chirality into their structures, facilitating complex applications such as enantioselective catalysis, recognition, and separation.¹²⁰ Chirality in CMOFs arises from the characteristics of either chiral molecular subcomponents with specific handedness, formation of helical secondary structures, or chiral metal centers in which chirality is preserved and transferred by coordination-driven self-assembly. The design and synthesis of CMOFs are rooted on three broad approaches. The direct approach calls for incorporating a chiral linker or auxiliary into the framework during synthesis to have direct control of the chirality of CMOF. For example, in 2001, Lin

and co-workers successfully introduced phosphorylated BINOL ligands in 2D CMOFs with Ln(III) salts.¹²¹ Subsequently, they used them as catalysts for cyanosilylation of aldehydes. The second method is the post-synthetic modification, which involves the chemical modification of an achiral MOF with chiral reagents post-synthesis. This increases the versatility of MOFs, for instance, Cohen and co-workers modified aminoterephthalic acid in a MOF (IRMOF-3) into chiral amides upon reaction with chiral anhydrides post-synthesis (Figure 1.21).¹²²

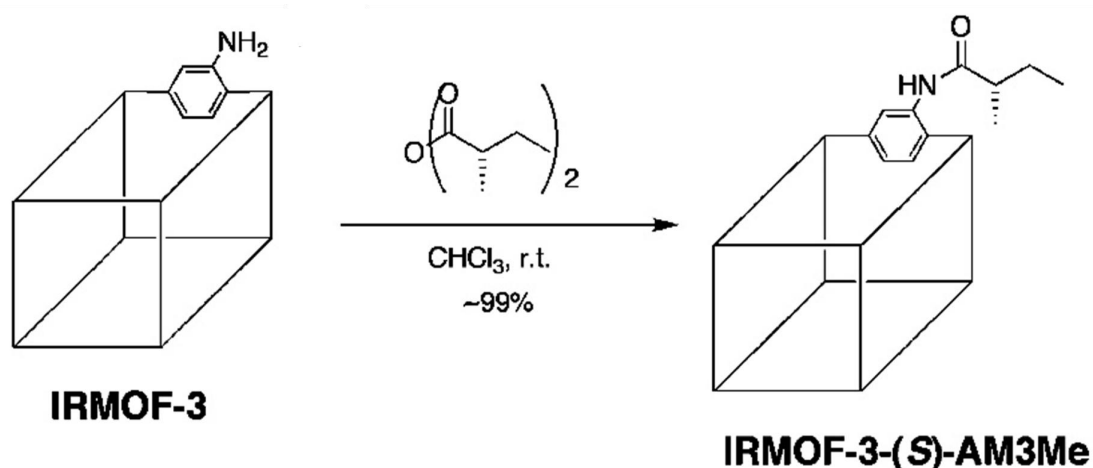


Figure 1.21. Postsynthetic Modification Reactions Performed with IRMOF-3.¹²² Reprinted with permission from Garibay, S. J.; Wang, Z.; Tanabe, K. K.; Cohen, S. M. Postsynthetic Modification: A Versatile Approach toward Multifunctional Metal–Organic Frameworks. *Inorg. Chem.* **2009**, 48, 7341–7349. Copyright © 2009, American Chemical Society.

The last method is spontaneous resolution and chiral induction, which relies on the asymmetric crystallization of achiral components that lead to the formation of chiral frameworks that usually possess chirality at the metal center and with helical structures demonstrated by Rosseinsky and Ciani groups.¹²³ They synthesized three-dimensional chiral frameworks from simple trimesic acid or 1,2-bis(4-pyridyl)ethyne and Ni(II) or Cu(II), respectively, in which the chirality of the framework arises from the helical packing of the building blocks across the crystal lattice. CMOFs combine chirality with porosity setting them apart from both achiral MOFs and nonporous chiral materials. Their extremely modular architecture enables diverse chiral structures of different levels of chirality to be conceived and can have a great impact on diversifying future enantioselective applications, which are otherwise not possible with existing materials.¹²⁴ Fine-tuning

CMOF architectures by modifying pore size and specific binding sites ensures that several advanced functionalities can be achieved efficiently. Further, the crystalline nature of CMOFs provides a fundamental understanding of enantioselective mechanisms on a molecular level which will keep improving design processes toward high-performance materials. The aforementioned cutting-edge utilities underscore the intrinsic properties of CMOFs like chirality, chiral pore environment, and substantial tunability.⁵⁵

Covalent organic frameworks (COFs) are a developing class of porous materials with tremendous prospects in various implementations, such as gas storage and molecular sieving, energy storage, catalysis, and sensing.¹²⁵ The precise selection of building blocks enables the development of advanced COF with several intrinsic properties such as ordered pore structure, structural versatility, easy functionalization, enhanced electrical conductivity, and high chemical stability.¹²⁶ Such fundamental properties make chiral COFs (CCOFs) a promising candidate for various enantioselective applications. However, a key challenge is to have a balance between the chirality of monomers and the crystallinity of the material. Therefore, precise control over chirality, functionality, and crystallinity remains a primary objective in developing advanced functional CCOFs. They can be synthesized using several strategies. One approach is post-synthesis modification, where chirality is introduced into an achiral COF framework via post-synthesis by covalently attaching chiral functional groups. For instance, Jiang and co-workers reported an achiral COF with a 2D layered structure and a 1D tetragonal tubular channel with a linear monomer that included allyl ether functional groups, making it competent for post-synthetic modification.¹²⁷ By functionalizing (*S*)-pyrrolidine to the achiral COF skeleton using a "click" reaction, they synthesized an enantiopure COF for catalyzing the asymmetric Michael addition reactions. Another strategy is direct synthesis, which involves self-assembling CCOFs directly from enantiopure monomers. For example, Wang and co-workers synthesized a pyrrolidine-embedded chiral monomer-based CCOF for catalyzing aldol reactions (Figure 1.22).¹²⁸ The third method is chiral induction synthesis which relies on using a chiral inducer to bias the formation of homochiral frameworks from achiral precursors.

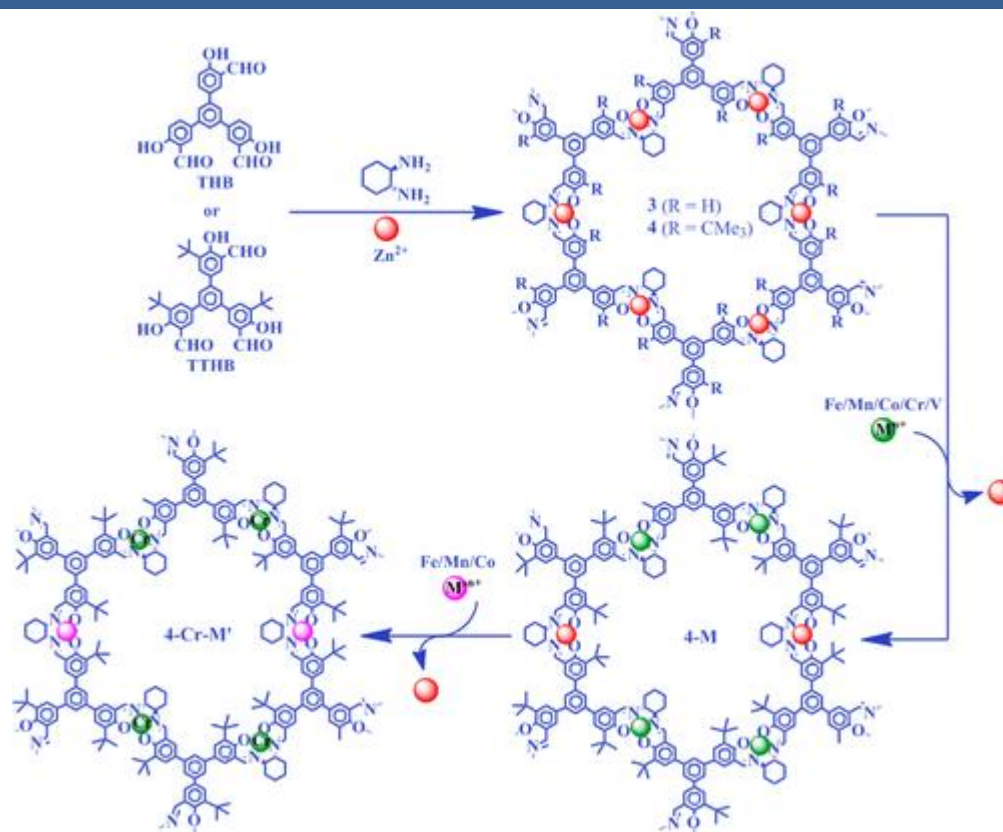


Figure 1.22. Synthesis of the CCOFs.¹²⁸ Reprinted with permission from Han, X.; Xia, Q.; Huang, J.; Liu, Y.; Tan, C.; Cui, Y. Chiral Covalent Organic Frameworks with High Chemical Stability for Heterogeneous Asymmetric Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 8693–8697. Copyright © 2017, American Chemical Society.

This approach enables control over handedness and crystallinity. Cui, Liu, and co-workers developed 2D CCOFs with controlled handedness through solvothermal synthesis.¹²⁹ This process involved the imine condensation of 1,3,5-triformylphloroglucinol with an achiral diamine or triamine linkers in the presence of enantiopure-1-phenylethylamine as a catalyst. Thus CCOFs are versatile materials with several applications in catalysis, chiral separation, and sensing. For example, Lotsch and co-workers synthesized a hydrazone-based COF, which was designed for photocatalytic hydrogen production from water.¹³⁰ In 2016, Yan and coworkers demonstrated the use of CCOF materials in chiral gas chromatography.¹³¹ They functionalized the CCOFs with chiral (+)-diacetyl-L-tartaric acid and fabricated chiral COF-bound capillary columns through an in situ growth method. These columns exhibited chiral separation of enantiomers, including (R)-1-phenylethanol, (S)-1-phenyl-1-propanol, (R)-limonene, and (S)-methyl lactate.

1.3. Chirality in metalorganic cages

Metal-organic cages, are discrete coordination structures characterized by their precise shapes, defined cavities, nanoscale dimensions, and symmetrical geometries. Unlike other self-assembled structures such as MOF and COFs, metal-organic cages are relatively small molecules classified as individual entities with internal "cavities" through which they can bind with selective complexes.¹³² These assemblies can adapt a variety of outer geometrical configurations. Introducing chirality into these metal-organic cages and the advantage of internal cavities enhances their potential for a broad spectrum of implementations like enantio recognition, separation, sensing, catalysis, drug delivery, etc. Moreover, these MOCs are soluble in organic solvents; thus, they are capable of being used as chiral selectors in gas chromatography, exhibiting enantioselectivity toward an extensive array of organic compounds.¹³³ Depending on the configuration of the cavity, the formation of window-to-window or window-to-face arrangements creating a channel network within the cavities can also be observed. Metal coordination has become one of the most potent and versatile non-covalent approaches for the design of complex assemblies. This methodology not only offers the construction of organized coordination architectures but also allows elegant control over their dimensions, shapes, and functions. The inherent high symmetry of polyhedral MOCs, characterized by multiple symmetrical elements such as inversion centers and mirror planes, has made achieving enantiopure chiral polyhedral MOCs a significant challenge. Despite this, considerable advances have been achieved over the previous decades in developing chiral MOCs with diverse configurations. The key strategy involves introducing stereogenic units and eliminating inversion center or mirror plane symmetries. Broadly, chirality can be incorporated into MOCs using two primary approaches. First, the "hard" approach, which utilizes optically pure chiral building blocks to establish predetermined chirality, ensuring that the ligands remain chiral even in the absence of metal coordination. Second, the "soft" approach, which involves achiral building blocks that generate chirality, though it dissipates upon the dissociation of its building blocks (Figure 1.23).¹³⁴

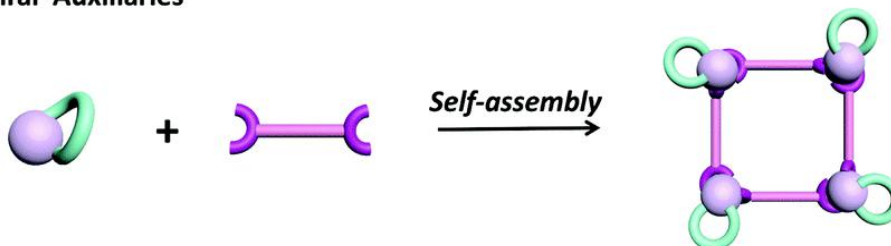
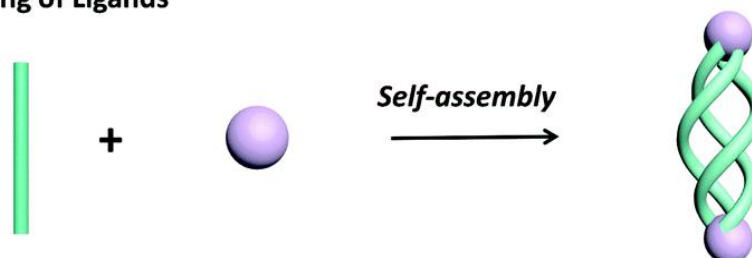
(i) Chirality from “Hard” Approach Employing Chiral Components**(a) Chiral Organic Bridging Units****(b) Chiral Auxiliaries****(ii) Chirality from “Soft” Approach Employing Achiral Components****(c) Metal Center****(d) Twisting of Ligands**

Figure 1.23. Different strategies for the synthesis of chiral metallo-supramolecular cages.

¹³⁴ Reprinted with permission from Chen, L.-J.; Yang, H.-B.; Shionoya, M. Chiral Metallosupramolecular Architectures. *Chem. Soc. Rev.* **2017**, *46*, 2555–2576. Copyright © 2017 Royal Society of Chemistry.

1.3.1. Hard approach

An easy and straightforward method to obtain enantiopure metallo-supramolecular assemblies is employing enantiopure building blocks. These materials may integrate a stereogenic center within a bridging ligand or as an auxiliary group bound to the metal center. The chirality of the supramolecular architecture is influenced by the enantiomerically pure ligands, and introduce chirality into the metallo-supramolecular architecture even before the self-assembly process begins.

1.3.1.1. Chiral organic bridging units

This method utilizes a range of inherently chiral bridging ligands, such as rigid ethylene bridges derived from binaphthyl group. It also offers significant flexibility to tailor the resulting chiral platforms. A preliminary instance of this approach was demonstrated by Lin and co-workers, who used chiral 1,1'-binaphthyl-derived bipyridyl ligands and fac-Re(CO)₃Cl units as vertices to construct a series of different chiral molecular squares (Figure 1.24).¹³⁵

In another noteworthy example, Nitschke and co-workers designed enantiopure tetrahedral Fe(II) cages with T-symmetry constructed through a subcomponent self-assembly strategy.¹³⁶ The chiral modification of the glyceryl group describes helical twists along each edge of the tetrahedron. Notably, the stereochemistry of the glyceryl groups influences the handedness of the Fe(II) centers, ensuring that all four vertices in a tetrahedral MOC share the same handedness, thereby generating four C₃-symmetry axes. Consequently, the (*S*, *S*)-L ligand produces the homochiral $\Delta\Delta\Delta\Delta$ -Fe₄L₆ cage, while its enantiomer (*R*, *R*)-L forms the $\Lambda\Lambda\Lambda\Lambda$ -Fe₄L₆ MOC.

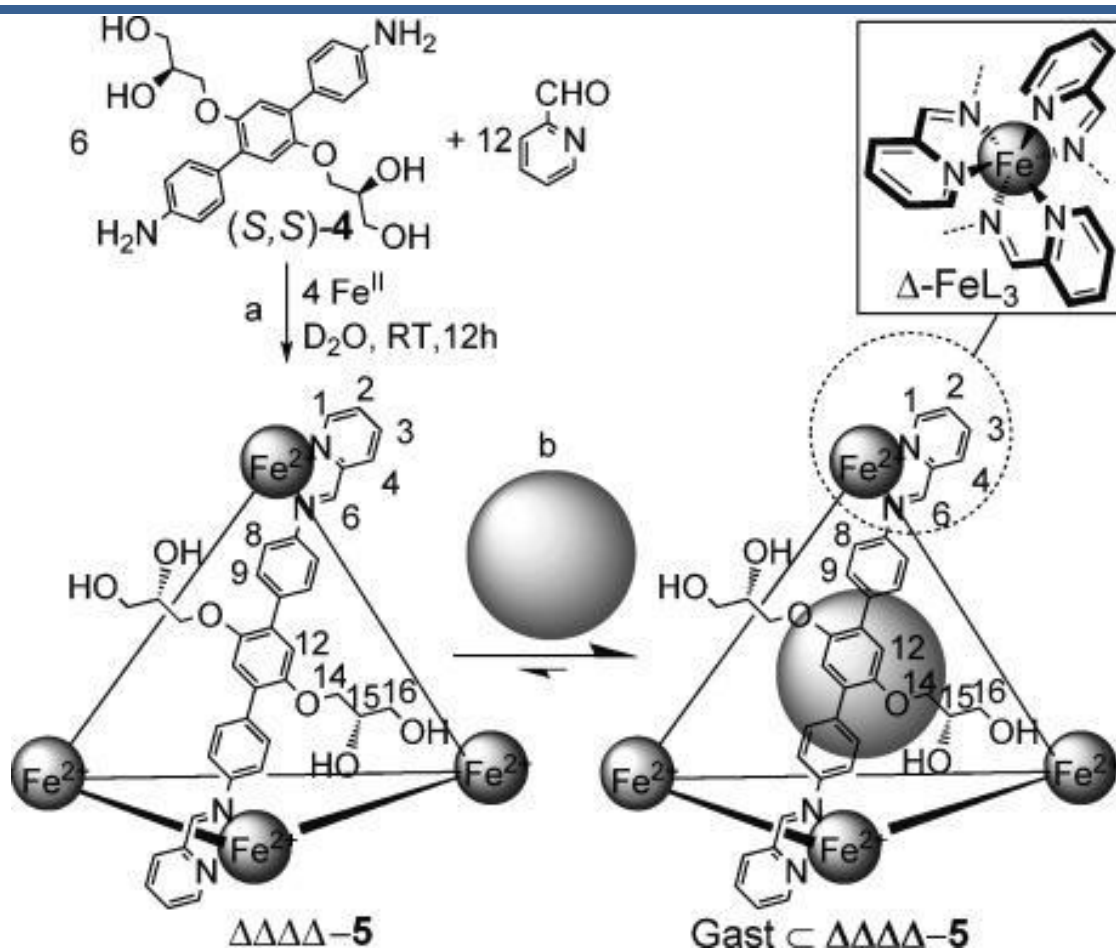


Figure 1.24. a) Enantioselective synthesis of $\Delta\Delta\Delta\Delta$ -5 from (S,S)-4, 2-formylpyridine, and $\text{Fe}^{\text{II}}\text{SO}_4$ by subcomponent self-assembly; b) Host-guest intercation of $\Delta\Delta\Delta\Delta$ -5.¹³⁶ Reprinted with permission from Bolliger, J. L.; Belenguer, A. M.; Nitschke, J. R. Enantiopure Water-Soluble $[\text{Fe}_4\text{L}_6]$ Cages: Host-Guest Chemistry and Catalytic Activity. *Angew. Chem., Int. Ed.* **2013**, 52, 7958–7962. Copyright © 2013 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

1.3.1.2. Chiral auxiliaries

In this method, chirality was incorporated through the corner units containing metal that were capped with chiral auxiliaries. Stang and co-workers utilized the optically active $[\text{M}(\text{R})\text{-BINAP}(\text{OTf})_2]$ (where $\text{M} = \text{Pd}(\text{II})$ or $\text{Pt}(\text{II})$) as the chiral auxiliary.¹³⁷ When reacted with specific ligands, such as bis(3-pyridyl)iodonium triflate, bis(4-(4-pyridyl)-phenyl)iodonium triflate, or anthracene-based diaza ligands like 2,6-diazaanthracene and 2,6-diazaanthracene-9,10-dione, a range of chiral molecular squares was obtained. Notably,

when 2,6-diazaanthracene linker was used in acetone at room temperature, only one diastereomer was obtained, out of six possible structures. Similarly in another example, In 2012, Lusby and co-workers synthesized a pair of chiral M_6L_4 -type MOC enantiomers (Δ - and Λ -OTf₆), which were based on cyclometalated Ir(III) metal nodes [Ir(ppy)₂]⁺ (where ppy = 2-pyridylphenylato) (Figure 1.25).¹³⁸

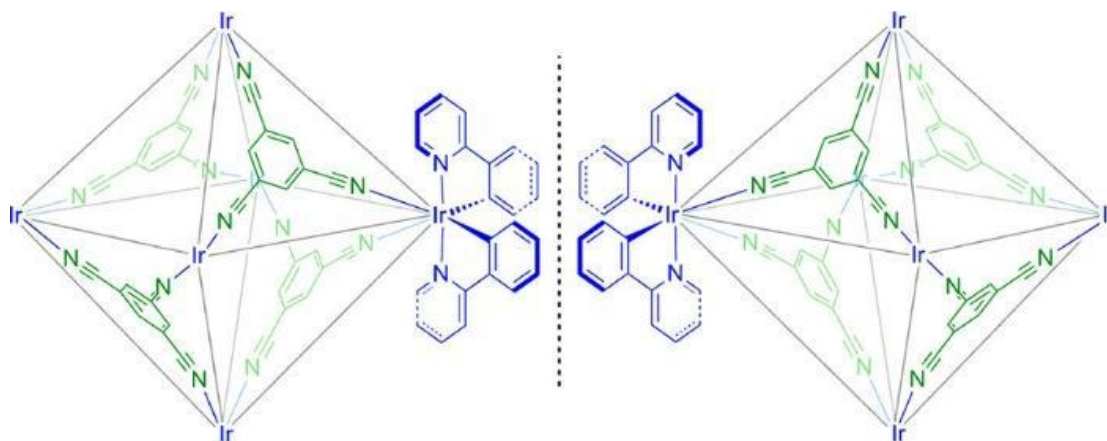


Figure 1.25. The enantiomers of M_6L_4 -MOCs from chiral Ir(III) vertices.¹³⁸ Reprinted with permission from Chepelin, O.; Ujma, J.; Wu, X.; Slawin, A. M.; Pitak, M. B.; Coles, S. J.; Michel, J.; Jones, A. C.; Barran, P. E.; Lusby, P. J. Luminescent, Enantiopure, Phenylatopyridine Iridium-Based Coordination Capsules. *J. Am. Chem. Soc.* **2012**, *134*, 19334–19337. Copyright © 2012 American Chemical Society.

1.3.2. Soft approach

Supramolecular chirality can also arise even with entirely achiral components by eliminating symmetry elements. When the self-assembly is formed from achiral building blocks, chirality can emerge through the three dimensional arrangement of achiral ligands bound to the metal center or through twisting of the ligands. In such scenarios, chirality is generated in the architecture during the process of aggregation or self-assembly. Furthermore, introducing an suitable guest molecule into the coordination assembly can sometimes introduce asymmetry to the supramolecular structure, thereby inducing chirality. A combination of both methods can also be used for the synthesis of chiral metallo-supramolecular cages.

1.3.2.1. Metal center

Although the components of metallo-supramolecular architectures may be achiral, chirality can emerge from the three-dimensional arrangement of the achiral ligands around the metal center.

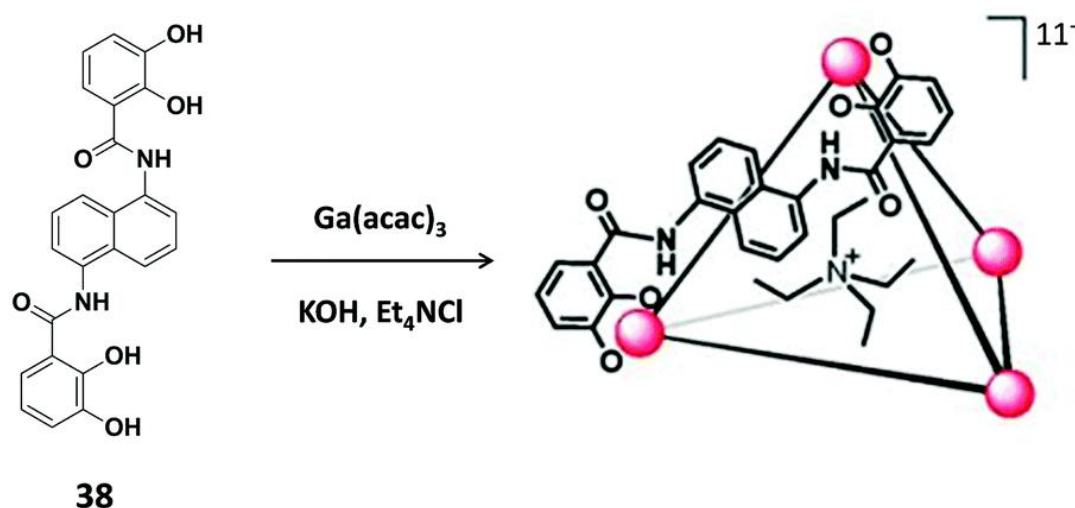


Figure 1.26. Synthesis of the enantiomeric tetrahedral clusters, $[\text{NEt}_4\text{Ga}_4\text{L}_6]^{11-}$.

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Typically, the corners of these architectures consist of metal coordination complexes with C_2 -symmetric pseudo-tetrahedral bis-chelate ligands that display D or L stereochemistry, or C_3 -symmetric pseudo-octahedral tris-chelate complexes, which can adopt either facial (fac) or meridional (mer) stereochemistry, alongside D or L handedness.

Saalfrank, Ward, Raymond, Nitschke, Lindoy, and co-workers have successfully synthesized various enantiopure M_4L_6 cages using metal ions containing octahedral geometry, such as Mn(II), Co(II), Zn(II), Al(III), Ga(III), Fe(III), as well as tetravalent ions like Ti(IV), Sn(IV), and Ge(IV), treated with either polytopic N-donor ligands or anionic biscatecholate ligands (Figure 1.26).¹³⁹⁻¹⁴³ For example, in the $[\text{NEt}_4\text{Ga}_4\text{L}_6]^{11-}$ cage assembly shown in Figure 1.26, each metal center adopted a D/L configuration and was coordinated by three arms of the bis-tetradentate ligands, forming each edges of the tetrahedron. The chirality recognized at one center was transferred to the other metal centers

because of the strong mechanical coupling between the metal centers via the rigid bridging ligands, resulting in a fully homochiral. Furthermore, Ward and coworkers reported the diastereoselective synthesis of the isomeric tetrahedral cages $\{[XCZn_4L_6][X]_7\}$ ($X = BF_4, ClO_4$), where the enantiomeric nature of the pinene determined the chirality of the all four metal centers at the vertex, derived from the chiral bispyrazolyl pyridine ligand separated by either 2,3-naphthalene or 1,2-phenylene spacers.

1.3.2.2. Twisting of ligands

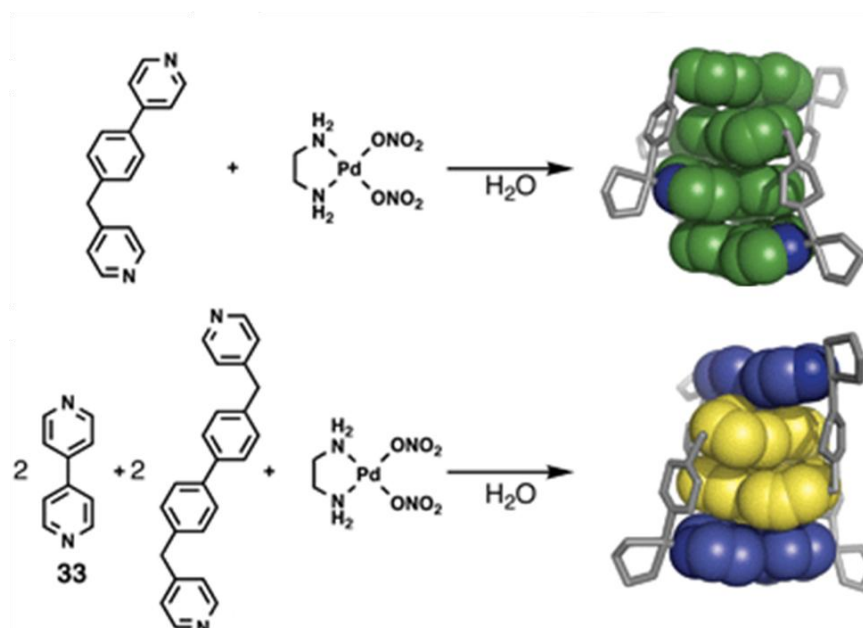


Figure 1.27. The synthesis of organometallic [2]-catenane and the SCXRD. Reprinted with permission from Klosterman, J. K.; Yamauchi, Y.; Fujita, M. Engineering Discrete Stacks of Aromatic Molecules. *Chem. Soc. Rev.* **2009**, 38, 1714–1725.

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Chirality in supramolecular assemblies can also arise from a conformational change, where the structure transitions from achiral to chiral due to the spatial twisting of the organic ligands. An early example of this was reported by Fujita and co-workers, who created a stable [2]-catenane exhibiting topological chirality.¹⁴⁴ This was achieved by the clockwise or counterclockwise interlocking of the 2nd ring onto the 1st ring of the ligand. Additionally, a moderately flexible catenane was formed using $Pd(NO_3)_2(en)$ and a ligand that was prolonged by introducing an extra phenylene ring into the parent ligand structure (Figure 1.27). Another example involved the construction of a hetero-ligand [2]-catenane from an

electron-deficient bipyridine and an electron-rich biphenyl ligand, which was predominantly stabilized by the donor-acceptor interactions. Furthermore, Robson, Müller, and co-workers have reported on chiral M_6L_4 truncated tetrahedra, which were obtained by the ligands derived from guanidine.^{145, 146} The chirality in these structures resulted from the apparent screw-like twisting of the ligands upon coordination with the metal centers at each face of the tetrahedron.

1.3.3. Applications

1.3.3.1. Sensing

CMOCs with well-defined internal cavities and functional sites are capable of sensing, owing to their distinct chemical environments and the structural rigidity of their internal cavities. There are numerous reports where the hydrophobic internal cavities of metallo-supramolecular self assemblies can accommodate various guests such as anions and organic molecules. These interactions are driven by specific host-guest interactions as well as non-specific, weak supramolecular forces, including Coulombic forces.

Cui and co-workers demonstrated a homochiral helicate cage, $[Zn_8L_4Cl_8]$, which was constructed from a $Zn(salen)$ complex ($L = N,N'$ -bis(3-tert-butyl-5-(4-pyridyl)-salicylidene)-1,2-diaminocyclohexane).¹⁴⁷ The SCXRD revealed a helicate cage, with its chiral binding pocket, with NH functional groups, and wide portal dimensions, is ideal for chiral recognition and separation of guest molecules. Fluorescence measurements demonstrated that amino acids like alanine, phenylalanine, and valine bind enantio-selectively to the chiral helicate cage, while the free ligand displays no enantioselectivity. In another example, Nitschke and co-workers reported a water-soluble tetrahedral cage to capable of encapsulating highly reactive white phosphorus (P_4), rendering it inert, water-soluble, and air-stable (Figure 1.28).¹⁴⁸ This particular tetrahedral cage was also used to store the greenhouse gas SF_6 efficiently in water.

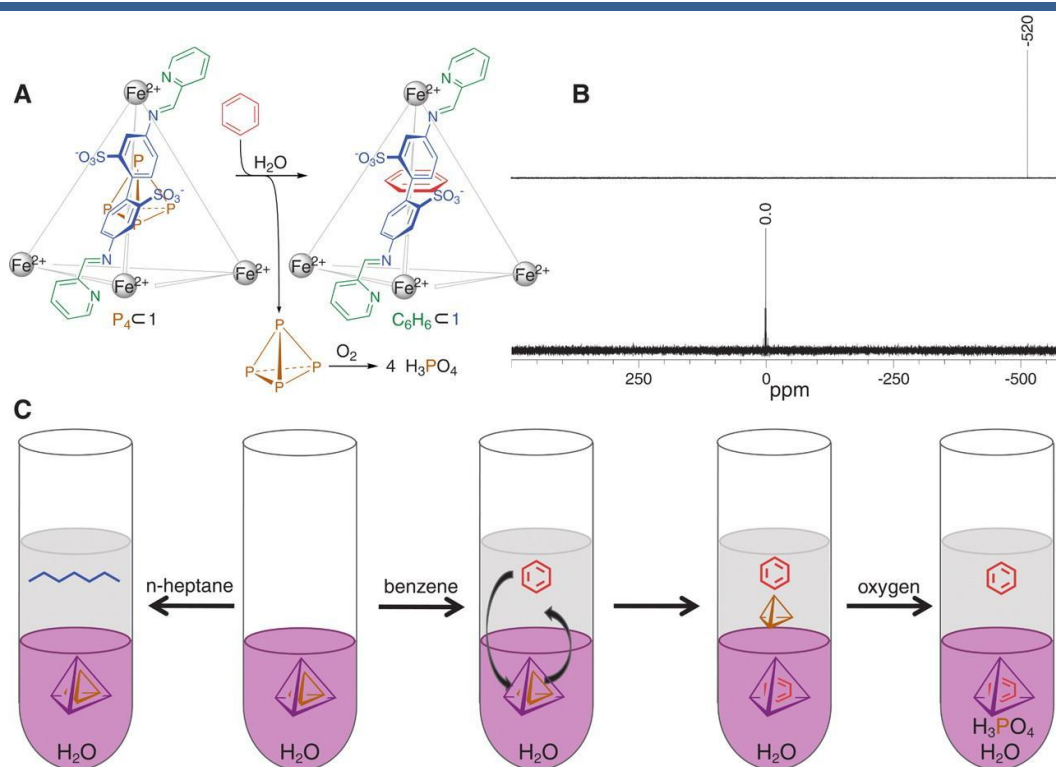


Figure 28. (A) Reaction scheme. (B) ³¹P NMR spectra of P₄ extracted into the benzene layer (top) and phosphoric acid found in the aqueous layer after reaction of P₄ in benzene with oxygen (bottom). (C) Schematic representation of the extraction process.¹⁴⁸ Reprinted with permission from Mal, P.; Breiner, B.; Rissanen, K.; Nitschke, J. R. White Phosphorus Is Air-Stable within a Self-Assembled Tetrahedral Capsule. *Science* **2009**, 324, 1697–1699.

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1.3.3.2. Catalysis

Chiral metallo-supramolecular architectures are capable of encapsulating a wide variety of guests while maintaining high configurational stability. As a result, these structures can function as hosts to trap reactive structures and be used as nano-vessels for conducting various stoichiometric and catalytic reactions.

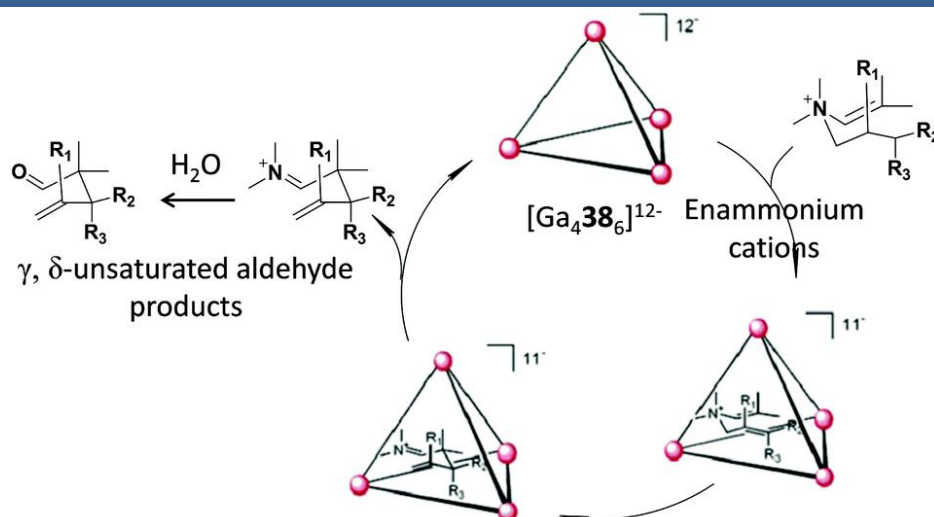


Figure 1.29. The 3-aza-Cope rearrangement catalytic cycle employing [Ga₄(L)₆]¹²⁻.¹⁴⁹

Reprinted with permission from Fiedler, D.; Bergman, R. G.; Raymond, K. N.

Supramolecular Catalysis of a Unimolecular Transformation: Aza-Cope Rearrangement within a Self-Assembled Host. *Angew. Chem., Int. Ed.* **2004**, *43*, 6748–6751. Copyright © 2004 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Raymond, Bergman, and their co-workers synthesized the complex [M⊂Ga₄L₆], in which cationic reactive organometallic complexes (M) were encapsulated by replacing the poorly bound NMe₄⁺ as the starting (Figure 1.29).¹⁴⁹ The cage [Ga₄(L)₆] was shown to encapsulate monocationic Ir complexes, such as [Cp^{*}(PMe₃)Ir(Me)(C₂H₄)]⁺, within its cavity, enabling particular C–H bond activation at high temperatures in the occurrence of an aldehyde in an aqueous medium. Similarly, Fujita and co-workers assembled chiral M₆L₄-type MOCs with chiral diamine auxiliaries at the periphery of the cages. Remarkably, this cage was able to control the asymmetric [2+2] olefin photoaddition of fluoranthene and N-cyclohexylmaleimide, producing photo-addition products with multiple chiral centers upon irradiation with an enantiomeric excess (ee) value of up to 50%.¹⁵⁰

1.3.3.3. Biological Studies

The biological applications of metallo-supramolecular architectures remain an emerging field. Researchers have only recently started exploring these applications, despite the fact that coordination metal complexes are common in biological systems. Chi and co-workers have designed metallo-supramolecular scaffolds, particularly those based on Pt(II) and Ru(II), significant to various biochemical and biomedical targets.¹⁵¹ Certain metallo-

supramolecular architectures could act as anticancer agents, definite sensors for significant analytes, and interact with proteins and DNA. Shionoya and co-workers demonstrated artificial metal-mediated base pairs with better thermal stability compared to the natural DNA.¹⁵² By selecting suitable combinations of ligand-containing nucleosides and specific metal ions, they showed that these metallobase pairs could be utilized to generate or induce higher-order structures, such as artificial DNA enzymes.

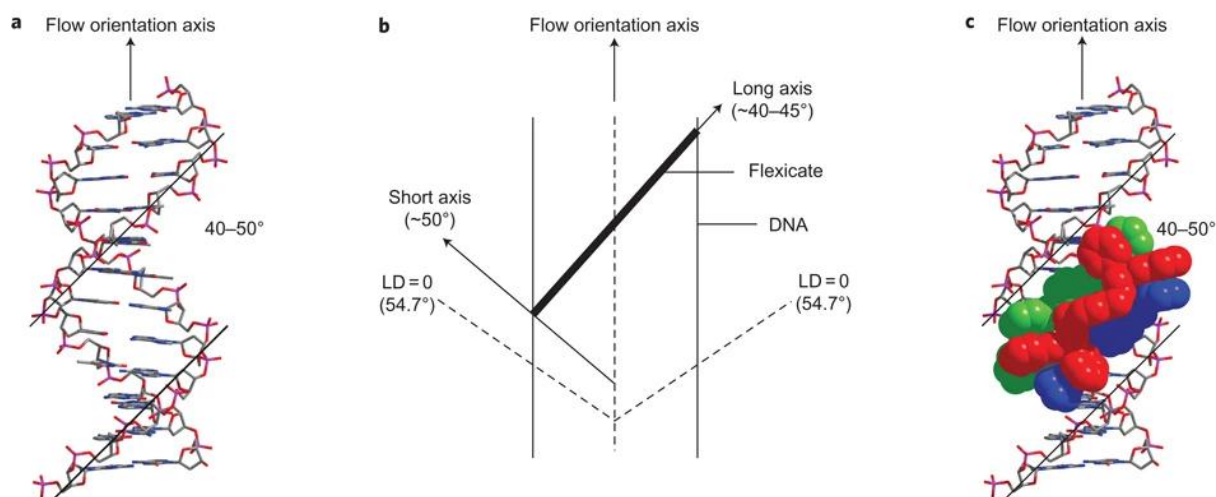


Figure 1.30. (a) Major groove highlighted in B-DNA, (b) Schematic showing the derived orientation of the flexicate on DNA, and (c) Schematic showing the flexicate sitting in the major groove of B-DNA. Reprinted with permission from Howson, S. E.; Bolhuis, A.; Brabec, V.; Clarkson, G. J.; Malina, J.; Rodger, A.; Scott, P. Optically Pure, Water-Stable Metallo-Helical ‘Flexicate’ Assemblies with Antibiotic Activity. *Nat. Chem.* **2012**, *4*, 31–36.

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Hannon and co-workers extensively studied the recognition of DNA by triple helicates of the type $[M_2L_3]^{2n+}$ that self-assemble from the interaction of metal ions with bis(pyridylimine) ligands containing a diphenylmethane spacer.¹⁵³ They discovered that the $[Fe_2L_3]^{4+}$ complex interacted with DNA at the center of Y-shaped DNA junctions, binding in a distinct mode aligned through major groove recognition, a preferred binding site of the protein. This interaction induces DNA bending followed by intramolecular coiling. Scott and co-workers developed a technique for controlling the chirality of M_2L_3 assemblies by utilizing enantiomerically pure monomers (Figure 1.30).¹⁵⁴ They constructed a bimetallic flexicate Δ_{Fe} , R_C - $[Fe_2L_3][ClO_4]_4$ by the self-assembly of the enantiomerically pure diamine

ligand derived from (*R*)-2-phenylglycinol with 2-pyridinecarboxaldehyde and $\text{Fe}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$. The opposite helicity (Δ_{Fe}) was synthesized similarly using (*S*)-2-phenylglycinol.

1.4. Outline of the Thesis

Chirality is an important fundamental property of molecular systems that is crucial in various fields, including chemistry, pharmacology, biology, and materials science. Research activities involving chiral recognition and separation play a major role in solving the complexities of homochirality and are instructive in terms of asymmetric catalysis and molecular recognition. Consequently, methods using supramolecular systems as host materials for the chiral recognition and separation of small organic molecules have garnered significant attention in recent years. Unlike purely covalent molecules with defined configurations and conformations, supramolecular assemblies can adopt chiral structures based on both the intrinsic chirality and spatial arrangement of components that are held together by non-covalent interactions. This thesis will describe the synthesis and structures of a series of chiral systems derived from P-N-based scaffolds possessing acyclic, cyclic, and polyhedral cage topologies and their chiral recognition capabilities. For the acyclic system, in Chapter 2, a simple phosphoramidate ligand, a formula $[\text{POPh}_2(\text{R}^*)]$, where R^* corresponds to an amide substituent (*R*)- $((\text{C}_6\text{H}_4)(\text{CO})(\text{NH})(\text{CH}(\text{CH}_3)\text{Ph}))$, has been synthesized and studied for chiral recognition capabilities. A family of chiral epoxides was screened for enantio-selective recognition capabilities. The highest binding selectivity of ~ 3000 was observed for the guest *R*-2-((benzyloxy)methyl)oxirane, employing the *R*-phosphoramidate ligand as a chiral host. Secondly, in Chapter 3, a cyclic P-N ring containing compounds, hexakis(α -methylbenzylamino)cyclotriphosphazene of formula, $[\text{P}_3\text{N}_3(\text{NHR}^*)_6]$, $[\text{R}^* = (\text{R})-(\text{CH}(\text{CH}_3)\text{Ph}) \text{ and } (\text{S})-(\text{CH}(\text{CH}_3)\text{Ph})]$, with six chiral α -methyl benzylamine groups, have been synthesized. The chiral recognition studies with various organic guest molecules indicated that the *R*-enantiomer of the phosphazene host exhibited the highest binding selectivity of ~ 2000 , with the guest *R*-binol. Subsequently, in Chapters 4 and 5, chiral cages built from trinuclear Pd(II) ions, cis-protected by imido-P(V) anions, as vertices were synthesized using a range of wide-angle chelating linkers and shown to exhibit chiral recognition and separation activity. These cages are characterized by distinct portals and well-defined intrinsic cavities, making them highly suitable for host-guest interactions with exceptional affinity and selectivity, particularly in the context of

chiral recognition of guest molecules with a wide variety of functional groups. Notably, the *R*-enantiomer of these cages, upon careful modulations on their portal functionalities, could successfully separate *S* enantiomer of epichlorohydrin up to 93% (ee) and *R* enantiomer of styrene oxides up to 98%(ee), showcasing the potential of these metalorganic cages for enantioselective applications.

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Chapter -2

A Chiral Phosphine Oxide for Enantioselective Recognition of Epoxides

2.1 Introduction

Chirality is ubiquitous in nature and plays a vital role in multidisciplinary fields ranging from biology, chemistry, and materials science to high-energy physics.¹ Due to their inherent asymmetry, chiral compounds can exhibit distinct behaviors in anisotropic biochemical environments despite being indistinguishable in most inanimate systems. Notably, the essential components in biological systems, amino acids, proteins, nucleosides, sugars, and their derivatives, are inherently chiral of which only one enantiomer of them are biologically relevant and exhibits physiological activity.^{2, 3} Chirality sensing involves distinguishing between right-handed and left-handed enantiomers.⁴ There are two major strategies for enantiomer discrimination: (i) employing chiral sensors that preferentially interact with one enantiomer of a given analyte over the other, forming transient diastereomeric complexes through enantiospecific interactions, leading to different responses in UV-Vis absorption, fluorescence, or NMR spectroscopy⁵ and (ii) utilizing achiral sensors, which acquire induced chirality upon binding with chiral analytes, producing signals detectable by chiral discriminating techniques such as circular dichroism or circularly polarized luminescence.⁶ Single-molecule chiral selectors have gained significant attention in recent years. These chiral selectors often associate with guests through noncovalent driving forces such as ionic, ion-dipole, and dipole-dipole interactions, hydrogen bonding, van der Waals forces, π - π stacking, and steric effects.^{7, 8} A spectrum of synthetic receptors have traditionally been employed for chiral guest recognition, including crown ethers,⁹ cyclodextrins,¹⁰ cryptophanes,¹¹ carcerands,¹² cucurbiturils,¹³ calixarenes,¹⁴ porous coordination polymers,¹⁵ metal-organic frameworks,¹⁶ and self-assembled cages.¹⁷ However, these systems often present challenges such as high costs, complex syntheses, intricate recognition mechanisms, and limited functional group accessibility, as they frequently require specific targeting groups for effective enantioselective recognition.¹⁸ A more straightforward approach to achieving efficient chiral recognition involves using simple organic receptors capable of identifying chiral guest molecules through various non-covalent interactions.

Chiral phosphine oxides are a family of versatile molecular scaffolds known for their diverse structural and functional properties. They possess strong P=O dipole, high Lewis basicity, and good stereochemical control, making them promising scaffolds in several implementations, such as pharmaceuticals, organocatalysis,¹⁸ chiral recognition,¹⁹ chemical sensing,²⁰ liquid crystals,²¹ and optoelectronics.²² These compounds feature a chiral backbone and a phosphine oxide functional group, enabling them to engage in various non-covalent interactions with the

analyte in an anisotropic environment, thereby acting as an efficient chiral selector. Chirality in phosphine oxides has mainly been achieved through unsymmetrical substitutions at the P center.²³ However, their synthesis remains challenging due to complex multistep procedures and the difficulty in separating the enantiopure compound from racemic mixtures.²⁴ Thus, a more straightforward approach to obtaining enantiopure chiral phosphine oxides involves incorporating carbon stereocenters into the substituents attached to the phosphorus atoms.

Spurred by the straightforward synthesis of chiral phosphine oxides, we aimed to develop an efficient chiral selector using its core featuring a carbon stereocenter at its substituents and investigating its enantio recognition properties. Herein, we report an enantiopure phosphine oxide **2.1-R** [$\text{POPh}_2(\text{R}^*)$], where R^* corresponds to an amide substituent (R)-((C_6H_4)(CO)(NH)($\text{CH}(\text{CH}_3)\text{Ph}$)), synthesized through the reaction of 4-(diphenylphosphaneyl)benzoic acid with Br_2 followed by treatment with the chiral R -alpha-menthylbezyllamine (Scheme 1). The chiral recognition abilities of **2.1-R** were evaluated against both R and S -enantiomers of a family of epoxide molecules possessing diverse functional groups, including epichlorohydrin (**EP**), propylene oxide (**PO**), styrene oxide (**SO**), and 2-((benzyloxy)methyl)oxirane (**BO**) (Figure 2.1c). The results demonstrated a stronger binding affinity of **2.1-R** towards the R -isomers of **PO**, **EP**, **SO**, and **BO**, particularly the **R-BO** species exhibiting a highest selectivity factor of 3214 over its S -enantiomer. It is observed that both binding affinity and binding selectivity of **2.1-R** increase as the number of interaction sites, as well as the steric bulk of guest molecules, increases for this family of epoxides guest. The high binding affinities observed for these epoxides can be attributed to a synergistic effect of hydrogen bonding and π - π interactions, as confirmed by density functional theory (DFT) optimized structures of the respective host-guest complexes.

2.2 Experimental Details

2.2.1 General Remarks

Dry solvents were obtained from local suppliers and used as received without further purification. The Chiral amines, 4-(diphenylphosphaneyl)benzoic acid, and bromine were purchased from Aldrich and used as received. NMR spectra were recorded on a Jeol 400 MHz spectrometer (^1H NMR: 400.13 MHz, ^{13}C { ^1H } NMR: 100.62 MHz, ^{31}P { ^1H } NMR: 161.97 MHz) or on a Bruker 400 MHz (^1H NMR: 500.00 MHz, ^{13}C { ^1H } NMR: 125.725 MHz, ^{31}P { ^1H } NMR: 202.404 MHz) spectrometer at room temperature using TMS (^1H , ^{13}C) and 85% H_3PO_4 (^{31}P). The mass spectrum (ESI-MS) was recorded on a Q Exactive Orbitrap mass spectrometer from Thermo Scientific. Thermal analysis data (TGA) were obtained

using a PerkinElmer STA-6000 thermogravimetric analyzer. Additionally, CD spectra ranging from 400 nm to 190 nm were collected using a JASCO J815 spectrometer, and elemental composition was determined with a Vario-EL cube elemental analyzer..

2.2.2 Synthesis of Enantiopure Chiral Phosphine oxide(2.1-R)

The compound **2.1-R** was synthesized following a modified version of a reported procedure. A solution of 4-(diphenylphosphanyl)benzoic acid (1.6 mmol) in dry dichloromethane (10 mL) was maintained at -10°C under a nitrogen atmosphere. While keeping the temperature at -10°C, liquid bromine (1.6 mmol) was gradually added dropwise. The reaction mixture was stirred under nitrogen at the same temperature for 40 minutes, leading to the formation of a yellow suspension. Subsequently, α -methylbenzylamine (3.2 mmol) and triethylamine (NEt₃) (3.32 mmol) were added sequentially at -10°C. The reaction mixture was then gradually brought to room temperature and stirred for an additional 120 minutes, with progress monitored by ³¹P NMR, ultimately yielding a yellow solid. To complete the process, distilled water (30 mL) was added, and the water-insoluble product was separated. Single crystals of the **2.1-R** were obtained from the slow evaporation of its MeOH solution.

2.1-R: Yield: 88% ¹H NMR (400 MHz, CD₃CN) δ 7.46 – 7.00 (m, 30H, aromatic), 4.34 – 4.18 (m, 6H, CH), 2.62 – 2.27 (m, 6H, NH), 1.25 (d, J = 6.9 Hz, 18H, CH₃). ¹³C NMR (101 MHz, CD₃CN) δ 148.69 (s), 128.22 (d, J = 9.12Hz), 51.31 (d, J = 10.2 Hz), 26.85 (s). ³¹P NMR (162 MHz, CD₃CN) δ 28.7 (s). HRMS-TOF-MS-ES⁺:426.4272(M⁺).

2.2.3 Host-guest Studies: General Procedure for ¹H-NMR Chiral Recognition Studies with 1-R

The samples of the chiral phosphineoxide **1-R** were prepared by dissolving 10 mg of **1-R** in 0.6 mL of CD₃Cl and the corresponding guests were prepared by dissolving 35 eq guest in 0.3 mL of CH₃Cl. We performed ¹H-NMR titrations for all the host-guest systems by adding 0-35 eq of guests in subsequent intervals to the 10⁻³ M hosts solutions from their stock solutions, and the spectrum was recorded. Chemical shift changes were monitored for the guest or the host protons, until the peak shifts are saturated. The titration data were analyzed and fitted in different host-guest binding models to get association constant values. Association constants of **1-R** with enantiomers of **BO**, **SO**, **EP**, and **PO** were obtained by fitting the corresponding ¹H NMR chemical shifts to a 1:1 binding model.

2.2.4 Theoretical Calculations

The gas-phase single molecule energies of all the participating species and the host–guest systems were calculated by using the Gaussian 09 software. These energies were computed by PM6 methods. For the host–guest complexes, the energies of the host cage **2.1-R**, the guests, and the host–guest complexes were separately calculated and the binding energy of a respective complex was calculated by (equation 3):

$$\text{Binding energy} = E_{\text{Guest} \subset \text{Host}} - (E_{\text{Host}} + E_{\text{Guest}}) \dots\dots\dots (3)$$

2.2.5 Crystallography

Data collection for compound **2.1-R** was carried out using a Bruker Kappa Apex Duo diffractometer at 100 K, employing Mo K α radiation ($\lambda = 0.71073 \text{ \AA}$). The crystal structures were determined via the intrinsic phasing method and refined using full-matrix least-squares on F² (G. M. Sheldrick, SHELXL, University of Göttingen, Germany, 2015). Unless stated otherwise, all non-hydrogen atoms were refined anisotropically. Hydrogen atoms were positioned geometrically and constrained to their corresponding parent atoms. Crystallographic details for all compounds can be found in Table A2.1-2. Additionally, all phenyl rings were restrained to maintain ideal six-membered ring geometries.

Table 2.1. Crystallographic Data for 2.1-R

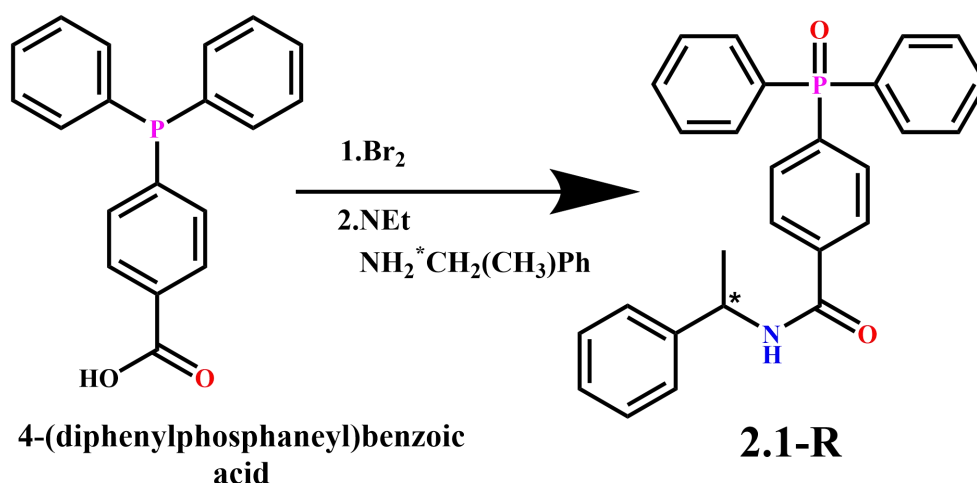
Compound	2.1-R
Chemical formula	C ₂₇ H ₂₄ N O ₂ P
Formula weight	425.44
Temperature	150(2) K
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁
<i>a</i> (Å); α (°)	8.952(4); 90
<i>b</i> (Å); β (°)	11.094(5); 92.367(11)
<i>c</i> (Å); γ (°)	11.052(5); 90
<i>V</i> (Å ³); <i>Z</i>	1096.8(9)
ρ (calc.) mg m ⁻³	1.288
μ (Mo K α) mm ⁻¹	0.150
2 θ max (°)	56.774
Flack parameter	-0.01(3)
R(int)	0.0553

Data / param.	5442/281
GOF	1.045
R1 [F>4 σ (F)]	0.0312
wR2 (all data)	0.0805
Max. peak/hole(e. $\text{\AA}^{-3}$)	0.296/-0.323

2.3 Results and Discussions

2.3.1 . Synthesis, Structure, and Characterization

Treatment of 4-(diphenylphosphaneyl)benzoic acid with Br₂ followed by the acid amine condensation reaction with *R*- α -methylbenzylamine in excess triethylamine as a base yielded the phosphine oxide derivative **2.1-R** [POPh₂(R*)], where R* corresponds to an amide substituent (*R*-((C₆H₄)(CO)(NH)(CH(CH₃)Ph)) (Scheme 1). The ³¹P NMR spectrum of **2.1-R** showed a singlet at 28.7 ppm, confirming the formation of phosphine oxide. The ¹H NMR spectra indicated well-resolved signals corresponding to the α -methylbenzylamino and phenyl substituents in the respective aliphatic and aromatic regions (Figures A2.1–A2.3). The ESI-MS mass spectrometry of **2.1-R** gave a peak at *m/z* = 426.4272 corresponding to its protonated molecular ion ([M-H]⁺) (Figures A2.4).



Scheme 2.1. Procedure for the synthesis of enantiopure phosphine oxide **2.1-R**.

The optical characterizations of **2.1-R** using CD spectrometry and specific rotation measurements confirm the enantio-purity of this compound. The circular dichroism (CD) spectrum of this compound suggests two prominent peaks at 236 and 263 nm (Figure A2.5).

The specific rotation (α_D) value of **2.1-R** was observed to be +43. The thermogravimetric analysis (TGA) suggests that the compound **2.1-R** is stable up to 400 °C (Figure A2.6).

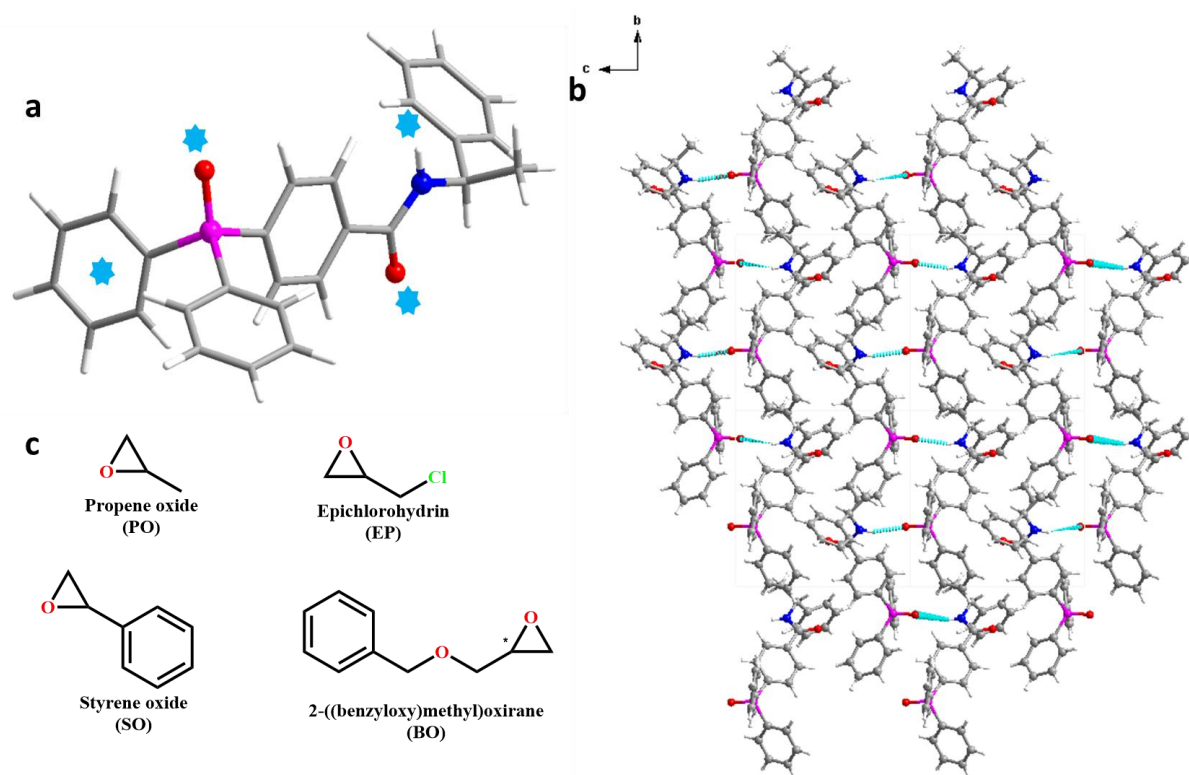


Figure 2.1. a) Crystal structure of **2.1-R** highlighted with the guest accessible binding sites (blue asterisks) b) The packing diagram of **2.1-R** along a-axis and (b) examined enantiomeric guests for chiral recognition studies.

Single-crystals of **2.1-R**, suitable for X-ray diffraction (SCXRD) analysis, were grown by the slow evaporation of their methanol solutions. They were crystallized in the chiral space group $P2_1$. The structural determination of these crystals also unambiguously confirmed the absolute stereochemistry of **2.1-R** (Figure 2.1a). The P-O distance is 1.560(8), and the corresponding O-P-C bond angles range from 111.928(4) to 112.738(5), are aligned with those found in previously reported phosphine oxides. Notably the structural analysis reveal that donor (P-O) and acceptor (N-H) groups of **2.1-R** display strong intermolecular bonding with two different neighbouring molecules. These intermolecular hydrogen bonding are perpendicular to the zig-zac arrangements of molecules along the b-axis (Figure 2.1b). The presence of multiple binding sites, including highly polar phosphoryl and carbonyl groups, which can act as hydrogen bond acceptors, amino groups that can act as hydrogen bond

donors, and phenyl groups that can facilitate π - π interactions along with the sterical parameters enables them a promising candidate for chiral recognition epoxides.

2.3.2 Chiral Recognition Studies

Inspired by the presence of multiple binding pockets present in **2.1-R** coupled with its good thermal and moisture stabilities, we set out to examine the guest-binding affinities for a family of chiral epoxides. To investigate the binding abilities of **2.1-R**, we performed ^1H -NMR titration experiments with optically pure guest molecules. The guest binding was calculated by monitoring changes in the ^1H -NMR chemical shift values of the host (or guest) protons, and the peak intensity gradients were fitted with the help of the online Bindfit Tool to obtain the binding constant.^{25, 26} The binding constants obtained from the Bindfit calculator indicated 1:1 stoichiometries in host-guest binding for **PO**, **EP**, **SO**, and **BO** guests with **2.1-R** host (Table 2.2, Figures A2.8–A2.11). The ^{31}P -NMR spectra for each host-guest complex were recorded after titration to confirm the stability of **2.1-R** in the solution during the experiment.

The ^1H NMR titration analysis of **1-R** with **R-BO** in CD_3Cl suggests a sharp downfield shift in the N-H proton signal of the amino substituent and the aromatic protons in the host **1-R**, which were accounted for the Bind Fit calculations. The Bind Fit analysis shows a characteristic strong and enantioselective 1:1 binding with a K_a of 12589. The titration analysis of **S-BO** does not display such downfield shifts in the amino protons, indicating the absence of strong H-bonding interaction. Instead, a moderate upfield shift in the aromatic protons was observed, and fitting these peak intensity profiles yielded a much lower 1:1 binding constant value of 3.9 in the case of **1-R+S-BO**. The obtained K_a values for both **1-R+R-BO** and **1-R+S-BO** are consistent with the difference in the binding constant procured for similar host-guest complexes (Figure 2.2).^{27, 28}

A closer look at the titration experiments of **1-R** with the enantiomers of **SO** shows a similar trend in the chemical shifts. The sequential addition of **R-SO** to **1-R** displayed a downfield shift for the N-H protons of the amino substituents of **1-R**, indicating a strong 1:1 binding with a K_a value of 3925 M^{-1} . In contrast, the ^1H NMR titration of **S-SO** with **1-R** does not display any significant shift in the N-H protons of the amino substituent. Whereas it shows moderate downfield shift CH and CH_2 protons of the epoxide ring, which gave a lower K_a value of only 0.22 M^{-1} for the **1-R+S-SO** complex, presumably owing to the absence of significant hydrogen-bonding interaction with the amino substituent as in the case of **1-R+R-SO** (Table 2.2, Figures A2.8–A2.9).

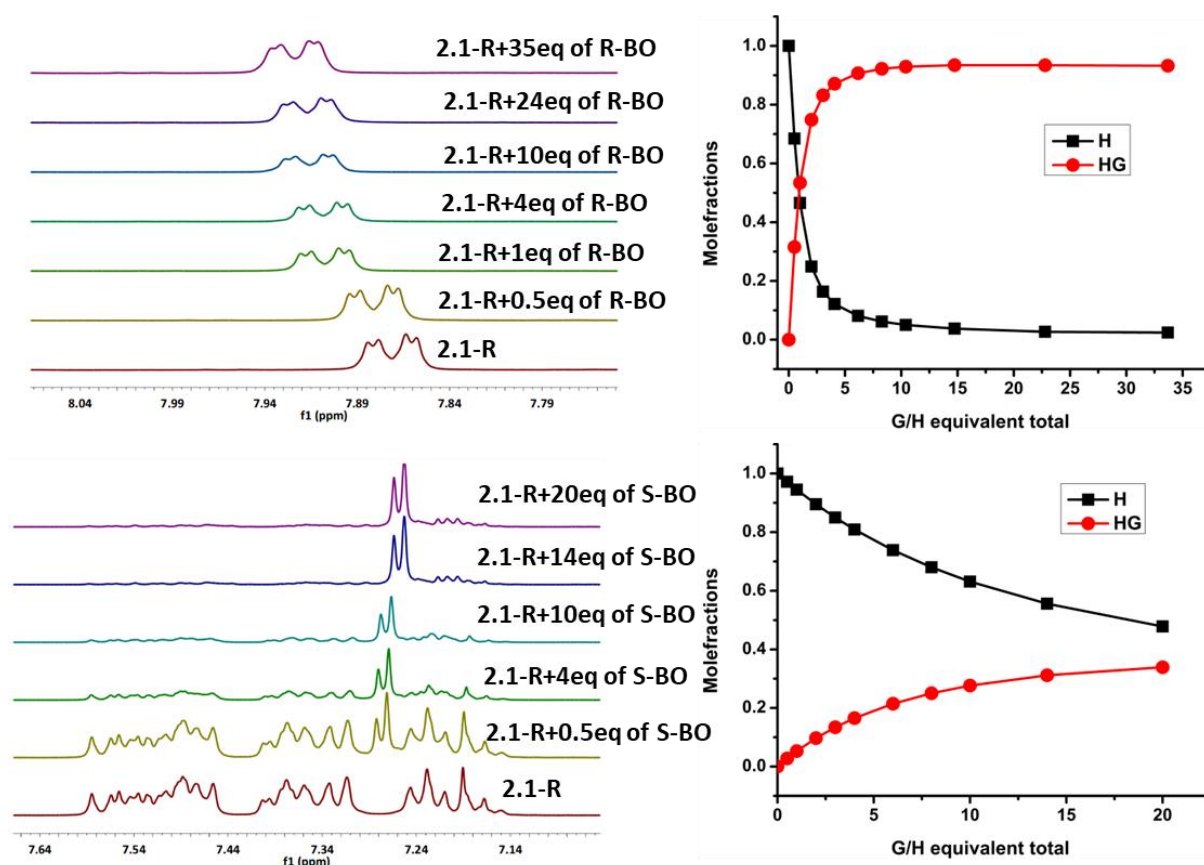


Figure 2.2. ^1H -NMR titration plots a) **2.1-R+R-BO** and b) **2.1-R+S-BO**, Bind fit plots for the for the host-guest complexes of c) **2.1-R+R-BO** and d) **2.1-R+S-BO**.

The titrations of **2.1-R** with **R-EP** also displayed a notable downfield shift for the N-H protons and aromatic C-H protons of the amino substituents. In contrast, only the aromatic CH protons of the amino substituents showed a downfield shift for the **2.1-R+S-EP** system. The CH_2 protons of the epoxide ring also displayed a moderate upfield shift in the case of the **2.1-R+R-EP** system, whereas the CH protons **S-EP** showed a moderate downfield shift in the case of the **2.1-R+S-EP** system. The BindFit analysis corresponding to each host-guest system indicates a relatively weak binding for the *S*-enantiomer of **EP** with **2.1-R** compared to its *R*-enantiomer (Table 2.2, Figures A2.10–A2.11), as the **2.1-R+R-EP** system shows a K_a of 3526 M^{-1} , while the **2.1-R+S-EP** system exhibits a much lower K_a of 0.22 M^{-1} for 1:1 host-guest complex.

Finally, the ^1H -NMR titrations of **2.1-R** with the enantiomers of **PO** in CD_3Cl displayed prominent downfield shifts for N-H protons of the amino substituent of the host protons, along with a moderate downfield shift in the case of aromatic protons in the case of **2.1-**

R+R-PO. In addition, it shows an upfield shift in the CH_2 protons of the epoxide ring as well. The binding curve obtained for the 1:1 complex of **2.1-R+R-PO** yields a large K_a of 202 M^{-1} . In contrast, such significant downfield shift in the N-H protons of the host in the **2.1-R+S-PO** system, instead a moderate downfield shifts were observed for the guest CH_2 and CH_3 protons with a smaller K_a value of 3.5 M^{-1} (Table 2.2 Figures A2.12–A2.13).

Further analysis of the titration data indicates significant differences in the obtained K_a values between the pair of enantiomeric guest molecules in all the host-guest systems. This can be quantified using the parameter of binding selectivity (ξ) determined using the expression $\xi = K_a(\text{larger})/K_a(\text{smaller})$ obtained from the differences in the binding constants for each of the enantiomeric pairs of the guest molecules (Table 2.2). Notably, the **2.1-R+R-BO** system exhibits the highest binding affinities as well as the highest ξ value of 3214. This also indicates a significant difference in the non-covalent interactions present in the **2.1-R+R-BO** compared to those in the **2.1-R+S-BO** system. A significantly higher ξ value of 1029 was obtained for **R-SO** over **S-SO** with **2.1-R**. With **EP** systems **2.1-R** displayed a moderate binding affinity towards each of its enantiomer, resulting in a ξ value of 809 in favor of the **2.1-R+R-EP** complex. The **PO** complexes with **2.1-R** show lower K_a values and a poor binding selectivity value of 57 in favour of its *R*-enantiomer. Notably, the binding selectivity of **BO** is 56 times higher compared to **PO**, which highlights the differences in the nature and strength of non-covalent interactions that govern selective guest binding, influenced by the presence of various functional groups in **2.1-R**.

Furthermore, to confirm the host-guest formation of **2.1-R** with the *R*-isomers of each of the guest molecules, we performed ^{31}P NMR spectra of **2.1-R** after adding 1eq of each enantiomer of guest molecules separately. Significant upfield shifts with δ values of 0.664, 0.315, and 0.243 ppm for **2.1-R+R-BO**, **2.1-R+R-SO**, **2.1-R+R-EP** and **2.1-R+R-PO**, respectively, with respect to **2.1-R** were observed for these host-guest mixtures. Meanwhile, their corresponding *S*-enantiomers displayed only negligible shifts in their ^{31}P NMR spectra for the host-guest complexes (Figure A2.14). This confirms the enantioselective host-guest formation of **2.1-R** with only the *R*-isomers of these guest molecule.

2.3.3 Single-Molecule Optimization Studies

The preliminary structural optimization studies were conducted with the help of density functional theory (DFT) to estimate the gas-phase binding energies of each host-guest assembly (Table A2.3). These optimized host-guest structures provided further insights into the multiple non-covalent interactions present in each of the host-guest complexes

showcasing the guest binding and chiral recognition capabilities of **2.1-R**.

Table 2.2. ¹H-NMR titration derived selective association constants (K [M^{-1}]) and binding selectivity (ζ) studies on **2.1-R**.

Guest	Recognition		ΔE_{pref} (%ee)
	K_{11} with 1-R	ζ	
R-BO S-BO	12589 3.9	3214 (R)	29.8
R-SO S-SO	3925 0.26	1029 (R)	18.1
R-EP S-EP	3526 0.22	802 (R)	16.4
R-PO S-PO	202 3.5	57 (R)	7.01

The DFT-optimized structures of 1:1 complexes of *R* and *S* enantiomers of **BO** with **2.1-R** exhibit a substantial difference in the binding mode of the guest molecule with the host. Notably, prominent H-bonding interactions between the amide N-H proton of **2.1-R** with the epoxide ring oxygen of the **R-BO** guest were noticed in the optimized gas phase structures (Figure 2.3). Furthermore, the epoxide ring oxygen exhibits bifurcate H-bonding interaction with the aromatic C-H protons, which was evident from the downfield shift of both amino N-H and aromatic C-H protons observed from the ¹H-NMR titrations. Additionally, two weak H-bonding interactions between the phosphoryl oxygen atom of **2.1-R** and aromatic C-H protons and alkyl CH_2 protons of the **R-BO** were observed for the **2.1-R+R-BO** complex. In contrast, the optimized structure of **2.1-R+S-BO** does not exhibit any such strong N-H $\cdots$ O type H-bonding interactions. Instead, **S-BO** displayed bifurcate H-bonding interaction between phosphoryl oxygen atoms and alkyl CH and CH_2 groups of the epoxide ring. Additionally, the aromatic C-H protons of **2.1-R** were engaged in C-H $\cdots\pi$ interaction with the benzyl group of **S-BO**, which resulted in the upfield shift of guest protons in ¹H-NMR titration studies. A comparative ΔE_{pref} (the difference in energy between the favored and unfavored enantiomers) value of approximately 29.8 was obtained, indicating that the optimized energy of the **2.1-R+S-BO** complex is much greater than that of the **2.1-R+R-BO** complex (Table 2.2). This implies that **2.1-R** preferentially binds to the *R*-enantiomer of **BO** compared to its *S*-enantiomer.

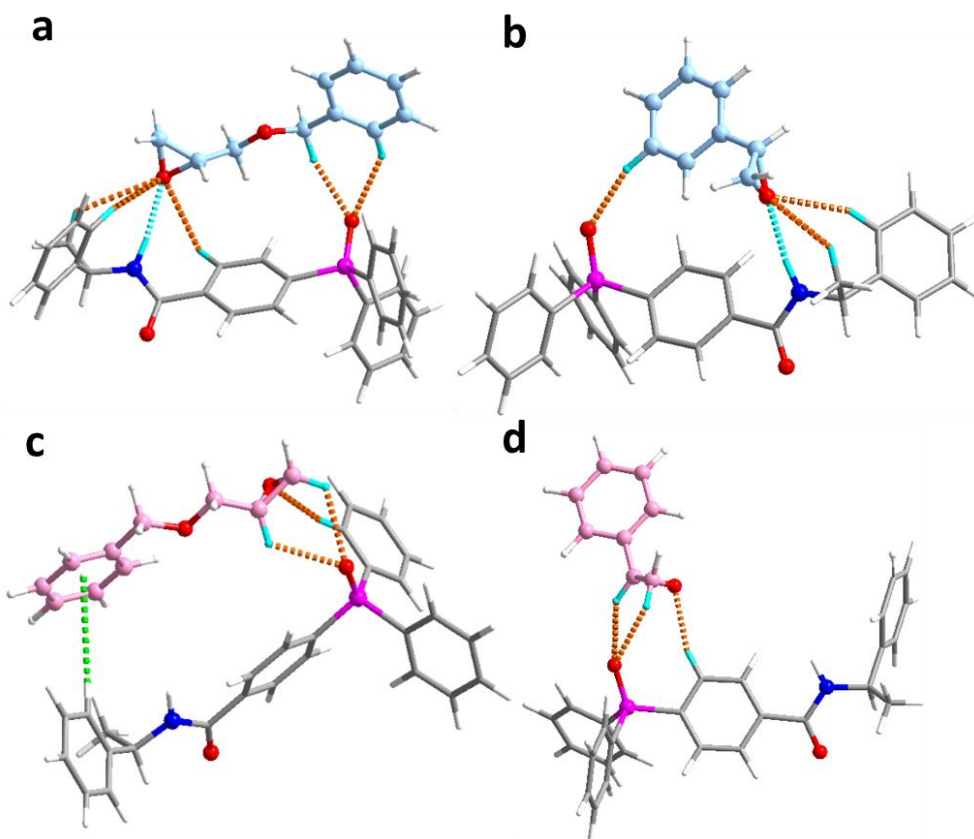


Figure 2.3. DFT optimized structures of a) **2.1-R+R-BO**, b) **2.1-R+S-BO**, c) **2.1-R+R-SO**, and d) **2.1-R+S-SO** complexes. P magenta; C grey; N blue; O red; Cl green; H white. The non-classical interactions (X = N, O) are shown in dotted lines: cyan N-H $\cdots$ X, purple $\pi\cdots\pi$, green C-H $\cdots\pi$, and orange polar X-H $\cdots\pi$.

Similarly, the optimized structure of **2.1-R+R-SO** showed the presence of a strong H-bonding interaction between the amide N-H protons of **2.1-R** and the epoxide ring oxygen atom of R-SO, along with the weak H-bonding interaction between the epoxide ring oxygen and methyl and aromatic CH protons (Figure 2.3). The downfield shift of N-H and the aromatic protons of **2.1-R** in $^1\text{H-NMR}$ titrations further confirms these non-covalent interactions in the **2.1-R+R-SO** complex. At the same time, the **S-SO** interacts with **2.1-R** via weak bifurcate H-bonding interactions between the phosphoryl oxygen atom and the CH and CH₂ protons of the epoxide ring. Additionally, there is a weak H-bonding interaction between the epoxide oxygen and the aromatic C-H protons of **2.1-R**. The **2.1-R+S-SO** complex does not show any strong H-bonding interaction such as N-H $\cdots$ O type interaction as in the case of **2.1-R+R-SO** and mostly relies on weak H-bonding interaction for the host-guest complexation. Thus, there is a significant difference in the binding energies of R-SO

and **S-SO** with **2.1-R**, which is about 18.1 in favor of *R*-enantiomer (Table 2.2).

The optimized structures of *R* and *S* enantiomers of **EP** and **PO** with **2.1-R** indicate that the *R*-enantiomer of both **EP** and **PO** form primary contact with **2.1-R** via strong N-H $\cdots$ O type H-bonding interactions between the N-*H* protons of the amino substituent and epoxide oxygen atom along with C-H $\cdots$ π interaction. (Figure A2.15). In the case of **R-EP**, an additional bifurcate interaction is observed between the Cl atom of the guest **R-EP** and the *CH* protons of the aromatic and methyl groups of **2.1-R**. In contrast, the **S-EP** form weak H-bonding interaction with the phosphoryl oxygen atom and the *CH* proton of the epoxied ring along with a bifurcate H-bonding interaction between the Cl atom of **S-EP** and *CH* and aromatic protons of the amino substituent. At the same time, the **S-PO** forms a bifurcate H-bonding interaction with the phosphoryl oxygen atom of **2.1-R** and a weak H-bonding interaction with the aromatic C-H protons of **2.1-R** (Figure A2.16). The variations in the nature and strengths of these interactions have resulted in a ΔE_{pref} of 16.4 and 7.01 for **EP** and **PO**, respectively, in favor of its *R*-enantiomer.

2.4 Conclusion

In this study, we reported the synthesis and structural analysis of an enantiopure phosphine oxide, **2.1-R**, with the molecular formula **2.1-R** [POPh₂(R*)], where R* corresponds to an amide substituent (*R*)-((C₆H₄)(CO)(NH)(CH(CH₃)Ph)). Since this novel chiral phosphine oxide **2.1-R** possesses multiple hydrogen bond donor and acceptor sites, we investigated the chiral recognition ability of **2.1-R** for a family of epoxides, including **BO**, **SO**, **EP**, and **PO** where the chiral host exhibits strong binding selectivities for the host-guest complexes with same chirality over those with opposite chirality. Notably, **2.1-R** exhibited significant binding selectivity for **R-BO**, **R-SO**, **R-EP**, and **R-PO** compared to their *S*-enantiomers. Remarkably, the highest binding selectivity of 3214 was observed for **R-BO** over its *S*-enantiomer, based on their estimated binding constants values from ¹H-NMR titrations. The observed trends in binding selectivity mainly depend on the functional groups present in the guest molecules and the steric of the guest molecules. DFT structural optimization studies further revealed that the enantioselective recognition process is governed by a combination of non-covalent interactions, including hydrogen bonding with the ring nitrogen, π - π interactions, and steric effects between the phosphine oxide and the guest molecules. These findings underscore the potential of enantiopure phosphine oxides as highly effective hosts for chiral recognition, demonstrating their promise for a wide range of enantioselective applications.

2.5 References

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Chapter -3

A Chiral Hexa-amino Cyclotriphosphazene for Enantioselective Recognition of Small Organic Compounds

3.1 Introduction

Chirality is a fundamental property for numerous molecules that are ubiquitous in nature.^{1, 2} Several vital biological components such as proteins, amino acids, nucleosides, sugars, and various hormones are chiral and serve as the building blocks of life.^{3, 4} Because of the natural asymmetry, chiral compounds exhibit different properties in anisotropic biochemical systems, even though they are indistinguishable in most inanimate environments. Considering a greater demand for applications involving enantioselective processes, the design and synthesis of new materials with chiral receptors have gained significant attention. Chiral recognition is an important process in which one enantiomer of an analyte is preferentially recognized over the other by a chiral selector via enantiospecific interactions with the formation of transient diastereomeric complexes.⁵ A range of synthetic receptors, such as crown ethers,⁶ cyclodextrins,⁷ cryptophanes,⁸ carcerands,⁹ cucurbiturils,¹⁰ calixarenes,¹¹ porous coordination polymers,¹² metal-organic frameworks,¹³ and self-assembled cages,^{14,15} have traditionally been utilized for chiral guest recognition. Nonetheless, these receptors encounter complexities like high cost, synthetic intricacy, intricate recognition mechanisms, and restricted functional group accessibility, given that these systems frequently require the integration of specific targeting groups for chiral recognition.¹⁶ One of the easiest ways to achieve efficient chiral recognitions is to employ simple organic receptors that can identify chiral guest molecules through various non-covalent forces such as ionic interactions, ion-dipole or dipole-dipole interactions, H-bonds, van der Waals interactions, π - π interactions and even steric repulsions.¹⁷

Cyclophosphazenes are a family of inorganic ring compounds with diverse structural and functional properties. They possess a robust cyclic P-N motif, mostly trimeric and tetrameric rings, which are widely explored as versatile building blocks for diverse functional materials.¹⁸⁻²⁰ For example, the functionalization of cyclotriphosphazene can be easily achieved by substituting the six chlorides of the precursor $P_3N_3Cl_6$ with the substituents of choice.²⁰⁻²³ Such efforts have led to molecules and materials that are applied as catalysts,²⁴⁻²⁸ flame retardant materials,^{29, 30} biomedical materials,³¹ anticancer agents,^{32, 33} fluorescent dyes³⁴, and largely as multisite coordination ligands.³⁶⁻⁴⁰ The realization of such diverse functionalities can be aided by the substituents on the phosphazene backbone and by the functionalization of N-atoms of the P_3N_3 core in some instances.^{34, 41-50} In addition, the trimeric phosphazene ring can exhibit both structural rigidity and flexibility as the hexameric ring can exist in planar and puckered configurations, providing the necessary pockets for

guest-binding and chiral recognition studies.⁵¹

Chirality in phosphazenes has mainly been achieved through unsymmetrical substitutions leading to axial, geometric, and P-centric chirality.⁵² However, their synthesis poses significant challenges, primarily caused by intricate multistep processes and the complexities associated with their separation from multiple product mixtures with distinct optical properties.^{53, 54} Hence, incorporating carbon stereo centers into the substituents on the P-atoms would offer a straightforward strategy for synthesizing cyclotriphosphazenes with absolute chirality. Nevertheless, cyclotriphosphazenes carrying such carbon stereo centers are the least explored so far.⁵⁵

Inspired by the facile procedures involved in the synthesis of hexakis(organoamino)cyclophosphazenes,⁵⁶ we set out to synthesize the hexa-amino derivative of the phosphazene containing carbon stereo-centers and study their enantio-recognition capabilities. Herein, we report an enantiomeric pair of hexakis(α -methylbenzylamino)cyclotriphosphazene of formula, $[P_3N_3(NHR^*)_6]$, $[R^* = (R)\text{-(CH(CH}_3\text{)Ph)}$ (**3.1-R**) and $(S)\text{-(CH(CH}_3\text{)Ph)}$] (**3.1-S**) obtained by the reaction of $P_3N_3Cl_6$ with the corresponding primary amines (Figure 3.1). The chiral recognition capabilities of **3.1-R** were further evaluated for the *R* and *S* isomers of various small organic molecules with a wide range of functionalities, such as binol (**BOL**), 4-benzyl-2-oxazolidinone (**BOZ**), 4-hydroxydihydrofuran-2(3*H*)-one (**HOF**), 2-((benzyloxy)methyl)oxirane (**BMO**) and phenylsuccinic acid (**PSA**) (Figure 3.1). These studies show a stronger binding of **3.1-R** with **R-BOL**, **R-PSA**, and **R-BOZ**, with **R-BOL** showing the highest binding selectivity of 2506 over **S-BOL**. The high binding affinities exhibited by these structurally diverse organic compounds result from a synergistic combination of H-bonding and π - π interactions, as confirmed by density functional theory (DFT) optimized structures of the corresponding host-guest complexes. To our knowledge, this is the first instance where a neutral chiral cyclotriphosphazene is utilized as a host for enantioselective recognition studies, achieving such high binding selectivity between a pair of enantiomeric guests.

3.2 Experimental Details

3.2.1 General Remarks

All manipulations involving phosphorus halides were performed under a dry nitrogen atmosphere in standard Schlenk glassware. Dry Solvents were purchased from local vendors and used without further purification. The chiral amines and hexachlorocyclotriphosphazene were purchased from Aldrich and used as received. NMR spectra were recorded on a Jeol

400 MHz spectrometer (^1H NMR: 400.13 MHz, ^{13}C { ^1H } NMR: 100.62 MHz, ^{31}P { ^1H } NMR: 161.97 MHz) or on a Bruker 400 MHz (^1H NMR: 500.00 MHz, ^{13}C { ^1H } NMR: 125.725 MHz, ^{31}P { ^1H } NMR: 202.404 MHz) spectrometer at room temperature using TMS (^1H , ^{13}C) and 85% H_3PO_4 (^{31}P). The mass spectrum (ESI-MS) was recorded on a Q Exactive Orbitrap mass spectrometer from Thermo Scientific. Thermal analysis data (TGA) were obtained using a PerkinElmer STA-6000 thermogravimetric analyzer. Additionally, CD spectra ranging from 400 nm to 190 nm were collected using a JASCO J815 spectrometer, and elemental composition was determined with a Vario-EL cube elemental analyzer.

3.2.2 Synthesis of Enantiopure chiral cyclotriphosphazenes (3.1-R and 3.1-S)

A 13 mL of α -methylbenzylamine (100.45 mmol) was added to a stirred solution of 5 g (14.35 mmol) hexachlorocyclotriphosphazene in 200 mL toluene and 16.5 mL triethylamine (180 mmol) at room temperature. The formation of a white precipitate indicated the forward reaction. The solution was heated to reflux until substitution was completed (Monitored by ^{31}P NMR) and cooled before filtration. The solvent was removed under reduced pressure, yielding the mixture of hexakis(*R/S*-1-Phenylethylamino)cyclotriphosphazene and its hydrochloride adduct. Hydrochloride adduct was stirred with finely ground potassium hydroxide in a water-methanol mixture for 3 hours. The methanol was removed under reduced pressure, and the residue was extracted with ether and dried over sodium sulfite to obtain the pale yellow semisolid product.

3.1-R: Yield: 88% ^1H NMR (400 MHz, CD_3CN) δ 7.46 – 7.00 (m, 30H, aromatic), 4.34 – 4.18 (m, 6H, CH), 2.62 – 2.27 (m, 6H, NH), 1.25 (d, J = 6.9 Hz, 18H, CH_3). ^{13}C NMR (101 MHz, CD_3CN) δ 148.69 (s), 128.22 (d, J = 9.12 Hz), 51.31 (d, J = 10.2 Hz), 26.85 (s). ^{31}P NMR (162 MHz, CD_3CN) δ 14.39 (s). HRMS-TOF-MS-ES $^+$: 856.4272(M^+).

3.1-S: Yield: 84% ^1H NMR (400 MHz, CD_3CN) δ 7.29 – 7.14 (m, 30H, aromatic), 4.24 – 4.21 (m, 6H, CH), 2.48 – 2.34 (m, 6H, NH), 1.21 (d, J = 6.8 Hz, 18H, CH_3). ^{13}C NMR (101 MHz, Acetone- d_6) δ 148.55 (s), 128.84 (s), 126.94 (d, J = 9.1 Hz), 50.96 (d, J = 10.2 Hz), 26.44 (s). ^{31}P NMR (162 MHz, CD_3CN) δ 14.39 (s). HRMS-TOF-MS-ES $^+$: 856.4273(M^+).

3.2.3 Host-guest Studies: General Procedure for ^1H -NMR Chiral Recognition Studies with 3.1-R and 3.1-S.

The samples of the chiral phosphazene **3.1-R** were prepared by dissolving 10 mg of **3.1-R** in 0.6 mL of $\text{CD}_3\text{CN}/\text{CD}_3\text{OD}$, and the corresponding guests were prepared by dissolving 30 eq guest in 0.5 mL of $\text{CH}_3\text{CN}/\text{CD}_3\text{OD}$. The ^1H -NMR titrations were performed for all the host-

guest systems by adding 0-30 eq of guests in subsequent intervals to the 10^{-3} M hosts solutions from their stock solutions, and the spectrum was recorded. Chemical shift changes were observed for the guest and/or the host protons. The titration experiment was continued until the peak shifts became constant, indicating the saturation point. The titration data were analyzed and fitted in different host-guest binding models to get association constant values. Association constants of **3.1-R** with enantiomers of **BOL**, **BOZ**, **HOF**, and **BOM** were obtained by fitting the corresponding ^1H NMR titration data to a 1:2 binding model. Similarly, association constants of **3.1-R** with enantiomers of PSA were obtained by fitting in a 2:1 binding model.

3.2.4 Theoretical Calculations.

The gas phase single molecule binding energies of the enantiopure receptor-guest complexes were calculated theoretically using the *Gaussian 09* software.³⁻⁴ These energies were computed by DFT methods by employing the b97d3 functional. Energy calculations were performed using the basis 6-311++G (d, p). The energies of the chiral receptor, chiral guests, and host-guest complex were separately calculated. The binding energy of a given host-guest complex was calculated using the following equation.

$$\text{Binding energy} = (E_{\text{host-guest}} + \text{ZPE}_{\text{host-guest}}) - [(E_{\text{host}} + \text{ZPE}_{\text{host}}) + (E_{\text{guest}} + \text{ZPE}_{\text{guest}})] + \text{BSSE}$$

E- Gas phase energy of respective systems calculated using DFT Methods

ZPE- Zero point energy of respective systems

BSSE- basis set superposition error

Further, the energy differences between the most favoured and least favoured enantiomers with the hosts have been calculated as the ΔE_{pref} . It illustrates the strength of interactions within the diastereomeric pairs (Host-guest complex) as the host-guest complexes with the lowest energy values were observed for the more strongly bound complex. The value of ΔE_{pref} necessarily gives the idea of how strong one enantiomer of the guest is held to a particular enantiomer of the host (**3.3.1-R**) compared to its opposite enantiomer.

3.2.5 Crystallography

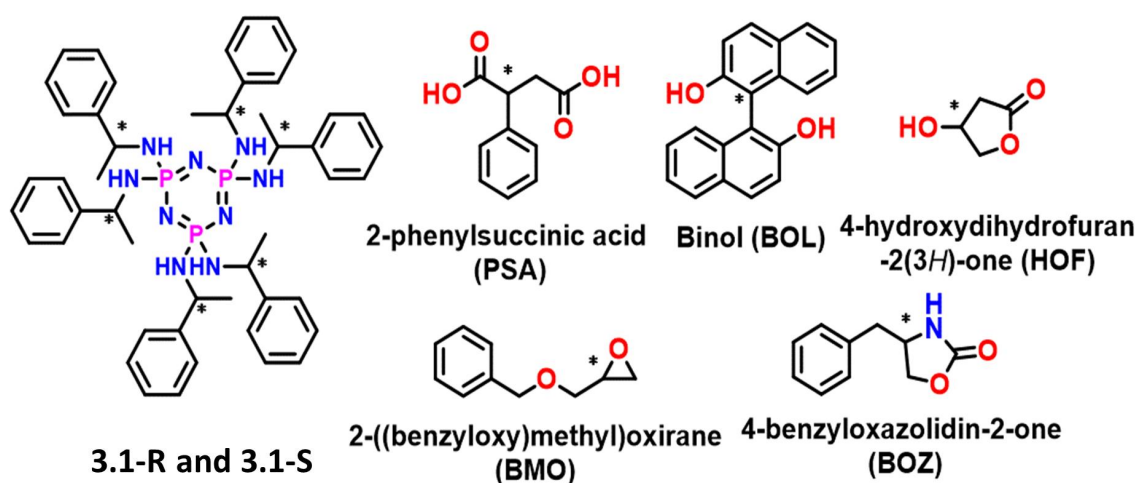
Reflections were collected on a Bruker Kappa Apex Duo diffractometer at 100 K using Mo $K\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$) for **3.2-R** and **3.2-S**. All structures were solved using the intrinsic phasing method and refined by full-matrix least-squares on F^2 (G. M. Sheldrick, SHELXL program for crystal structure refinement, University of Gottingen, Germany, 2015).⁵ All non-hydrogen atoms were refined anisotropically if not stated otherwise.

Hydrogen atoms were constrained in geometric positions to their parent atoms. Crystallographic data for all these compounds are listed in Table A3.2. The solvent molecules in **3.2-S** could not be modelled accurately. Hence, these were treated as diffuse contributions to the overall scattering and removed by the SQUEEZE/PLATON for better refinement data.⁶ All the phenyl rings are constrained to ideal six-membered rings.

3.3 Results and Discussions

3.3.1 Synthesis, Structure, and Characterization

Nucleophilic substitution of $P_3N_3Cl_6$ with *R/S*- α -methylbenzylamine in excess triethylamine as a base yielded the corresponding protonated derivatives $[P_3N_3H(NHR^*)_6]Cl$, [$R^* = (R)$ -(CH(CH₃)Ph) (**3.2-R**) and (*S*)-(CH(CH₃)Ph)] (**3.2-S**). The neutral chiral phosphazenes **3.1-R** and **3.1-S** were subsequently obtained by their treatment with KOH in a methanol/water mixture. The ³¹P NMR spectra of **3.1-R** and **3.1-S** showed a singlet at 14.3 ppm, confirming the complete substitution of the phosphazene core. The ¹H NMR spectra gave well-resolved signals at both the aliphatic and the aromatic regions for their α -methylbenzylamino groups (Figure A3.1– A3.5). The ESI-MS mass spectrometry of both **3.1-R** and **3.1-S** gave a peak at $m/z = 856$ corresponding to their protonated molecular ion ($[M-H]^+$) (Figure A3.6– A3.7).



Scheme 3.1. Chemical structure of the cylotriphosphazenes **3.1-R** and **3.1-S** and the examined enantiomeric guests for chiral recognition.

The circular dichroism (CD) spectra of these compounds exhibit identical bisignate bands, at 236 and 263 nm confirming their enantio-enriched nature (Figure 3.1). The absolute

configuration (α_D) values of **3.1-R** and **3.1-S** are observed to be +111 and -119, respectively, as indicated by the optical rotation measurements (Table A3.1). The thermogravimetric analysis (TGA) indicated the thermal stability of these compounds up to 260 °C (Figure A3.8).

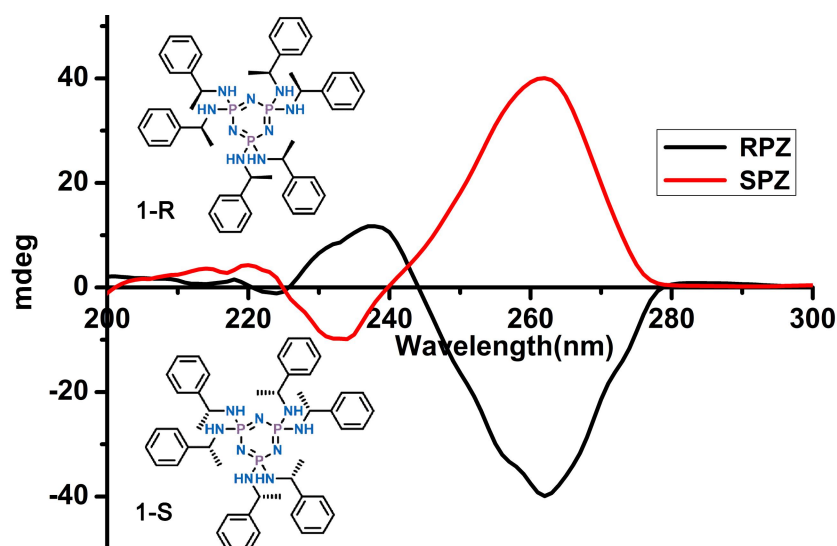


Figure 3.1. Circular dichroism spectra of **3.1-R** and **3.1-S**.

The ring-protonated derivatives **3.2-R** and **3.2-S** were crystallized in the polar monoclinic $P2_1$ space group (Figures 3.2a and A3.9). The asymmetric unit of both **3.2-R** and **3.2-S** contains one protonated phosphazanium cation, one chloride ion, and solvent molecules. The obtained structures confirm the absolute chirality of **3.2-R** and **3.2-S**. One of the three-ring N-atoms (N3) of the phosphazenes is protonated and primarily interacts with the chloride ion. As a result, the P-N bonds associated with N3 are longer (ranging from 1.637(8) to 1.652(3) Å), while the rest of the P-N bonds are shorter (ranging from 1.549(6) to 1.607(8) Å) (Table A3.3). Furthermore, the chloride anion interacts with one of the peripheral N-H protons of the amino group, leading to the formation of a 1D-chain structure.

The neutral phosphazenes **3.1-R** and **3.1-S** were semi-solids and could not be crystallized. Hence, we optimized their gas-phase single-molecule energies using DFT methods (Figure 3.2b). The metric parameters observed in the optimized structures of **3.1-R** and **3.1-S** correlate well with those observed in **3.2-R** and **3.2-S** and other well-known hexakis(alkylamino)cyclophosphazenes.⁵⁷ However, unlike **3.2-R** and **3.2-S**, all the P-N bonds of the phosphazene ring in **3.1-R** and **3.1-S** are equivalent, with an average bond

length of $\sim 1.6712(5)$ Å.

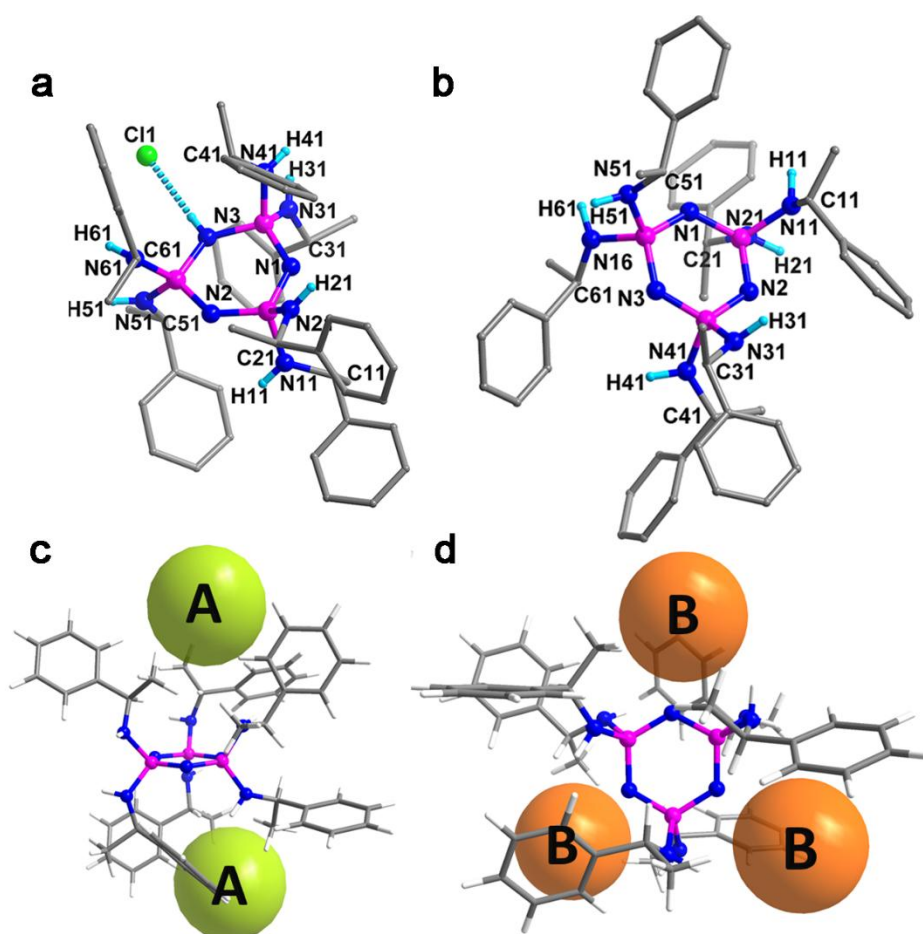


Figure 3.2. a) Crystal structure of **3.2-R**. b) DFT optimized structure of **3.1-R**. c) and d) locations of the two types of guest-accessible binding pockets, *A* and *B*, present in chiral-phosphazene **3.1-R**.

The phosphazene core exhibits a nearly planar structure in both the cationic and neutral assemblies. The arrangement of six amino substituents around the P₃N₃ ring provides five unique binding pockets for host-guest studies (Figure 3.2c–d). Two out of the five pockets (denoted by *A*) are located above and below the ring of alternating P and N atoms. The remaining three binding sites, termed *B*, are laterally located around the phosphazene core flanked by two amino substituents on either side of the N_{ring} atoms (Figure 3.2c–d). These binding pockets differ in terms of the size and accessibility of functional groups for the incoming guest molecules. The chiral aminophosphazene, with dual H-bond donor (via N–H groups) and H-bond acceptor (via the ring N-atoms) sites, selectively enables multiple non-covalent interactions with the chiral guest molecules in pocket *B*. However, guest molecules

accessing pocket *A* will experience poor interactions with the H-bond donor and acceptor functionalities around the phosphazene due to the bulky nature of the amino substituents in the pocket. Such attributes indicate that these phosphazenes could be efficient hosts for chiral recognition studies.

3.3.2 Chiral Recognition Studies

Spurred by the presence of distinct binding pockets present in the neutral phosphazenes, we set out to probe their guest-binding affinities. Moreover, both **3.1-R** and **3.1-S** exhibit moisture stability and good solubility in several organic solvents (with polarities ranging from hexane to methanol), promising their utility for enantioselective studies of small chiral organic compounds. Notably, we performed binding studies of **3.1-R** using ^1H -NMR titrations in the presence of optically pure guest molecules and by monitoring the changes in the chemical shift value of the host (or guest) protons and fitting the peak intensity gradients using the online Bindfit Tool.^{58, 59} The binding constants derived from the Bindfit calculator gave the best fits for the 1:1 host-guest stoichiometry for **BOL**, **BOZ**, **HOF**, and **BMO** guests and 2:1 host-guest stoichiometry for **PSA** guests (Table 3.1, Figure A3.10– A3.17). The ^{31}P -NMR spectra for each host-guest pair were recorded with excess guest molecules to confirm the stability of **3.1-R** in the solution during the titration experiment.

A closer look at the ^1H -NMR titration of **3.1-R** with **R-BOL** in CD_3CN indicates a sharp downfield shift for the N-H protons of the amino substituents on the phosphazene backbone (Figure 3.3a). Fitting these peak profiles in the Bindfit calculator yielded a 1:1 binding curve with a K_a value of 135.3 M^{-1} for the **3.1-R+R-BOL** system (Figure 3.3c and Table 3.1). In contrast, the titration of **3.1-R** with **S-BOL** shows no prominent shifts for the N-H protons, indicating the difference in the modes of binding of the enantiomers of **BOL** with **3.1-R**. However, a moderate upfield shift of the methyl protons was observed for the **3.1-R+S-BOL** system, yielding a relatively low K_a value of 0.054 M^{-1} , signifying the high binding selectivity of **3.1-R** towards the enantiomers of **BOL** (Figure 3.3c–d, Table 3.1). The K_a values obtained from these titrations are consistent with the differences in binding constants observed for similar host-guest systems.^{60–62} Similar titration of **3.1-R** with **Rac-BOL** showed comparatively lower ^1H -NMR chemical shifts for the N-H and aromatic protons of **3.1-R** with binding constant value intermediate between the corresponding enantiopure complexes (Figure A3.18).

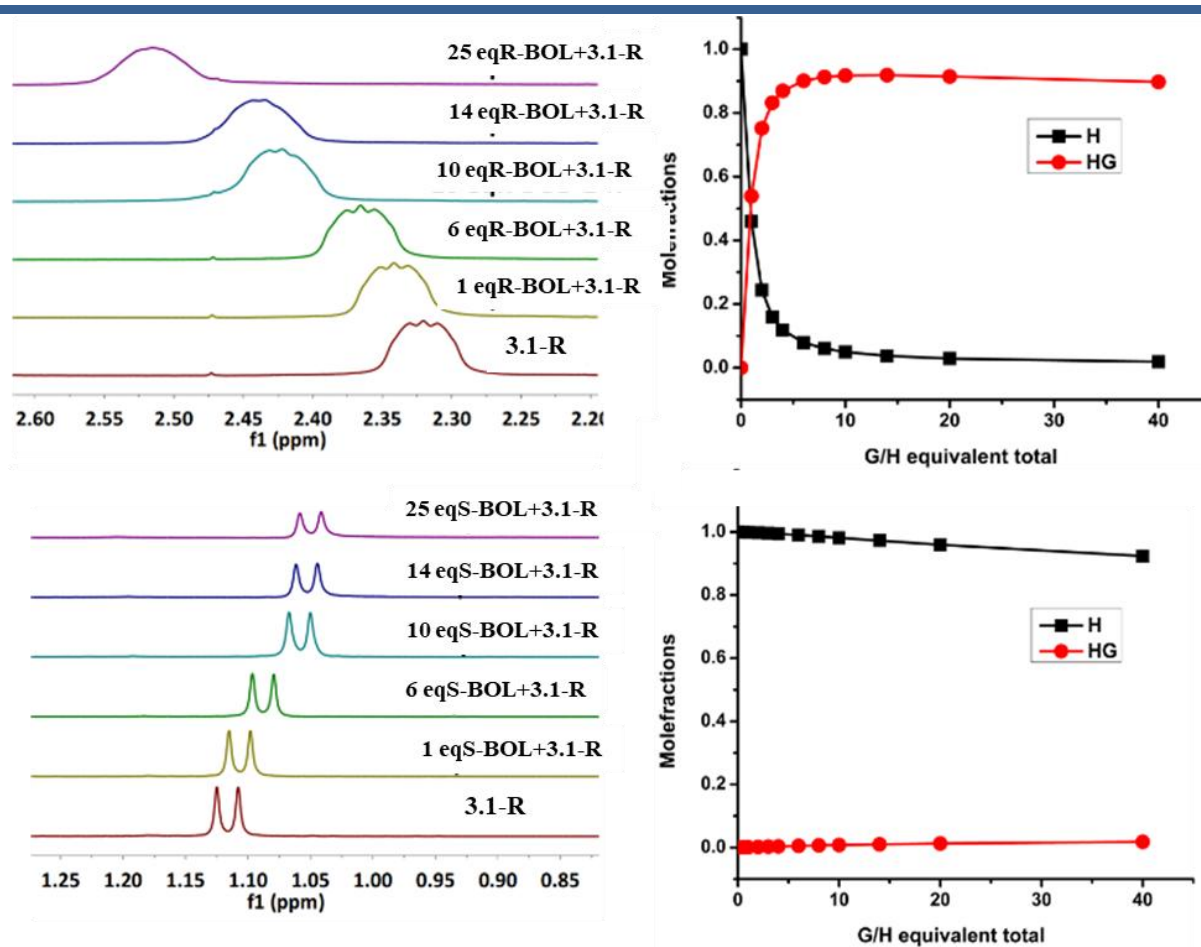


Figure 3.3. ¹H-NMR titration plots a) **3.1-R+R-BOL** and b) **3.1-R+S-BOL**, Bind fit plots for the for the host-guest complexes of c) **3.1-R+R-BOL** and d) **3.1-R+S-BOL**.

The titration experiments of **3.1-R** with the enantiomers of **HOF** show a similar trend in the chemical shifts. The sequential addition of **R-HOF** to **3.1-R** showed a downfield shift for the amino (N-H) protons of the phosphazene. However, there is an overlap of the resonances of guest protons with that of the N-H group. Nevertheless, a clear shift in the aromatic C-H protons has been observed, amounting to a K_a value of 30.6 M^{-1} . Though moderate shifts of methyl protons of the amino groups were observed in the case of **S-HOF**, a lower K_a value of only 0.94 M^{-1} was observed for the **3.1-R+S-HOF** complex, presumably due to weak association **S-HOF** with the phosphazene N-H protons (Table 3.1, Figure A3.10–A3.11).

The titrations of **3.1-R** with **R-BMO** displayed a notable downfield shift for the methyl protons and aromatic C-H protons of the amino substituents, while only the aromatic C-H protons showed a shift for the **3.1-R+S-BMO** system. Also, the amino (N-H) protons showed a negligible shift in both of these titrations, indicating a relatively weak binding for

the enantiomers of **BMO** with **3.1-R** (Table A3.1, Figure A3.12– A3.13). This is evident from their Bindfit profiles, where the **3.1-R+R-BMO** system shows a K_a of 18.7 M^{-1} , and the **3.1-R+S-BMO** system exhibits a further lower K_a of 2.8 M^{-1} .

The ^1H -NMR titrations of **3.1-R** with the enantiomers of **BOZ** show prominent downfield shifts for both phosphazene N-H protons and the oxazole N-H protons of the **BOZ**. In addition, it shows shifts in the methyl and aromatic C-H protons of the phosphazene amino groups as well. Owing to the significant overlap of signals of the phosphazene N-H with the oxazole protons of **BOZ**, the shifts in oxazole N-H groups and methyl protons have been considered for the Bindfit calculations for both the enantiomers of **BOZ**. The binding curve obtained for the 1:1 complex of **3.1-R+R-BOZ** yields a large K_a of 1032.5 M^{-1} , whereas the fitting observed for **3.1-R+S-BOZ** corresponds to a much smaller K_a value of 10.3 M^{-1} as the degree of the downfield shift was much larger in case of **R-BOZ** compared to **S-BOZ** (Table 3.1, Figure A3.14– A3.15).

Table 3.1. ^1H -NMR titration derived selective association constants ($K [\text{M}^{-1}]$) and binding selectivity (ξ) studies on **3.1-R**.

Guest	Recognition		ΔE_{pref} (%ee)
	K_{11} with 3.1-R	ξ	
R-BOL S-BOL	135.5 0.054	2506(R)	14.02
R-BOZ S-BOZ	1032.5 10.3	100.2(R)	14.0
R-HOF S-HOF	30.6 0.94	32.6(R)	7.6
R-BMO S-BMO	18.7 2.8	6.7(R)	2.3
R-PSA S-PSA	10236.8 102.2	100.1(R)	18.81

A closer look at the titrations of **3.1-R** with enantiomers of **PSA** in CD_3OD indicates a sharp downfield shift for the methyl protons in both cases, corroborating a strong binding of phosphazene to both the enantiomers of **PSA** (Table 3.1, Figure A3.16– A3.17). Evaluation of their binding constants gave an enantioselective 2:1 binding with the K_a values of 10236.8 and 102 M^{-1} for the **3.1-R+R-PSA** and **3.1-R+S-PSA** species, respectively. Notably, the phosphazene N-H proton chemical shifts could not be observed in both of these titrations, presumably due to the proton exchange with the residual protons of the deuterated methanol

solvent.

These titration data show that the binding constant values are reasonably different for the enantiomers of the guest molecules in most instances. Hence, the difference in the binding selectivity (ζ) has been determined for each of the enantiomeric pairs of the guest molecules using the relationship $\zeta = K_a(\text{larger})/K_a(\text{smaller})$ (Table 3.1). Despite the modest binding affinities, the complexation of **3.1-R** with **BOL** exhibits the highest ζ value of 2056, illustrating the importance of structurally rigid and planar guest molecules in the selective complexation process. This implies that the non-covalent interactions present in the **3.1-R+R-BOL** complex are different from those in the **3.1-R+S-BOL**. A moderate ζ value of 32 was obtained for the enantiomers of **HOF**, indicating the strong binding of **R-HOF** over **S-HOF** with the host **3.1-R**. A closer look at **BMO** systems showed a low K_a for both its enantiomers and a poor ζ value of 6.7 in favour of the **3.1-R+R-BMO** complex. This indicates a weak interaction of **3.1-R** with the enantiomers of **BMO**, presumably due to the bulky nature of **BMO**, which causes a steric hindrance with the substituents at the phosphazene periphery. The significantly higher ζ values of ~ 100 have been noted for the **BOZ** and **PSA** systems with the preference for *R*-enantiomer in both these instances (Table 3.1). It is also worthwhile to note that the K_a value of **3.1-R+R-PSA** is ten times higher than that of **3.1-R+R-BOZ**, indicating the variations in the strengths of non-covalent interactions in governing the selective guest binding process for each of these guest molecules.

Furthermore, the ^{31}P NMR spectra of **3.1-R** before and after the addition of 1 eq **R-BOL**, **R-PSA** and **R-BOZ** guests showed significant upfield shifts (with δ - δ values 0.664, 0.315 0.243 ppm) for their respective host guest mixtures of **3.1-R+R-BOL**, **3.1-R+R-PSA** and **3.1-R+R-BOZ**. Whereas, for the corresponding **3.1-R+S-BOL**, **3.1-R+S-PSA** and **3.1-R+S-BOZ** mixtures, only negligible shifts have been observed (Figure A3.20). This signifies the definitive host-guest formation of **3.1-R** with the *R*-isomers of the guest molecules.

3.3.3 ^1H -2D-DOSY NMR Studies.

^1H -2D-diffusion-ordered spectroscopy (DOSY) measurements were carried out for the best-performing host-guest pairs to determine the existence of the host-guest species in the solution. For the host, the diffusion of methyl protons (α -methyl benzyl groups) of **3.1-R** as a function of magnetic field gradient was monitored, while appropriate protons from the guest molecules were chosen for the DOSY analysis. The ^1H -2D-DOSY NMR of the **R-BOL**-treated sample of **3.1-R** exhibited two diffusion coefficient (*D*) values for the phenyl

protons of the guest BOL species, with D-values of 15.9×10^{-10} and $7.5 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$. The faster diffusing species corresponds to the free molecules of R-BOL, while the slower ones are attributed to the bound R-BOL guest in the host-guest assembly. Notably, at the bound state, both R-BOL and **3.1-R** diffuse at almost similar rates ($6.9 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$), confirming the formation of a strong host-guest assembly between R-BOL and **3.1-R** in the solution. A similar trend in the diffusion was observed for R-BOZ the guest molecules, showing D-values 18.6×10^{-10} and $4.8 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ for the free and bound R-BOZ molecules. For the **3.1-R+R-PSA** system, the observed D (bound) value of $7.1 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ of R-PSA closely matches the host D value of $7.2 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$, confirming the definite formation of host-guest assembly (Figure A3.19, and Table A3.4).

3.3.4 Single-Molecule Optimization Studies

The structural optimization studies were performed to estimate the gas-phase binding energies of these host-guest assemblies using density functional theory (DFT) methods (Table A3.5). These studies provided more profound insights into the guest binding and chiral recognition abilities of the phosphazene **3.1-R**.

The energy-optimized structures of the 1:1 complexes of **3.1-R+R-BOL** and **3.1-R+S-BOL** systems indicate that the enantiomeric guests bind distinctly with the phosphazene **3.1-R**. The optimized structure of **3.1-R+R-BOL** showed the presence of two strong H-bonding interactions. The first one, GO1-GH1 $\cdots$ N1_{ring} (G indicates that the atom is located on the guest molecule), involves the phosphazene ring nitrogen atom located near pocket B, which acts as an H-bond acceptor for one of the O-H protons of the BOL (Figure 3.4a). On the other hand, one of the phosphazene amino groups located in the same binding pocket serves as a H-bond donor to the other OH group of the BOL, N51_(amino)-H51 $\cdots$ GO2. The formation of the later interaction is evident from the observed shifts for the N-H protons in the ^1H -NMR titrations (Figure 3.3a). In addition, a few more non-classical C H $\cdots$ O, C-H $\cdots\pi$ and O-H $\cdots\pi$ type interactions have also been observed in the optimized structure of the **3.1-R+R-BOL** pair strengthening the host-guest interactions (Figure 3.4a). In contrast, the **3.1-R+S-BOL** system did not show any classical O-H $\cdots$ N and N-H $\cdots$ O type H-bonding interactions (Figure A3.21a–b and Table A3.6). Instead, the S-BOL interacts with one of the benzyl substituents of the phosphazene (located outside pocket A) via the non-classical C-H $\cdots\pi$, and O-H $\cdots\pi$ contacts (GC2-GH2 $\cdots\pi_G$ and GO1-GH1 $\cdots\pi_G$), consistent with the observed shifts in the methyl protons of the phosphazene substituents (Figures 3.3b–5b). From the optimized binding energy of the respective **3.1-R+R-BOL** and **3.1-R+S-BOL**

systems, a comparative ΔE_{pref} (the difference in energy between the favored and unfavored enantiomers) value of ~ 14.0 was observed, which indicates that the optimized structural stability of the **3.1-R+R-BOL** system is higher than **3.1-R+S-BOL** by that factor (Table 3.1).

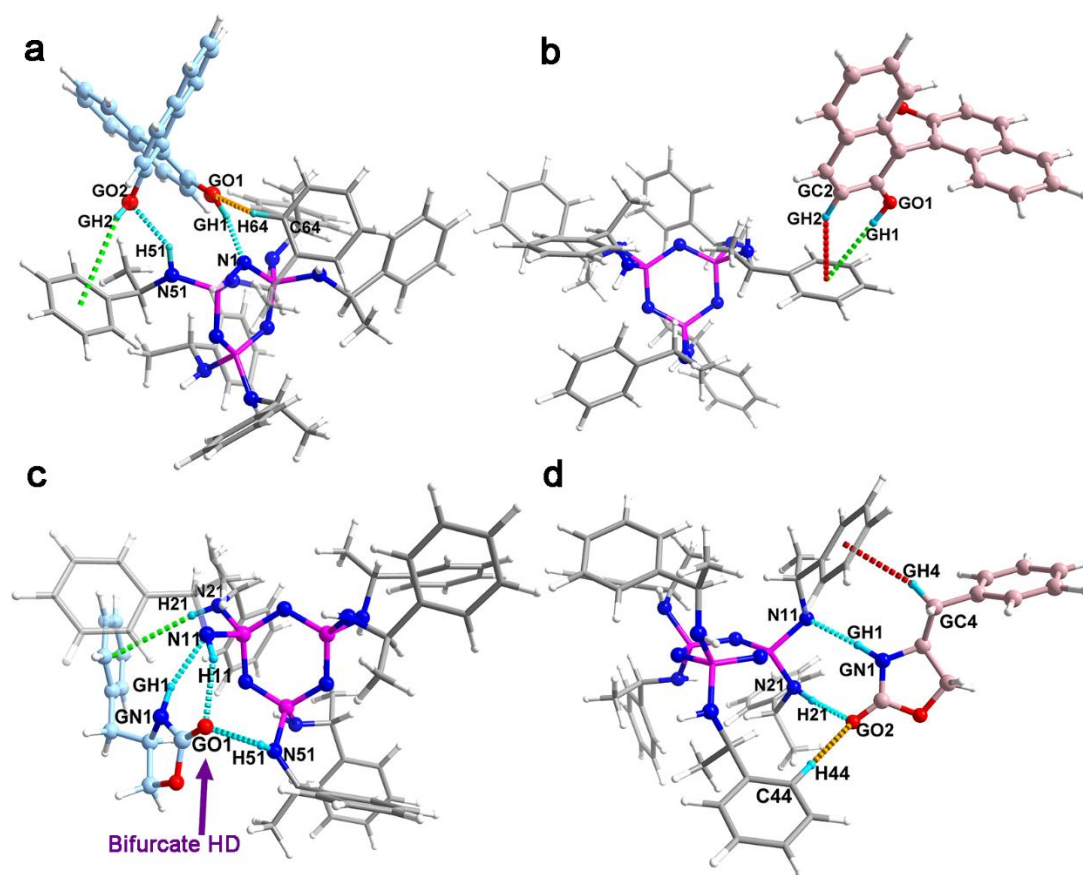


Figure 3.4. DFT optimized structures of a) **3.1-R+R-BOL**, b) **3.1-R+S-BOL**, c) **3.1-R+R-BOZ**, and d) **3.1-R+S-BOZ** complexes. P magenta; C grey; N blue; O red; Cl green; H white. The non-classical interactions (X = N, O) are shown in dotted lines: cyan N-H $\cdots$ X, purple $\pi\cdots\pi$, red C-H $\cdots\pi$, and orange polar X-H $\cdots\pi$. (G indicates that the atom is located on the guest molecule).

The interaction of **R-HOF** with **3.1-R** takes place again in the pocket *B* with a classical N12-H12 $\cdots$ GO3 and a non-classical GC2-GH2a $\cdots$ N1_(ring) H-bonds serving as the primary force. (Figure A3.22a). Whereas the **S-HOF** interacts with **3.1-R** at the exterior of pocket *A* via C-H $\cdots$ O contacts involving benzyl ring C-H and methyl protons of **3.1-R**. It is evident that the steric crowding at the *A*-sites provides hindered access to the guest molecules,

making the host-guest interactions weaker for the **3.1-R+S-HOF** system (Figure A3.22b, Table A3.6). The variations in the strengths of these interactions have resulted in a ΔE_{pref} of ~ 7.6 in favour of the **3.1-R+R-HOF** complex (Table 3.1).

In contrast, both **R-BMO** and **S-BMO** were found to interact with **3.1-R** at the exterior of pocket *A* via non-classical C-H $\cdots$ O interactions involving the epoxide oxygen atoms. No strong H-bonding interactions involving the phosphazene amino groups or the N-atoms of the P₃N₃ ring were found in both cases. As a result, both enantiomers of **BMO** bind weakly and lead only to a low ΔE_{pref} of 2.3 in favour of **R-BMO** (Figure A3.23a–b, Table A3.5).

The DFT-optimized structures of **3.1-R+R-BOZ** and **3.1-R+S-BOZ** indicate that the carbonyl oxygen of the **BOZ** forms the primary contact with the phosphazene via its N-H groups at pocket *B* (Figure 3.4c–d, Table A3.6). In both instances, the oxygen atom GO1 is involved in bifurcate interactions with the phosphazene. Thus, **R-BOZ** forms two N-H $\cdots$ O (N11-H11 $\cdots$ GO1 and N51-H51 $\cdots$ GO1) interactions, while the bifurcate interactions in **S-BOZ** involve one N-H $\cdots$ O (N21-H21 $\cdots$ GO2 and C44-H44 $\cdots$ GO2) and N-H $\cdots$ O (GN1-GH1 $\cdots$ N11) contacts (Figure A3.24a–b). Also, the N-H groups of these enantiomers engage in N-H $\cdots$ N (GN1-GH1 $\cdots$ N11) type interactions with **3.1-R**, as evident from the downfield shifts observed for the guest N-H groups in the ¹H-NMR titrations (Figure A3.14). In addition, one of the N-H groups of **3.1-R** is engaged in additional N21-H21 $\cdots$ π interaction with the benzyl group of **R-BOZ**. Thus, the stronger bifurcate interactions and additional non-classical interactions have led to better binding energy and a 100-fold higher experimental *K_a* value for **3.1-R+R-BOZ** over **3.1-R+S-BOZ** (Table 3.1, Figure A3.14–A3.15).

The optimized structures of **PSA** with **3.1-R** suggest that the pair with similar chirality **3.1-R+R-PSA** shows stronger interactions than the opposite pair with complimentary chirality **3.1-R+S-PSA** for their 2:1 complexes (Figure 3.5, Table A3.6). One of the carboxylic acids of **R-PSA** (located adjacent to the aliphatic C-atom) engages in donor-acceptor-type interactions with a phosphazene N_{ring}-atom (complementary acceptor) and one of the amino protons (complementary donor) at pocket *B*, forming the well-known *R*₂²(8) type ring structure (Figure A3.25a–b).^{63, 64} The other carboxylic acid (attached to the chiral C-atom) interacts with both the phosphazenes far from their *B* pockets via a bifurcate C-H $\cdots$ O interaction. Both the carboxylic acids of **S-PSA** are pointed towards pocket *A* of one of the phosphazene rings and involved in weak C-H $\cdots$ O and O-H $\cdots$ π interactions (2C12-2H12 $\cdots$ GO12 and C32-2H32 $\cdots$ GO2), while the N_{ring} atom of the other phosphazene

engages in C-H $\cdots$ N_{ring} interactions with the guest phenyl groups adjacent to pocket *B* (GC5-GH5 $\cdots$ N1_{ring}). Such disparities in the interactions account for a high guest selectivity of ~ 100 in favour of **3.1-R+R-PSA** (Table 3.1, Figure 3.5a, Table A3.6).

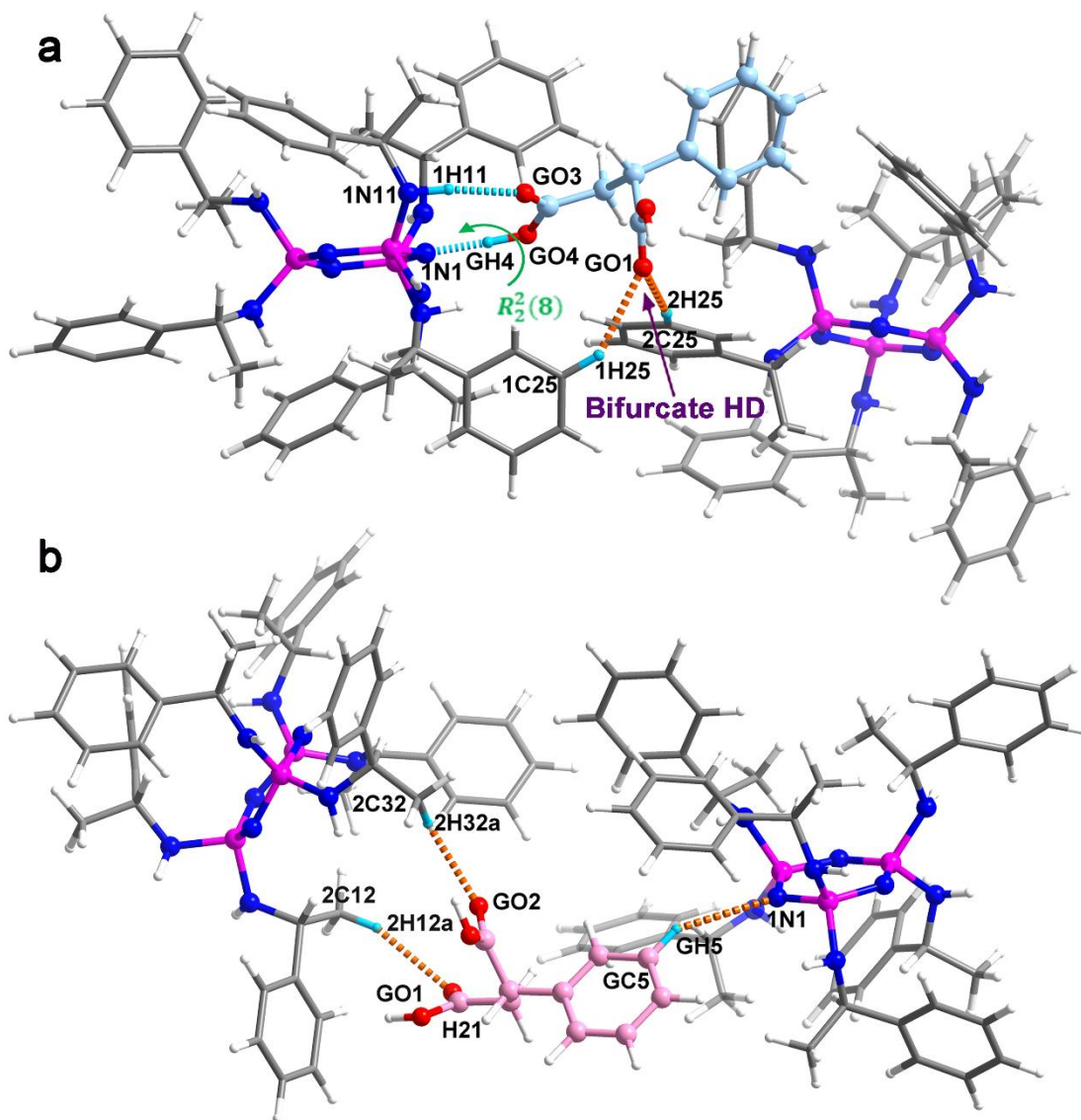


Figure 3.5. DFT optimized structures of the a) **3.1-R+R-PSA** and b) **3.1-R+S-PSA** host-guest complexes. P magenta; C gray; N blue; O red; Cl green; H white. The non-classical interactions (X = N, O) are shown in dotted lines: cyan N-H $\cdots$ X, purple $\pi \cdots \pi$, red C-H $\cdots \pi$, and orange polar X-H $\cdots \pi$. (G indicates that the atom is located on the guest molecule)

To further validate the structures of the DFT-optimized host-guest models, we have performed ^1H -2D-NOESY studies for the best-performing **3.1-R+R-BOL**, **3.1-R+R-BOZ**,

and **3.1-R+R-PFA** systems. From Figure A3.26, the correlation between the phenyl rings of **3.1-R** and the aromatic protons of **R-BOL** can be seen clearly. For the **3.1-R+R-BOL** system, cross-peaks corresponding to the four unique spacial pairs consisting of (i) NH groups of **3.1-R** and oxazole moiety, (ii) methyl groups of **3.1-R** and CH₂ group of oxazole ring, (iii) chiral C-H group **3.1-R** and N-H of oxazole moiety, and (iv) the aromatic protons of **3.1-R** and **R-BOZ** (Figure A3.27). Three such cross-peaks were identified for the **3.1-R+R-PSA** mixtures formed from (i) the chiral CH proton of **R-PSA** with the MeH protons of **3.1-R**, (ii) the CH₂ group of **R-PSA** with aromatic protons of **3.1-R** and (iii) the chiral CH proton of **R-PSA** with the N-H protons of **3.1-R**, and (iv) between the aromatic groups of **3.1-R** and **R-PSA** (Figure A3.28). Overall, the NOESY studies support the DFT-optimized structure of these host-guest pairs by showing clear spacial interactions of **3.1-R** with the various functional groups present in these diverse guest molecules.

3.4 Conclusion

In summary, we have described the synthesis of an enantiomeric pair of cyclotriphosphazenes, **3.1-R** and **3.1-S**, of formula (P₃N₃H(NH*CH(CH₃)Ph)₆) and their structural studies. Owing to the presence of multiple H-bond donor and acceptor sites in them, the phosphazene *R*-enantiomer was employed in the chiral recognition of several small organic compounds such as **BOL**, **BOZ**, **HOF**, **PSA**, and **BMO**, where strong affinities were observed for the host-guest assemblies of same chirality over those with complementary chirality. Thus, **3.1-R** shows a significant binding selectivity for **R-BOL**, **R-PSA**, and **R-BOZ** over their *S*-isomers. Notably, the highest guest selectivity value of 2056 was achieved for **R-BOL** over **S-BOL**, as determined from their binding constant values. Remarkably, the functional groups on the guest molecules and the specificity of the host-guest interactions at the two uniquely different binding pockets at the phosphazene backbone determine the observed trends in the binding selectivity. The DFT optimization studies suggest that the enantioselective guest recognition process relies on a variety of interactions, primarily including hydrogen bonding with the ring nitrogen, π - π interactions, and steric interactions between the phosphazene and the guest molecules. These findings highlight the versatility of the enantiopure cyclotriphosphazenes as suitable hosts for chiral recognition studies, promising their potential for a range of enantioselective applications.

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Chapter -4

Squarate-Tethered Enantiomeric Imido-Pd(II) Cages for Recognition and Separation of Chiral Organic Molecules

4.1 Introduction

Coordination cages with intrinsic cavities are a fascinating class of porous materials due to their unique compositional and geometric tunability.¹⁻⁸ Chiral coordination cages^{9,10} are promising scaffolds for exploring chiral recognition and separation,¹¹⁻¹³ asymmetric catalysis,^{14,15} polarized luminescence,¹⁶ and capillary electrophoresis,¹⁷ etc. While many task-specific porous materials are investigated for chiral recognition and separation, there is a substantial challenge to efficiently separate the enantiomers with similar physical properties.¹⁸ In this regard, chiral cages are attractive owing to their enantio-selective host-guest relationships.¹⁹ However, accessing chiral cages with suitable binding pockets is synthetically challenging due to the limited number of available building blocks that support their formation in an enantiomerically pure form.

Though several pathways are explored for introducing chirality in cages, the incorporation of carbon stereocenters into the ligand backbone yields cages in optically pure form by preventing any racemization.²⁰⁻²⁷ Moreover, the separation efficiency of cages can be enhanced by optimizing the host-guest interaction via the precise control of pore size, pore shape, and functional groups that reside along the pore.^{28,29} In addition, the synergy between the intrinsic and extrinsic (packing) cavities of the cage assemblies in the solid state can maximize the binding of the guests with improved enantiomeric separation capabilities.³⁰⁻³²

In recent years, our group has been designing chiral cages and supramolecular assemblies for the enantiomeric recognition and separation of small organic molecules.^{11,12,35} Herein, we report an enantiomeric pair of tetrahedral cages **4.1-R** and **4.1-S** of formula $[(\text{Pd}_3\text{X}^*)_4(\text{C}_4\text{O}_4)_6]$ ($[\text{X}^*]^{3-} = \text{RRR- or SSS-[PO(N}^*\text{CH(CH}_3\text{)Ph)}_3]^{3-}$) and their chiral separation attributes (Scheme 1). The extended chelating angles provided by the squarate (C_4O_4)²⁻ moieties result in a new tetrahedral cage structure for **4.1-R** and **4.1-S** with a different coordination mode of the chelating squarate ligand (Scheme 1).^{11,12} These cages exhibit an intrinsic cavity volume of 289 Å³, the highest amongst all known tetrahedral cages of this family, with much larger portal sizes of ~5.8 Å.^{11,12,33-35} Subsequently, a range of biologically and synthetically important chiral organic molecules, such as epichlorohydrin (**EP**), 4-benzyl-2-oxazolidinone (**DO**), propylene oxide (**PO**), mandelic acid (**MA**) and 4-hydroxydihydrofuran-2(3H)-one (**HO**) (Figure 4.3a) were probed for the enantiomeric recognition and separation using the cage **4.1-R**. The highest recognition selectivity of 67 for **R-HO** and an enantiomeric excess (%*ee*) of 93% for **S-EP** were achieved in these studies. These results promise the utility of imido-Pd(II) cages as efficient host materials for chiral separation applications.

4.2 Experimental Details

4.2.1 General Remarks

All manipulations involving phosphorus halides were performed under a dry nitrogen atmosphere in standard Schlenk glassware. Dry Solvents were purchased from local vendors and used without further purification. The Chiral amines, squaric acid, and palladium acetate were purchased from Aldrich and used as received. POCl_3 was purchased locally and was distilled prior to use. The ligand $\text{L}^{\text{RRR}}\text{H}_3$ and $\text{L}^{\text{SSS}}\text{H}_3$ was synthesized according to the earlier reported procedure.¹ NMR spectra were recorded on a Jeol 400 MHz spectrometer (^1H NMR: 400.13 MHz, ^{13}C { ^1H } NMR: 100.62 MHz, ^{31}P { ^1H } NMR: 161.97 MHz) or on a Bruker 400 MHz (^1H NMR: 500.00 MHz, ^{13}C { ^1H } NMR: 125.725 MHz, ^{31}P { ^1H } NMR: 202.404 MHz) spectrometer at room temperature using TMS (^1H , ^{13}C) and 85% H_3PO_4 (^{31}P). The mass spectra were obtained on an Applied Bio system matrix-assisted laser desorption ionization time-of-flight (MALDITOF)/ TOF spectrometer. A PerkinElmer STA-6000 thermogravimetric analyser has provided the thermal analysis (TGA) results. A JASCO J815 spectrometer was used to measure CD spectra between 400 and 190 nm. A Vario-EL cube elemental analyser was used for the elemental studies. Agilent Technologies 1260 Infinity equipment with a UV detector was used for all HPLC analyses.

4.2.2 Synthesis of Enantiopure Chiral Tetrahedral Cages (4.1-R and 4.1-S)

The ligand $\text{L}^{\text{RRR}}\text{H}_3$ or $\text{L}^{\text{SSS}}\text{H}_3$ (0.049 mmol), Palladium acetate (0.147 mmol), and squaric acid (0.073 mmol) in THF were stirred in a 15 mL closed cap vial for 48 hrs to yield a yellowish orange colored precipitate. The precipitated compound was filtered, washed with THF several times and dried under vacuum. Single crystals of the cage assemblies' **4.1-R** or **4.1-S** were obtained from the slow evaporation of their corresponding dichloromethane solution.

4.1-R: Yield: 71% (based on P). ^1H NMR (400 MHz, CDCl_3) δ 7.69 (d, $J = 7.2$ Hz, 2H), 7.51 – 7.31 (m, 3H), 3.20 (dq, $J = 36.4$, 6.9 Hz, 1H), 1.35 (d, $J = 6.9$ Hz, 3H). ^{31}P NMR (162 MHz, CDCl_3) δ 73.35 (s). MALDITOF/TOF (Reflector): 3675.09 ($[\text{M}+\text{DCM}+\text{Na}]^+$). Elemental Analysis (%): Calcd for $\text{C}_{120}\text{H}_{108}\text{N}_{12}\text{O}_{28}\text{P}_4\text{Pd}_{12}$: C, 40.41; H, 3.05; N, 4.71; O, 12.56; P, 3.47; Pd, 35.80. Found: C, 39.98; H, 2.86; N, 4.21.

4.1-S: Yield: 68% (based on P). ^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, $J = 7.2$ Hz, 2H), 7.50 – 7.34 (m, 3H), 3.21 (dq, $J = 36.2$, 6.8 Hz, 1H), 1.36 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 196.86 (s), 196.29 (s), 139.99 (s), 129.64 (s), 128.91 (s), 128.76 (d, $J = 28.4$ Hz), 60.86 (s), 22.15 (s). ^{31}P NMR (162 MHz, CDCl_3) δ 73.35 (s). MALDITOF/TOF (Reflector):

3675.09 ([M+DCM+Na]⁺). Elemental Analysis (%): Calcd for C₁₂₀H₁₀₈N₁₂O₂₈P₄Pd₁₂: C, 40.41; H, 3.05; N, 4.71; O, 12.56; P, 3.47; Pd, 35.80. Found: C, 41.98; H, 3.01; N, 4.02.

4.2.3 ¹H-2D-DOSY NMR Studies

The ¹H-2D-DOSY NMR experiments were carried out on a Bruker AVANCE III NMR spectrometer operating at a ¹H frequency of 600 MHz, and a constant temperature of 298 K. 2.50 mM solutions of the host-guest complexes were prepared in CDCl₃ and allowed to equilibrate for 1 h before data acquisition. Diffusion Ordered Spectroscopy (DOSY) experiments were performed by varying gradient strength. The standard Bruker protocol using Topspin 3.1 software was used for processing the DOSY data. The fitting of the diffusion 4 dimension in the 2D-DOSY² spectra was carried out using a one-parameter mono-exponential (equation 1) or two-parameter bi-exponential fits (equation 2).

$$I = I_0 \exp [-D \gamma^2 g^2 \delta^2 (\Delta - \delta/3)] \dots \dots \dots (1)$$

$$I = I_{0A} \exp [-D_A \gamma^2 g^2 \delta^2 (\Delta - \delta/3)] + I_{0B} \exp [-D_B \gamma^2 g^2 \delta^2 (\Delta - \delta/3)] \dots \dots \dots (2)$$

In this equation, I is the observed integral, I₀, I_{0A}, and I_{0B} are the reference or un-attenuated integrals, D, D_A, and D_B are the diffusion coefficients, γ is the gyromagnetic ratio of the detected nucleus, g is the gradient strength, δ the length of the gradient pulse, and Δ the diffusion time.

4.2.4 Host-guest Studies: General procedure for ¹H-NMR experiment

The samples were prepared by dissolving 5 mg of **4.1-R** in 600 μl CDCl₃ (Sigma Aldrich). The 5 eq of guest molecules were added individually to host and allowed to equilibrate for 12 hr (unless otherwise specified) before data acquisition.

4.2.5 Procedure for Encapsulation-Separation Experiment and Resolved Results for Racemic Substrates by **4.1-R**

In a typical encapsulation-separation experiment, excess of racemic guests were separately added to **4.1-R** in dry DCM (10ml). For rac-epichlorohydrin (**EP**), rac-4-benzyl-2-oxazolidinone (**DO**) and rac-mandelic acid (**MA**) the reaction mixture was stirred for 1-h and left for slow evaporation to yield the crystalline solids of the host-guest complexes. The excess of guest molecules were removed from the surface of the complexes by repeated washing with ice-cold diethyl ether (3-5 times). The adsorbed guest molecules were subsequently removed from the complexes by soaking in MeOH and analysed by gas chromatography. The HPLC methods employed in the study along with the HPLC chromatogram and analysis plots are given in the last section of document (Figures A4.35-

A4.47).

4.2.6 Theoretical Calculations

The gas-phase single molecule energies of all the participating species and the host–guest systems were calculated by using the Gaussian 09 software. These energies were computed by PM6 methods. For the host–guest complexes, the energies of the host cage **4.1-R**, the guests, and the host–guest complexes were separately calculated and the binding energy of a given complex was calculated by (equation 3):

$$\text{Binding energy} = E_{\text{Guest} \subset \text{Host}} - (E_{\text{Host}} + E_{\text{Guest}}) \dots\dots\dots (3)$$

4.2.7 Crystallography

Reflections were collected on a Bruker Kappa Apex Duo diffractometer at 100 K using Mo K α radiation ($\lambda = 0.710\,73\text{ \AA}$) for **4.1-R** and **4.1-S**. All structures were solved using the intrinsic phasing method and refined by full-matrix least-squares on F^2 (G. M. Sheldrick, SHELXL program for crystal structure refinement, University of Gottingen, Germany, 2015).⁴⁻⁵ All non-hydrogen atoms were refined anisotropically if not stated otherwise. Hydrogen atoms were constrained in geometric positions to their parent atoms. Crystallographic data for all these compounds are listed in Table 4.1 and A4.3. The diffuse solvent molecules in **4.1-R** and **4.1-S** could not be modelled accurately. Hence, these were treated as diffuse contributions to the overall scattering and removed by the SQUEEZE/PLATON for better refinement data.⁸ The squeezed volumes and the excluded electron densities in **4.1-R** and **4.1-S** were found to be 2960.9 and 2969.5 $\text{\AA}^3$ and 729.6 and 937.7 $\text{e\AA}^{-3}$. All the phenyl rings are constrained to ideal six-membered rings. The crystals of **4.1-R** and **4.1-S** diffracted very weakly at higher angles, and hence the data are truncated to $2\theta = 45.0^\circ$. One of the FCF reflections in **4.1-S** differed more than 10 times of σW , and hence it was omitted from the final least-squares refinements.

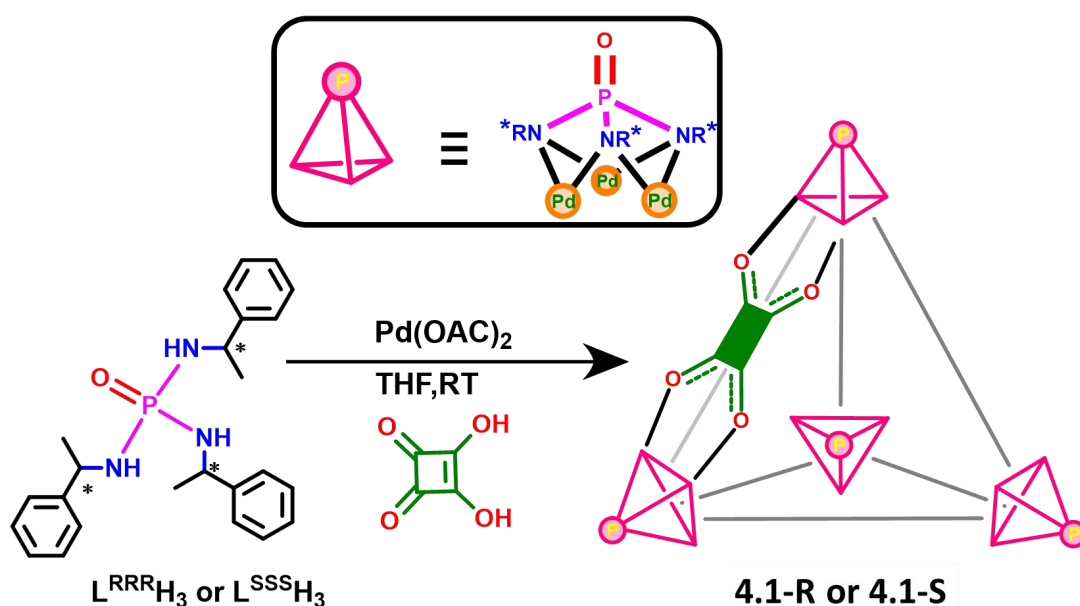
Table 4.1. Crystallographic Data for 4.1-R and 4.1-S

Compound	4.1-R	4.1-S
Chemical formula	C ₁₂₀ H ₁₀₈ N ₁₂ O ₂₈ P ₄ Pd ₁₂	C ₁₂₀ H ₁₀₈ N ₁₂ O ₂₈ P ₄ Pd ₁₂
Formula weight	3566.86	3566.86
Temperature	100(2) K	100(2) K
Crystal system	Cubic	Cubic
Space group	F 4 3 2	F 4 3 2
a ($\text{\AA}$); $\alpha(^{\circ})$	34.898(6); 90	34.885(4); 90
b ($\text{\AA}$); $\beta(^{\circ})$	34.898(6); 90	34.885(4); 90

c (Å); γ (°)	34.898(6); 90	34.885(4); 90
V (Å ³); Z	42501(22)	42452(14)
ρ (calc.) mg m ⁻³	1.115	1.116
μ (Mo K α) mm ⁻¹	1.064	1.066
2 θ max (°)	44.994	45.014
Flack parameter	0.01(14)	0.02(4)
R(int)	0.0805	0.1491
Data / param.	2344/123	2348/91
GOF	1.289	1.146
R1 [F>4 σ (F)]	0.0266	0.0343
wR2 (all data)	0.0768	0.0942
Max. peak/hole(e.Å ⁻³)	0.359/-0.386	0.569/-0.421

4.3 Results and Discussions

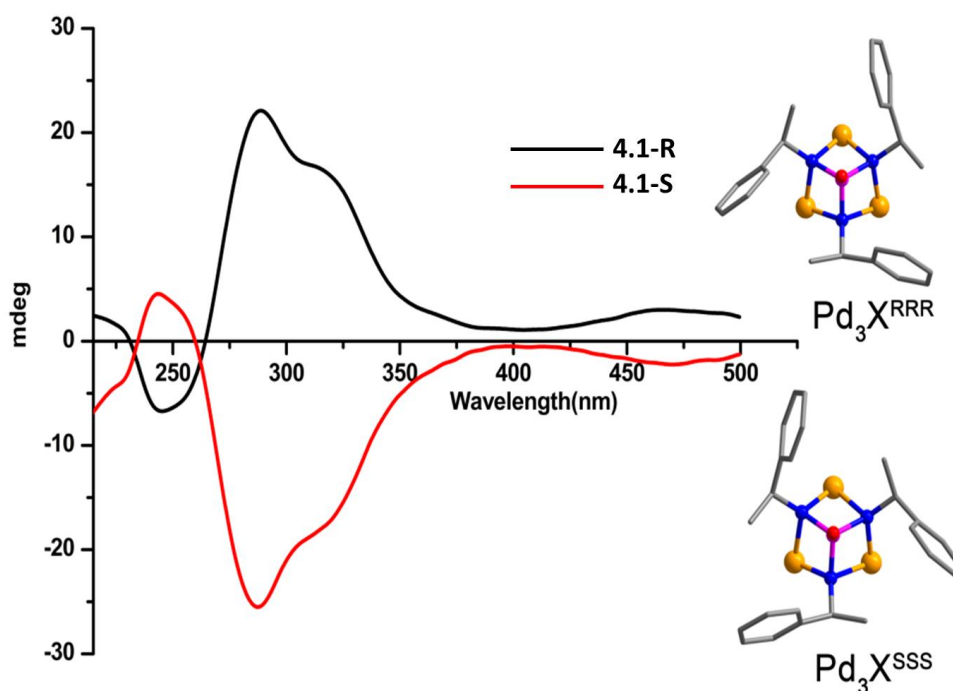
4.3.1 . Synthesis, Structure, and Characterization



Scheme 4.1. Synthesis of enantiopure cages **4.1-R** and **4.1-S** from the chiral ligands $L^{RRR}H_3$ and $L^{SSS}H_3$. The Pd-Pd bonds shown here are the guide to the eyes. Only one of the six squarate bridges of the cage assembly is shown for clarity

The tetrahedral cage assemblies **4.1-R** and **4.1-S** were synthesized by a direct reaction of $Pd(OAc)_2$ with the respective chiral-phosphoramides, $L^{RRR}H_3$ and $L^{SSS}H_3$ in THF, in the

presence of squaric acid (Scheme 1). The MALDI-TOF mass spectrum of **4.1-R** and **4.1-S** unveiled m/z peaks centred at 3675, corresponding to the $[M+DCM+Na]^+$ species. The $^{31}\text{P}\{^1\text{H}\}$ -NMR spectra of cages indicated a singlet at 73.4 ppm, characterizing the presence of trianionic imido-P(V) species. The ^1H NMR spectra showed well-resolved signals at aliphatic and aromatic regions for both **4.1-R** and **4.1-S** (Figures A4.1– A4.7). The thermogravimetric analysis (TGA) shows high stability for these new cages (Figures A4.9– A4.10). The ^1H -2D diffusion ordered spectroscopy (DOSY) measurements for **4.1-R** and **4.1-S** gave single diffusion coefficient (D) values of 5.812×10^{-10} and $5.735 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$, respectively, confirming the existence of only one species in the solution. The CD spectra of these cages exhibit identical bisignate bands, confirming their enantio-enriched nature. The peaks at 275 and 325 nm correspond to the respective ligand-centric $\pi-\pi^*$ and MLCT transitions present in them (Figure 4.1). The absolute configuration (α_D) values of **4.1-R** and **4.1-S** are observed to be +671 and -689, respectively (Table A4.1).



Scheme 4.2. Circular dichroism spectra of the chiral cages **4.1-R** and **4.1-S** along with their respective $[\text{Pd}_3\text{X}^*]$ motifs that display the opposite rotational chirality.

Crystals of **4.1-R** and **4.1-S** suitable for single-crystal X-ray diffraction (SCXRD) data were obtained by slow evaporation of their corresponding dichloromethane solutions. They were crystallized in the chiral cubic space group $F432$ (octahedral ‘ O ’) (Figures 4.2a and 4.2b).

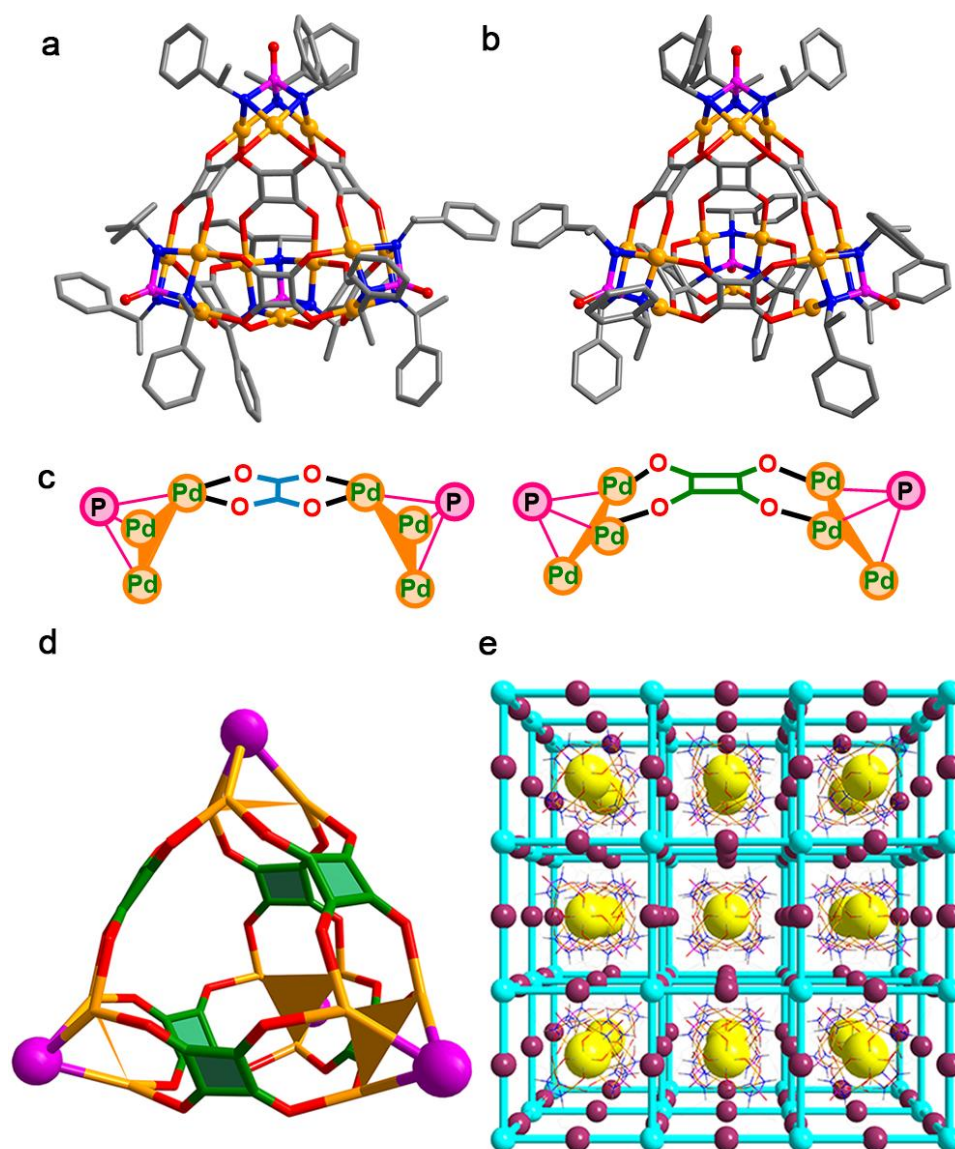


Figure 4.2. SCRXD structures of a) **4.1-R** and b) **4.1-S**. c) A comparison of the coordination modes in the earlier reported chiral imido-Pd(II) cages (left) and the isomeric cages of **4.1-R** and **4.1-S** (right). The Pd-Pd bonds are drawn as a guide to the eyes

The structure of **4.1-R** and **4.1-S** consists of four Pd_3X^* clusters at the corners of a tetrahedron consisting of a triangular array of Pd(II) ions capped by the chiral trianionic $[\text{PO}(\text{N}(*\text{CH}(\text{CH}_3)\text{Ph})_3)]^{3-}$ units and bridging dianionic squarate ligand at each of the six edges. The average Pd-Pd distance in each of the Pd_3 units were found to be 3.48 Å, which is significantly longer than the typical Pd-Pd bonds confirming the absence of Pd-Pd bonds in **4.1-R** and **4.1-S**.^{36,37} The chiral imido-phosphate trianions at each vertex exhibit trigonal

symmetry, and all the α -Me groups of the imido ligands provide additional rotational chirality with their clockwise (**4.1-R**) or anticlockwise (**4.1-S**) orientation. The squarate ligands are located along the four-fold axis.

Each Pd(II) atom resides in square planar coordination and is bonded to two N_{imido} contacts and two squarate O-contacts. (Scheme 4.1 and Figure 4.2c and 4.2d). Each squarate ligand coordinates with four different Pd(II) atoms at the opposite corners in an unusual non-geminal coordination. This is in contrast to the other known cages from this family where the four oxygen atoms of the bridging ligands interact with two Pd(II) centres in chelating (geminal) coordination (Scheme 4.1, Figure 4.2c, and A4.11–A4.12).^{11,12} The presence of the rigid four-membered ring in the squarate linkers creates strip-like edges with a wider chelating angle of ($\sim 140^\circ$), in comparison with oxalate linkers ($\sim 117^\circ$ found in $[(\text{Pd}_3\text{X}^*)_4(\text{C}_2\text{O}_4)_6]$), that hinders the typical chelating coordination with a single Pd(II) center.¹¹ A closer look at the coordination of the squarate ligands at these cages shows that the four-membered rings of the squarate ligands are lifted by about 0.72 Å, giving an inclination of around 11.7° from the plane of four Pd(II) atoms to maintain the two 90° coordination at each of the Pd(II) centres. These values are much larger than those found in the known oxalate-tethered $[(\text{Pd}_3\text{X}^*)_4(\text{C}_2\text{O}_4)_6]$ cages (Figures A4.12,). As a result, **4.1-R** and **4.1-S** exhibit a larger portal diameter of ~ 5.8 Å compared to the oxalate (4.5 Å) and chloranilate (3.8 Å) based cages.^{11,12}

To probe the volume of their intrinsic cavities, MSROLL calculations, built into the XSEED software, were performed.^{38,39} The obtained void volume of 289 Å^3 (probe radius 1.4 Å) is the highest among all the known neutral tetrahedral cages assembled from imido-Pd₃ motifs. The packing structures of **4.1-R** and **4.1-S** indicate a close-packed cubic network (FCC lattice) with total solvent-accessible void volumes of $\sim 12135 \text{ Å}^3$, which amounts to $\sim 28\%$ of their total unit cell volume (Figures A4.13- A4.14). Remarkably, both **4.1-R** and **4.1-S** exhibit a tighter packing structure compared to the earlier reported cages based on oxalate (51%) and chloranilate (33%) linkers (Table A4.4,).^{11,12} Figure 4.2e indicates the presence of three unique voids in their packing lattice. The intrinsic pores (yellow spheres) are present at the body centres, while the extrinsic pores are located at the corners (cyan spheres) and edges of the cube (purple spheres). The intrinsic pores are connected only to edge-centred extrinsic voids that are in turn connected to the voids at the corners (Figure A4.15,). Enhanced intrinsic void volumes of these cages and comparatively tighter lattice packing encouraged us to probe one of these cages, **4.1-R**, for chiral recognition and separation studies. First, the host-guest properties of **4.1-R** were examined with various chiral guest

molecules such as epichlorohydrin (**EP**), 4-benzyl-2-oxazolidinone (**DO**), propylene oxide (**PO**), mandelic acid (**MA**) and 4-hydroxydihydrofuran-2(3H)-one (**HO**) (Figure 4.3a). The MALDI-TOF mass-spectrometry of **4.1-R** treated with various guest molecules gave m/z peaks centred at 3658 (**EP+4.1-R**), 3668 (**HO+4.1-R**), 3743 (**DO+4.1-R**), 3614 (**PO+4.1-R**) and 3719 (**MA+4.1-R**) for the corresponding Guest $\subset$ Host species. The ^1H -NMR spectra of the host-guest mixtures gave clear peaks corresponding to the guest protons. The **DO** and **MA** treated samples gave marginal down-field shifts for the guest protons indicating the formation of definite host-guest assemblies in their mixtures (Figures A4.17-A4.25 and Table A4.5). However, no noticeable shifts were observed for the rest of the guest molecules, as observed for the previously known host-guest systems based on neutral imido-Pd(II) cages.¹¹

4.3.2 ^1H -2D-DOSY NMR Studies.

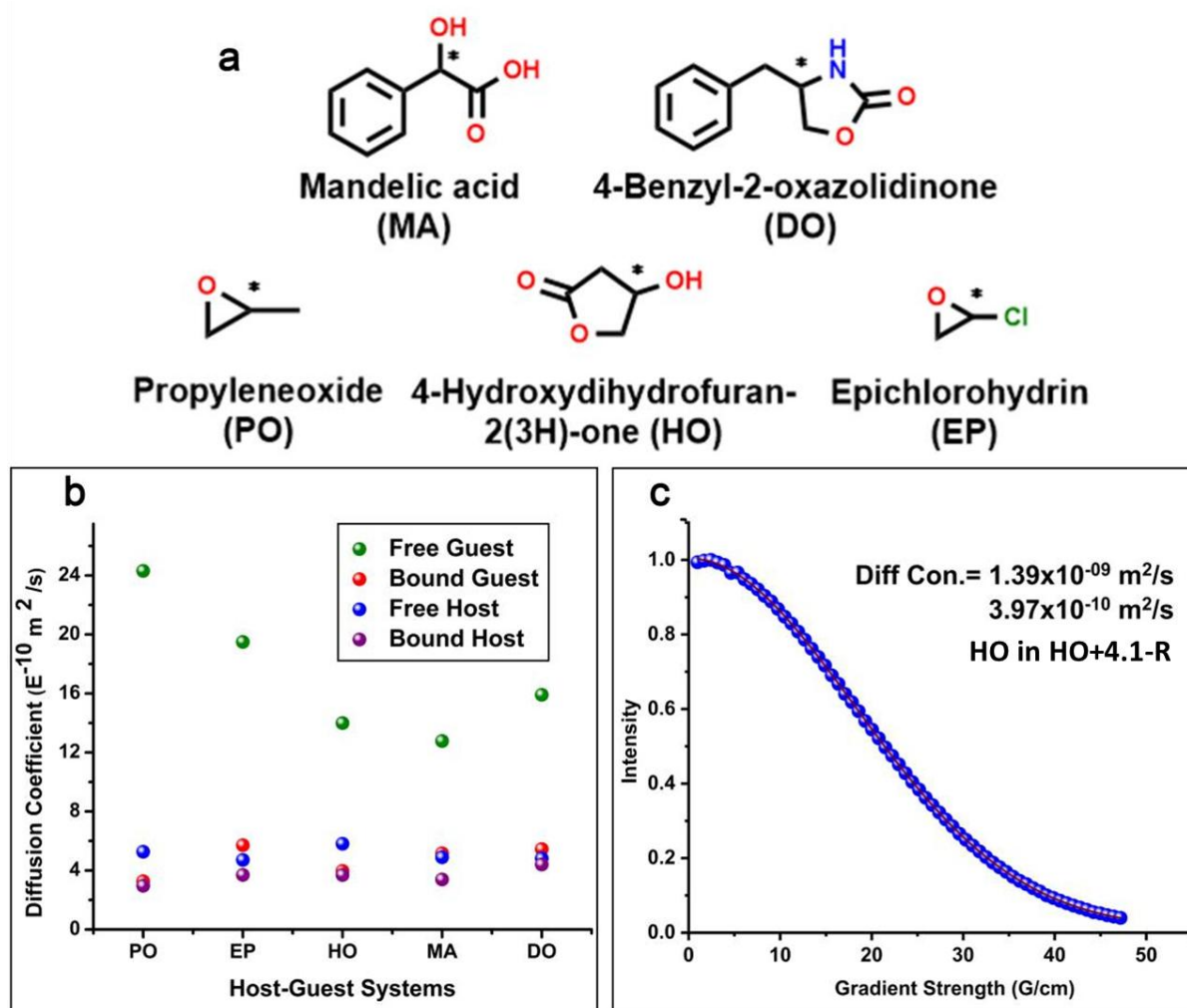


Figure 4.3. a) Enantiomeric guest molecules examined for the chiral studies. b) Summary of

the D values for the host and guest protons studied for the **Guest+4.1-R** systems. c) Integral decay profile of **HO** guest proton (CDCl₃, 298 K) in **HO+4.1-R**.

To gain more insights into the formation of host-guest assemblies, ¹H-2D-diffusion-ordered spectroscopy (DOSY) measurements were performed for all the host-guest mixtures. For the DOSY analysis, the CH or the methyl protons of the α-methyl benzyl groups on the cage were monitored to record the diffusion of the cages. Similarly, appropriate protons were chosen to monitor the diffusion of these guest molecules in their racemic form. The ¹H-2D-DOSY NMR of the **PO** treated sample of **4.1-R** exhibited two diffusion coefficients each for the host and guest signals, 5.27×10^{-10} and 2.96×10^{-10} m² s⁻¹ for **4.1-R** and 24.3×10^{-10} and 3.27×10^{-10} m² s⁻¹ for **PO**, indicating the presence of two independent host and guest species in solution. The faster diffusing species corresponds to the independent (free) guest and host molecules, while the slower ones are attributed to a single (bound) assembly of host-guest species.

Notably, at the bound state, both **PO** and **4.1-R** diffuse at almost similar rates, suggesting a close interaction of **PO** with **4.1-R** confirming the formation of a strong host-guest assembly in the solution. A similar trend in the binding was observed for the **HO**-treated sample of **4.1-R** (Figures A4.3b-3c, A4.26- A4.27, and Table A4.6). However, for the rest of the guest molecules, **EP**, **MA**, and **DO**, the bound guests were found to exhibit slightly faster diffusion rates of 5.71×10^{-10} , 5.16×10^{-10} and 5.45×10^{-10} m² s⁻¹, respectively, (than those of bound **HO** and **PO**) pointing to weaker binding of these guests with **4.1-R**. In the case of the **DO+4.1-R** system, the observed D (bound) value of 4.4×10^{-10} m² s⁻¹ for **4.1-R** is much higher than the rest of the systems, presumably due to its interactions at the cage exteriors.

4.3.3 Chiral Recognition Studies

To further estimate the enantiomeric guest recognition capabilities of **4.1-R**, UV-Visible titrations were performed for **4.1-R** in the presence of optically pure guest molecules and by monitoring the gradual decrease in the absorbance value of **4.1-R**. The Binding constants (K_a) were further derived by fitting the peak intensity gradients using the online Bindfit Tool.⁴⁰ The Bind fit plots show a prominent 1:1 binding of **4.1-R** with all guest molecules (Figures A4.28- A4.37).⁴¹

Amongst all, the highest binding constant was observed for the 1:1 **4.1-R+S-EP** system ($K_a = 41525$ M⁻¹). By contrast, the **4.1-R+R-EP** ($K_a = 1010$ M⁻¹) shows a much smaller K_a value. The difference in the binding constants between these two systems shows a Guest selectivity ($\zeta = K_a(\text{larger})/K_a(\text{smaller})$) of 41.1. Notably, the highest ζ value of 67 has been observed in

the case of **HO**, as the observed K_a value for the **4.1-R+R-HO** system (16736.5 M^{-1}) is much larger than that of the **4.1-R+S-HO** (249.7 M^{-1}) indicating the strong association of **R-HO** with **4.1-R**. The higher selectivity and high binding affinities of **EP** and **HO** can be attributed to the possible classical and non-classical hydrogen bonding interactions with guest molecules. Moreover, the optimal size of these **EP** and **HO** molecules facilitates better diffusion of these guests at the cavities of the cages.

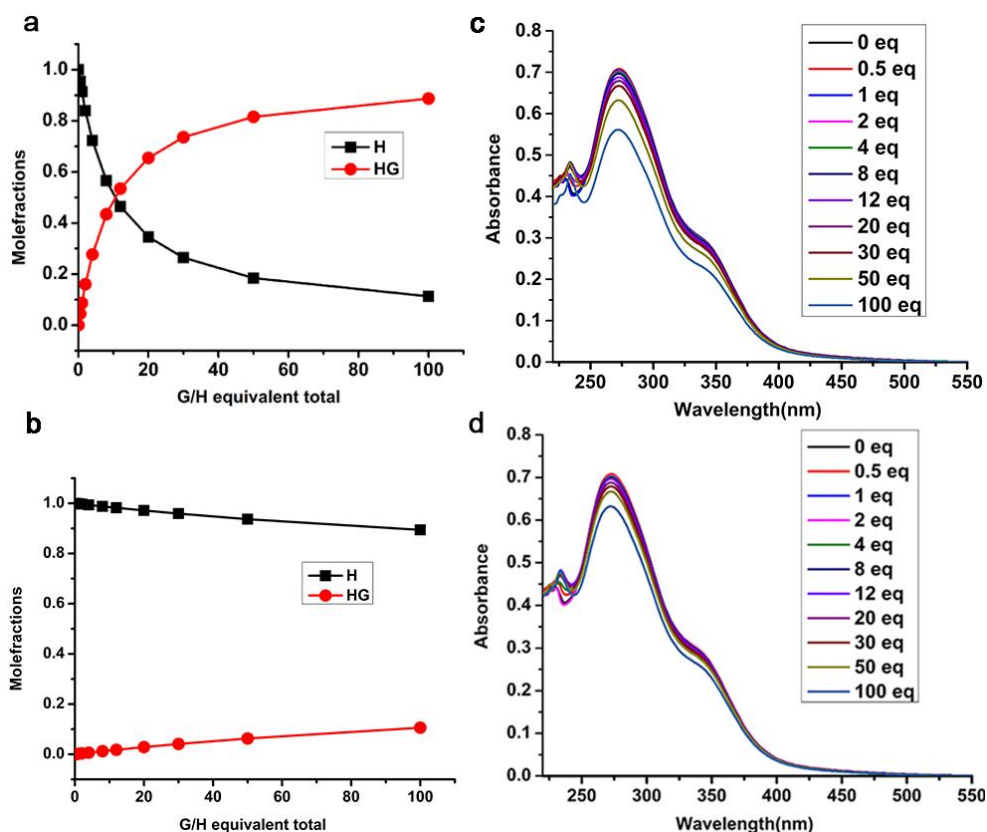


Figure 4.4. Bind fit plots for the a) **R-HO+4.1-R** and b) **S-HO+4.1-R** systems. UV-Visible titration plots for the host-guest complexes of c) **R-HO+4.1-R** and d) **S-HO+4.1-R** mixtures.

DO and **PO** exhibited similar binding selectivity with moderate ζ values (Table 4.2). The overall lower K_a values for **PO** systems over **EP** and **HO** systems could presumably be due to their smaller sizes and the absence of additional functional groups for strong interactions. The UV-Visible titrations resulted in the lowest enantioselectivity ζ value of 1.7 in favour of **4.1-R+R-MA** system. This can be attributed to similar and equally strong non-classical interactions for both the enantiomers of this pair due to the presence of multiple donor sites in them. Control experiments using the chiral ligand $L^{RRR}H_3$ as well as the precursor

hexameric cluster **2-R** could not show efficient recognition capabilities. Also, poor binding constant values were noticed in both these experiments, suggesting the role of the supramolecular cage in the chiral recognition studies (Figures A4.38- A4.47 and Table A4.9). In contrast, the multiple chiral moieties present at each of the tetrahedral corners of the cage (**4.1-R**) rendered maximum interactions with the guest moieties, resulting in efficient chiral recognition events.

Table 4.2. UV-Visible titration derived selective association constants (K [M^{-1}]) and binding selectivity (ξ) and the HPLC chiral separation studies of chiral hosts resolved by **4.1-R.**

Guest	Recognition		Separation (%ee)
	K_{11} with 4.1-R	ξ (selectivity)	
R-HO S-HO	16737 250	67 (R)	NA ^[a]
R-EP S-EP	1010 41525	41.1 (S)	93 (S)
R-PO S-PO	493 2871	5.8 (S)	NA ^[a]
R-MA S-MA	7164 4353	1.7 (R)	71 (R)
R-DO S-DO	14401 2920	5.9 (R)	85 (R)

4.3.4 Single-Molecule Optimization Studies

Preliminary structural optimization studies were performed for each host-guest pair using PM6-modeling to obtain comparative insights into the nature and strength of the interactions exhibited by the enantiomeric guest molecules with **4.1-R**. The optimized host-guest complexes of **HO** show predominant O–H $\cdots$ O interactions between the squarate oxygen atoms and the guest OH groups along with other non-classical H-bonds showing the interaction of guest molecules with the chiral exterior of the cages (Figure A4.42,). The optimized structures of enantiomers of **MA** and **DO** with **4.1-R** primarily display O–H $\cdots$ O_P and N–H $\cdots$ O_P interactions between the oxygen atoms from the imido ligands and O–H and N–H groups from the guest molecules, respectively. In addition, the **S-DO+4.1-R** system shows strong C–H $\cdots$ π interactions (Figure A4.43- A4.44). In the case of **EP** and **PO**,

different non-classical H-bonds that involve the guest C-H protons and the P=O groups of the imido ligands have been observed (Figure A4.45- A4.46). The relative binding energies of each of the host-guest pairs are in agreement with the chiral recognition trends observed from the UV-Visible titration studies (Figure A4.47). Notably, most of the favourable host-guest systems show more number of stronger interactions.

4.3.5 Chiral Separation Studies

Spurred by the efficient binding abilities of **4.1-R**, we set out to probe its enantioseparation capabilities with these guest molecules. We implemented the crystallization inclusion method, where the guest molecules are recognized at both the intrinsic and extrinsic cavities of the cage.^{11,42} This procedure involves the mixing of the host **4.1-R** with an excess of the racemic mixture of the desired guest molecule in chloroform and leaving the solution for crystallization at room temperature. After evaporation of the solvent, the crystalline residue was washed several times with cold diethyl ether (where the cage is insoluble) to remove the excess guest molecules. A representative mass spectrum and $^{31}\text{P}\{^1\text{H}\}$ -NMR of the precipitate indicates stability of the cage and the formation of the host-guest assembly after the crystallization inclusion procedure (Figures A4.48). The bound guest molecules were then extracted with methanol and analysed with the High-performance liquid chromatography (HPLC) technique. As observed from the HPLC profiles (Figures A4.49- A4.60), the highest %ee value of 93% was obtained for **EP** desorbed from **4.1-R** for its S-isomer (Table 4.2). Also, the **R-DO** and **R-MA** enantiomers showed relatively high %ee values of 85 and 71%, respectively. The observed trends in the %ee qualitatively compare well with the obtained binding selectivity (ξ) data of these guest molecules. The apparent disparity between the magnitudes of ξ and %ee could be due to the differences in the host-guest interactions in the solution and solid states. Furthermore, from the separation efficiency data, it is evident that the size and specificity of interactions are more crucial in yielding high %ee values. The existing commercial method for producing enantiopure **EP** is the hydrolytic kinetic resolution of $\pm\text{EP}$ by a salen-Co(II) catalyst, with a %ee of >99%.⁴³ However, this method is limited by the high cost of the catalyst, low yield (<50%) of the **EP** and metal leaching issues. Recent developments in using synthetic enzymatic methods for **EP** suffer from one or the other issues related to the purity of the product, limited choice of biocatalysts⁴⁴ and inactivation of the enzymes under certain conditions.⁴⁵ Thus, using **4.1-R** to recognize and separate **EP** is efficient and relatively simple under non-HKR conditions. The improved chiral separation abilities of the **4.1-R** could be attributed to the tighter

packing and reduced external cavity volumes that maximize the interaction of the moderately sized guests with the chiral centres present in the cage exteriors. Moreover, the improved portal diameters of **4.1-R** provide a synergy between the intrinsic and extrinsic pores of the cage for efficient recognition of the guest molecules. Also, **4.1-R** is the first self-assembled system to separate the enantiomers of **DO** and **MA** with relatively high %*ee* values. The control experiments carried out with chiral phosphoramidate ligands could not resolve the enantiomers of the examined substrates under identical conditions, indicating that the more open structure of the chiral cage assembly plays a role in the enantioselective recognition and separation. Similar observations have also been reported with the isostructural Pd(II) cages based on oxalate linker and imido P(V) trianion.¹

4.4 Conclusion

In conclusion, an enantiomeric pair of tetrahedral cages **4.1-R** and **4.1-S** of formula $[(\text{Pd}_3[\text{PO}(\text{N}(\text{*CH}(\text{CH}_3)\text{Ph})_3])_4(\text{C}_4\text{O}_4)_6]$ was synthesized and structurally characterized. These cages exhibit a pore window of 5.8 Å and a void volume of 289 Å³, which are known to be the highest among the tetrahedral cages of this family due to the unusual non-geminal mode of coordination of the squarate (C_4O_4)²⁻ ligands to the Pd(II) centres. These cages were used efficaciously to recognize and separate chiral organic molecules with varied functionalities, such as ketone, carboxylic acid, epoxide, etc. The highest 1:1 binding selectivity of 67 was achieved for **R-HO** over its antipodal enantiomer **S-HO** using **4.1-R**. Remarkably, the highest %*ee* value of 93% has been observed for the **S-EP**, which is the highest obtained from any supramolecular-based host system. Moreover, **4.1-R** is the first self-assembled system showing a high %*ee* for the enantiomers of **DO** and **MA**. Notably, the size of the guest molecules and the specificity of the host-guest interactions are the key factors for the trends observed in the binding selectivity and separation efficiency. These findings show the versatility of the chiral imido-Pd(II) cages for the recognition and separation of chiral molecules and promise their utility as tools for several enantioselective applications. Also, observation of a new mode of metal-ligand linkage isomerism in these tetrahedral Pd(II) cages encourages further studies in search of newer cage assemblies and their unusual functionalities.

4.5 References

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 42. The crystal structure of the studied host-guest complex reported in reference 11, with racemic β -butyrolactone shows the guest binding both at the intrinsic and extrinsic cavities of the cages.
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Chapter -5

Fine-tuning of Window Size of Enantiomeric Imido-Pd(II) Cages for Effective Enantio Separation of Organic Molecules

5.1 Introduction

The continued development of molecular architectures as the consequence of both longstanding and newly recognized problems demands ever-evolving synthetic routes, characterizations, and applied studies.¹ Metal and polytopic ligand self-assemblies have garnered much interest in the past decades for their rich structural chemistry and host-guest studies.² Various non-covalent interactions and symmetry considerations play an important role in the design of such assemblies, which have led to the development of various convergent synthetic protocols.³ These include directional bonding,⁴ symmetry interaction,⁵ panneling,⁶ and weak-link approaches.⁷ Amongst these, directional bonding is the most prevalent since diverse protocols have been established in this approach for the self-assembled syntheses of two-dimensional metal-organic macrocycles and three-dimensional metal-organic cages (MOCs).⁸⁻¹⁰ These assemblies, particularly the 3-D cages, have been found to be applicable in catalysing reactions,¹¹ stabilizing molecules by providing a chemically unique and favourable environment inside its pore,¹² and in chemo-selective recognition of various molecules.¹³ The physical and chemical properties of cage molecules can be tuned by the choice of metal ions,¹⁴ the nature of the ligand, the charge on the cages, and the functionality of the pore.¹⁵ Moreover, studies have been conducted on the varying size and shape of the interaction sites and pore sizes with the view of exploring these molecules as efficient host-guest systems.^{16, 17} In fact, the guest encapsulation ability of the cage molecules has been exploited for reactions involving size-selective catalysis¹⁸ and template-directed synthesis of nanoparticles.¹⁹ For example, a bipyridyl-substituted phosphine ligand used in conjunction with rhodium for hydroformylation catalysis was selectively encapsulated in a Fe-Zn MOC.²⁰ Combining chirality with guest-binding in the cage molecules unlocked a wider range of possibilities as stereochemistry is the essence of biological systems and, hence, in drug formulations as well.^{21, 22}

Enantiopure styrene oxides are of interest because they are useful intermediates for the synthesis of chiral pharmaceuticals and agrochemicals. In particular, styrene oxide is a significant precursor of many useful compounds such as pesticides (for example, nematocides), antifungal drugs (ketoconazole), cardiovascular drugs (metoprolol), anti-inflammatory drugs (ibuprofen), and antiviral drugs (hyperolactone C).²³⁻²⁷ Also, the strained epoxide ring is widely known to react with nucleophiles, Lewis acids, radicals, reducing agents, oxidizing agents, acids, and bases.²⁸ However, nature's pool has not been found to provide a reliable or direct source of optically active epoxides. Thus, one of the most accepted methods for the

resolution of epoxides is hydrolytic or aminolytic kinetic resolution (HKR), usually catalysed by Co/Cr-(salen) complexes or enzymes such as lipases and hydrolases.²⁹⁻³¹ This process faces challenges such as the high cost of catalysts, low yield, and issues regarding metal leaching. Similarly, the enzymatic methods encounter issues like product purity, a limited selection of biocatalysts, and enzyme inactivation under specific conditions. Hence, the development of an effective host in supramolecular systems has been explored for the enantiomeric separation of epoxides owing to their economical and environment-friendly approaches for effective chiral separation.³²⁻³⁴

The amido and imido P(V) group has novel P-N bonds and acts as a cis-blocking group; hence, it can be used as a building block for MOCs to yield discrete units.³⁵ This also makes the process of introducing chirality to the cage backbone much more straightforward by employing chiral phosphoramides as the precursors.³⁶ A wide array of molecular assemblies with chiral P-N groups have been employed for numerous applications such as chiral recognition and separation.³⁷ Our group has been interested in the development of neutral Pd(II) cages supported by tris(imido)phosphate trianions and various wide-angle chelating dicarboxylate ligands.^{32, 36, 38} Particularly, the incorporation of chiral substituents on the imido-nitrogen atoms yields chiral cages that can aid in the chiral recognition and separation of enantiomers. In this study, we studied the chiral recognition abilities of two chiral metal-organic cages supported by haloanilate linkers and showed the effect of halogen substituents on the overall binding and separation abilities of these cages. The imido-Pd₃ cage assemblies [(Pd₃X*)₄(C₆O₄Cl₂)₆] (**5.1-R**)³² and [(Pd₃X*)₄(C₆O₄F₂)₆] (**5.2-R**)³⁹ (where [X*]³⁻ = RRR-[PO(N(*CH(CH₃)Ph)₃]³⁻) based on the chloroanilate and fulroainalte linkers, earlier reported by our group, were probed for the chiral recognition and separation of the enantiomers of styrene oxide (**SO**), epichlorohydrin (**EP**), 4-benzyl-2-oxazolidinone (**DO**). Remarkably, the highest recognition selectivity value of 88 and enantiomeric excess (% ee) of 98.1 were observed **R-SO** by using the **5.2-R** cage. Detailed computational analysis indicated that the observed selectivities and separation efficiencies are attributed to the selective encapsulation of these guest molecules within the intrinsic cavities of **5.2-R**. These findings emphasize the application of neutral imido-Pd(II) cages as proficient host materials for enantioselective applications..

5.2 Experimental Details

5.2.1 General Remarks

NMR spectra were recorded on a Jeol 400 MHz spectrometer (¹H NMR: 400.13 MHz, ¹³C {¹

^1H NMR: 100.62 MHz, ^{31}P { ^1H } NMR: 161.97 MHz) or on a Bruker 400 MHz (^1H NMR: 500.00 MHz, ^{13}C { ^1H } NMR: 125.725 MHz, ^{31}P { ^1H } NMR: 202.404 MHz) spectrometer at room temperature using TMS (^1H , ^{13}C) and 85% H_3PO_4 (^{31}P). The mass spectra were obtained on an Applied Bio system matrix-assisted laser desorption ionization time-of-flight (MALDITOF)/ TOF spectrometer. A PerkinElmer STA-6000 thermogravimetric analyser has provided the thermal analysis (TGA) results. A JASCO J815 spectrometer was used to measure CD spectra between 400 and 190 nm. A Vario-EL cube elemental analyser was used for the elemental studies. Agilent Technologies 1260 Infinity equipment with a UV detector was used for all HPLC analyses.

5.2.2 Host-guest Studies: General Procedure for Chiral Recognition Studies with **5.1-R** and **5.2-R**

The enantio-recognition abilities of **5.1-R** was evaluated for the enantiomeric *R*- and *S*-isomers of styrene oxide (**SO**), epichlorohydrin (**EP**), and 4-benzyl-2-oxazolidinone (**DO**), using UV-Visible titrations. The stock solutions of guests (1 mM, **R** or **S**) were freshly prepared by dissolving them in chloroform (HPLC grade). The guest **R** or **S** (0.5eq- 100eq) was added by using a micro pipette to the host solution of **5.1-R** (0.25 mM in 2 mL chloroform) placed in a 10 mm cuvette (3.0 mL). The change in absorption values was monitored during the UV- Visible titration experiments. Based on the data obtained in the 190-500 nm range, association constants of **5.1-R** and **5.2-R** with enantiomers of **SO**, **EP**, and **BO** were obtained by fitting the corresponding UV- Visible titration data to a 1:1 binding model by using the online Bind Fit tool. (Figures A5.7- A5.18 and Table A5.1).

5.2.3 Procedure for Encapsulation-Separation Experiment and Resolved Results for Racemic Substrates by **5.1-R** and **5.2-R**

In a typical encapsulation-separation experiment, excess of racemic guests were separately added to **5.1-R/5.2-R** in dry DCM (10ml). The reaction mixture containing rac-epichlorohydrin (**EP**), rac-4-benzyl-2-oxazolidinone (**DO**), and styrene oxide (**SO**) was stirred for one hour and then left to slowly evaporate, leading to the formation of crystalline host-guest complexes. Any excess guest molecules present on the surface of these complexes were removed by multiple washes (3-5 times) with ice-cold diethyl ether. To eliminate any remaining adsorbed guest molecules, the complexes were soaked in methanol and subsequently analyzed using chiral HPLC methods. Details of the HPLC methods used, along with chromatograms and analytical plots, can be found in the final section of the supporting information document (Figures A5.29–A5.43).

5.2.4 ¹H-2D-DOSY NMR studies:

The ¹H-2D-DOSY NMR experiments were conducted using a Bruker AVANCE III NMR spectrometer operating at a ¹H frequency of 600 MHz and maintained at 298 K. Solutions of the host-guest complexes (2.50 mM) were prepared in CDCl₃ and allowed to equilibrate for 1 hour before data collection. Diffusion Ordered Spectroscopy (DOSY) experiments were carried out by varying the gradient strength. The DOSY data were processed using the standard Bruker protocol in Topspin 3.1 software. The diffusion dimension in the 2D-DOSY spectra was analysed using either a one-parameter mono-exponential fit (Equation 1) or a two-parameter bi-exponential fit (Equation 2).

$$I = I_0 \exp [-D \gamma^2 g^2 \delta^2 (\Delta - \delta/3)] \dots\dots\dots (1)$$

$$I = I_{0A} \exp [-D_A \gamma^2 g^2 \delta^2 (\Delta - \delta/3)] + I_{0B} \exp [-D_B \gamma^2 g^2 \delta^2 (\Delta - \delta/3)] \dots\dots\dots (2)$$

In this equation, I is the observed integral, I₀, I_{0A}, and I_{0B} are the reference or un-attenuated integrals, D, D_A, and D_B are the diffusion coefficients, γ is the gyromagnetic ratio of the detected nucleus, g is the gradient strength, δ the length of the gradient pulse, and Δ the diffusion time.

5.2.5 Theoretical Calculations:

The gas-phase single-molecule energies of all participating species and host-guest systems were determined using the Gaussian 09 software. These energy calculations were performed employing the PM6 method. For the host–guest complexes, the energies of the host cage **5.1-R**, the guests, and the host–guest complexes were separately calculated and the binding energy of a given complex was calculated by (equation 3):

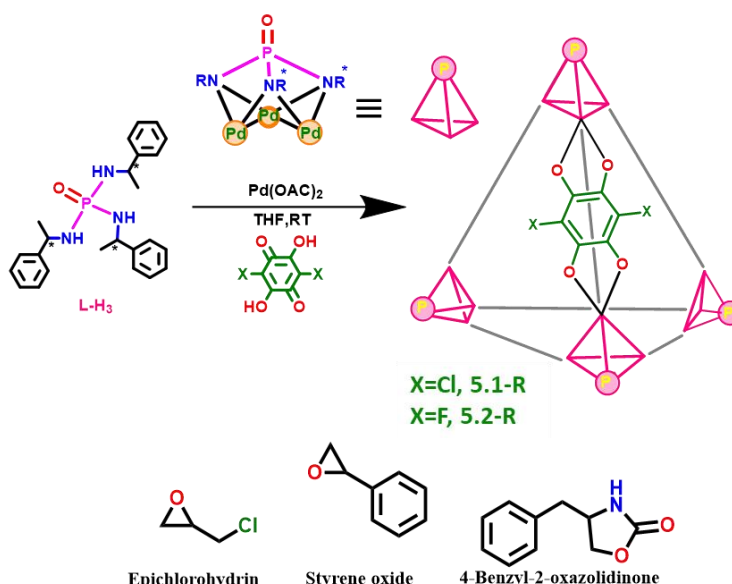
$$\text{Binding energy} = E_{\text{Guest} \subset \text{Host}} - (E_{\text{Host}} + E_{\text{Guest}}) \dots\dots\dots (3)$$

5.3 Results and Discussions

5.3.1 Structure and Packing

The enantiopure imido P(V) trianion-supported Pd(II) cages **5.1-R** and **5.2-R** have been synthesized and characterized by the previously reported procedures. Single-crystal X-ray diffraction analysis of these cages showed that **5.1-R** crystallized in the chiral cubic space group *I23* and **5.2-R** in the chiral orthorhombic space group *P21212*. Both cages feature an isostructural core consisting of four trinuclear Pd₃X* (X* = ^{RRR}CH(CH₃)Ph)₃ chiral clusters located at the corners of a tetrahedral arrangement that are connected by dianions chloranilate (**5.1-R**) or fluoranilate (**5.2-R**) linkers along the six edges of the tetrahedron. The trinuclear Pd₃ cluster is cis-protected by the hexa-dentate coordination of the

tris(imido)phosphate ligand, which allows each Pd(II) ion to offer two 90° cisoidal sites for the wide-angle O,O-chelation of the anilate anions. The α -Me groups of the imido ligands introduce additional rotational chirality via their clockwise orientation. Despite their identical molecular structure, the unit cell of **5.2-R** exhibits tighter packing with solvent-accessible void volume of 651 Å³, corresponding to 6% of the total unit cell volume, while **5.1-R** shows solvent-accessible void volumes of 3000 Å³, accounting for 33% of the total unit cell volume. To further explore the volume of the intrinsic cavities, MSROLL calculations, integrated into the XSEED software, were conducted. These calculations revealed that the intrinsic void volumes of cages **5.1-R** and **5.2-R** are 224 Å³ and 238 Å³, respectively. Notably, **5.2-R** possesses a slightly larger portal diameter of 4.44 Å than **5.1-R** (3.3u6 Å), attributed to the size difference between the F and Cl atoms and structural differences in the cages.



Scheme 5.1. Schematic diagram of enantiopure Pd(II) cages **5.1-R** and **5.2-R**, and Enantiomeric guest molecules examined for the chiral studies.

Typically, larger intrinsic portals and smaller packing cavities are desired for enantio-separation applications via the crystallization inclusion method. The cage **5.1-R** was earlier shown to exhibit a chiral separation ability of 80% *ee* for **F-SO** and 7% *ee* for **SO**.³² However, its full enantio-recognition studies have not been studied in detail. The enhanced intrinsic portal diameters and tighter lattice packing of the **5.2-R** cage prompted us to investigate its chiral recognition and separation abilities along with those of **5.1-R**. In view

of the initial results from **5.1-R** for styrene oxide derivatives. We chose to study the epoxides, styrene oxide (**SO**), and epichlorohydrin (**EP**) in detail. We have also probed an example of oxazolidinone, 4-benzyl-2-oxazolidinone (**DO**), to study the enantio-recognition of guest molecules of different sizes aided by the effect of portal size. This study aims to elucidate the influence of functional groups and portal dimensions on the enantioselectivity and separation processes of these cages.

The MALDI-TOF mass spectrometry analysis of **5.1-R** and **5.2-R** in the presence of these guest molecules revealed m/z peaks centred at 4279 (**SO+5.1-R+K**), 4057 (**SO+5.2-R+K**), 4268 (**EP+5.1-R+K**), 4068 (**EP+5.2-R+K**), 4353 (**DO+5.1-R+K**), and 4292 (**DO+5.2-R+K**), corresponding to the respective host-guest complexes. Additionally, ^1H NMR spectra of these host-guest mixtures exhibited distinct peaks associated with the protons of the guest molecules.

5.3.2 Chiral Recognition Studies

UV-visible titrations have been carried out for cages **5.1-R** and **5.2-R** in the presence of optically pure guest molecules to further quantify the enantiomeric guest recognition capabilities of the cages. The decrease in the absorbance values of cages was gradually monitored during the titration process. Using the online Bindfit Tool, the peak intensity gradients were fitted in order to obtain the binding constants (K_a).⁴⁰ A clear 1:1 binding of **5.1-R** and **5.2-R** with all guest molecules is evident in the Bind Fit Plots (Figures A5.7-A5.18 and Table A5.1).

Of all these systems, the **5.2-R+R-SO** system had the highest 1:1 binding constant value of 116618 M^{-1} . The **5.2-R+S-SO**, on the other hand, has a substantially lower K_a value ($K_a = 1318\text{ M}^{-1}$). Thus, the highest Guest selectivity ($\zeta = K_a(\text{larger})/K_a(\text{smaller})$) of 88 is obtained by the difference in binding constants between these two systems, indicating a significant association between **R-SO** and **5.2-R**. Meanwhile, in the case of **5.1-R+R-SO**, a significantly lower binding constant value of 952 M^{-1} is obtained, and a much lower binding constant value of 538 M^{-1} was obtained for the **5.1-R+S-SO** system, indicating a marginally poor association of **R-SO** with **5.1-R** compared to **5.2-R**.

The preferential selectivity between the **EP** enantiomers has a high ζ value of 26, as the observed K_a value for the **5.2-R+R-EP** system (254 M^{-1}) is significantly higher than that of the **5.2-R+S-EP** (10 M^{-1}). In contrast, a much lower ζ value of 3, arising from the respective K_a values of 519 and 173 M^{-1} of the **5.1-R+R-EP** and **5.1-R+S-EP** systems, indicates not only a poor selectivity but also the poor recognition ability of **5.1-R** for both the

enantiomers of **EP**. Similar results were observed in the case of **DO**, where **5.2-R** is 12 times more selective for **R-DO** with respect to its *S* enantiomer, and **5.1-R** is six times more selective for **R-DO** compared to **S-DO** with good to moderate binding constant values of 5221, 445, 1550, and 265 M⁻¹, respectively, which suggests a moderate binding of both *R* and *S* isomers of **DO** with **5.1-R** and **5.2-R**. The presence of better classical and non-classical hydrogen bonding interactions of **5.2-R** over **5.1-R** with guest molecules explains the better selectivity and high binding affinities of **SO** and **EP**. Additionally, the cooperative compatibility of the intrinsic cavities of the cages and their portal dimensions with the guest **SO** and **EP** molecules could facilitate the improved dispersion of these guests at the cage cavities for better guest recognition.

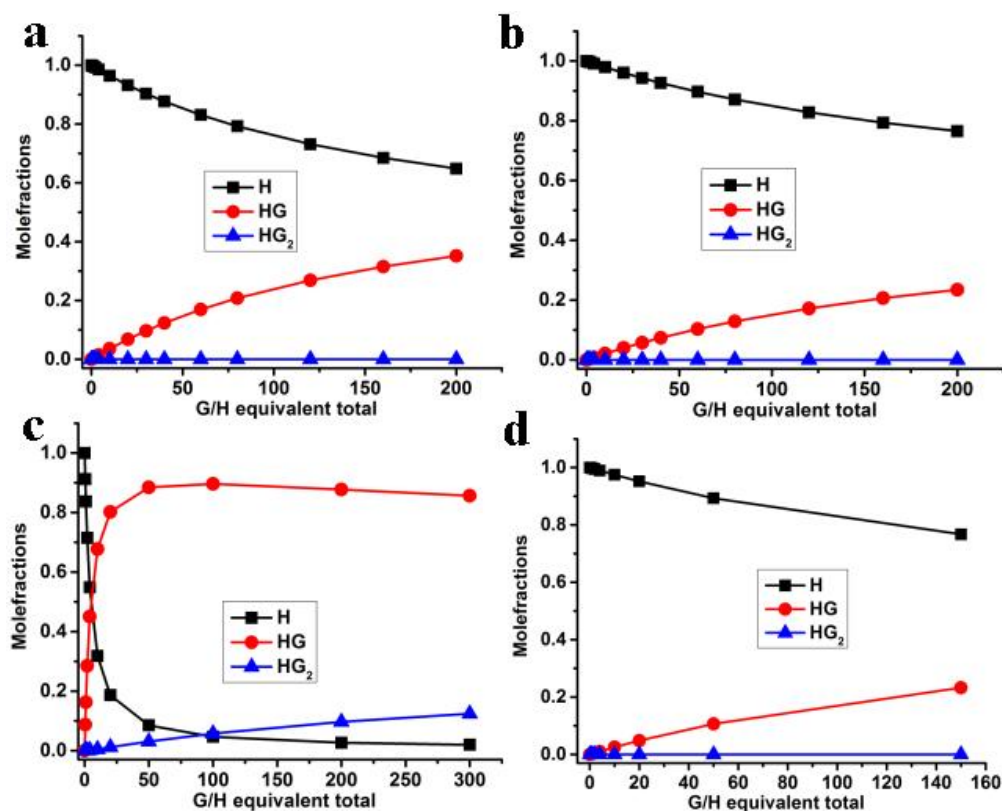


Figure 5.1. Bind fit plots for the for the host-guest complexes of a) **5.1-R+R-SO**, b) **5.1-R+S-SO**, c) **5.2-R+R-SO**, and d) **5.2-R+S-SO**.

5.3.3 ¹H-2D-DOSY NMR Studies.

To gain a deeper understanding of host-guest assembly formation, ¹H-2D-DOSY NMR measurements were performed on all host-guest mixtures. During the analysis, the CH or

methyl protons of the α -methyl benzyl groups on the cage were monitored to assess the diffusion nature of the cages. Likewise, appropriate protons were selected to track the diffusion of the guest molecules. The ^1H -2D-DOSY NMR analysis of the **R-SO**-treated sample of **5.1-R** revealed two distinct diffusion coefficients for both the host and guest: 5.25×10^{-10} and $3.93 \times 10^{-10} \text{ m}^2/\text{s}$ for **5.1-R**, and 15.28×10^{-10} and $9.7 \times 10^{-10} \text{ m}^2/\text{s}$ for **R-SO**. These findings indicate the presence of two separate species for both the host and guest in solution. The species exhibiting higher diffusion rates correspond to free (unbound) host and guest molecules, while the slower-diffusing species represent the host-guest complex, representing a single entity. Similarly, the **5.2-R+R-SO** system showed two separate diffusion coefficients for both the host and guest signals. Like before, the bound and free diffusion rates were measured to be 4.51×10^{-10} and $4.32 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ for **5.2-R** and 15.55×10^{-10} and $4.41 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ for **R-SO**, respectively. Notably, in the bound state, both **R-SO** and **5.2-R** exhibited nearly identical diffusion rates, indicating a strong interaction between **R-SO** and **5.2-R** and confirming the formation of a stable host-guest complex in solution. In contrast, the **R-SO**-treated samples of **5.1-R** exhibit slightly higher diffusion coefficients for the guest **R-SO** molecules compared to **5.1-R** in the bound state, implying a weak association of the **5.1-R+R-SO** system in comparison with **5.2-R+R-SO**. (Figures A5.19- A5.20 and Table A5.2).

For other guest molecules, **R-EP** and **R-DO**, the bound guests exhibited comparable and slightly higher diffusion coefficients. The results of all the DOSY data are tabulated in Table Sx. From this table, it is evident that both **5.1-R+R-EP** and **5.2-R+R-EP** systems show better host-guest formation (with D_{bound} values of 3.89 and 4.24 for the **EP** guest), while **R-DO** systems exhibit slightly weaker interactions with both **5.1-R** and **5.2-R** (with D_{bound} values of 8.98 and 9.02 for the **R-DO** guest), presumably due to its binding at the cage exteriors.

5.3.4 Calculation for the Hydrodynamic Radius Using DOSY Data.

The hydrodynamic radius (R_H) of each of the diffusing species were calculated further to confirm the formation of well-defined host-guest assemblies, offering a clear difference between internally encapsulated guest and externally bound guests. The R_H values were derived from the diffusion coefficients (D) obtained through DOSY ^1H -NMR measurements using the Stokes–Einstein equation. For each host and guest species, distinct R_H values were determined in their free and bound states. For example, in the **5.2-R+R-SO** system, two R_H values of 11.44 Å (free) and 11.81 Å (bound) were observed for cage **5.2-R**, while **R-SO**

exhibited R_H values of 4.78 Å (free) and 11.62 Å (bound). The close agreement between the R_H values of the host and guest molecules, 11.81 Å and 11.62 Å, respectively, in the bound state, clearly confirms the encapsulation of **R-SO** within the intrinsic cavity of cage **5.2-R** (Table XX). Similar trends were observed for both the **5.1-R+R-EP** (12.87 and 12.84 values) and **5.2-R+R-EP** (11.90 and 11.99 values) systems, with host and guest diffusion coefficients having nearly the same values in the bound state. However, the R_H value of the bound **R-SO** guest in the **5.1-R** system (6.52 Å) and **R-DO** guest in the **5.1-R** and **5.2-R** systems (6.31 and 6.40 Å) differed slightly from that of **5.2-R+R-SO** (and **5.1-R+R-EP** and **5.2-R+R-EP** as well), which is attributed to a weaker interaction of these guest molecules presumably at the exterior of the respective cages. (Table 1).

5.3.5 Structural optimization studies.

To further understand the host-guest behavior of these cages, structural optimization studies were conducted using the PM6 model for each of the host-guest scenarios. These calculations provide comparative insights into the interactions between enantiomeric guest molecules and the enantiopure cages **5.1-R** and **5.2-R**. Notably, these guest molecules interact via the non-classical C-H $\cdots$ O and two C-H $\cdots$ X (X = Cl, F) type interactions between the C-H protons of the guest molecules and the heteroatoms (O, X) of the anilate linkers of the cage forming a 1:1 host-guest complex. For the host-guest complexes of **SO**, the optimized structures of **5.2-R** revealed that the guest molecules are stabilized within the internal cavity for both the guest enantiomers (Figure 5.2). Although both enantiomers are stabilized within the cavity, the nature and strengths of the non-classical interactions that stabilize their encapsulation differ significantly. In the **5.2-R+R-SO** system, four C-H $\cdots$ O and two C-H $\cdots$ F non-classical interactions between the CH groups of the **R-SO** motifs and the linker scaffolds of the cage (oxygen and fluorine atoms) were observed at the internal surface of the cages. In contrast, the **5.2-R+S-SO** system exhibited only three interactions, two C-H $\cdots$ O and one C-H $\cdots$ F. The H-bonding distances were found to be shorter in the **5.2-R+R-SO** than in **5.2-R+S-SO**, accounting for the observed difference in binding constant values derived from their respective UV-visible titration studies. For the **5.1-R+R-SO** and **5.1-R+S-SO** systems, the guest molecules were stabilized outside the cage through several non-classical interactions involving the anilate oxygen, chlorine atoms, and CH groups of the guest molecules. Notably, **5.1-R+R-SO** exhibited higher stabilization energy and a more significant number of non-classical interactions than **5.1-R+S-SO** as noted from their titration experiments.

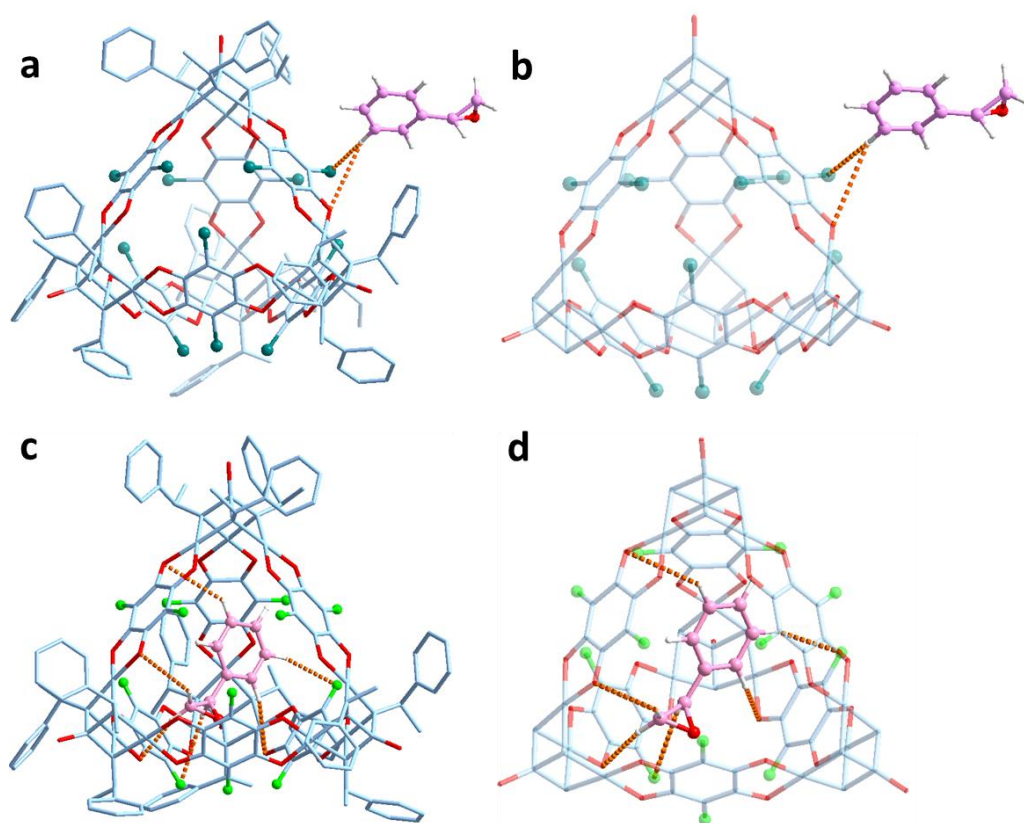


Figure 5.2. Potential non-covalent interactions responsible for the stabilization of the host-guest assemblies in a) **5.1-R + R-SO**, b) **5.2-R + S-SO**, and the zoomed-in images of c) **5.1-R + R-SO** and d) **5.2-R + S-SO** complexes are shown in energy optimized structures of the respective host guest complexes. N blue; O red; F green; Cl dark green; H white. The non-classical interactions (X=N, O) are shown in dotted lines: orange C-H $\cdots$ X and red C-H $\cdots$ π .

The optimized structures of the enantiomers of **EP** with **5.1-R** and **5.2-R** indicate that the guest molecules were stabilized within the internal cavities of these cages for all of the host-guest pairs. However, the number and strength of the non-classical, C-H $\cdots$ O and C-H $\cdots$ Cl, interactions differ in each of the host-guest pairs. Like before, the enantiomer **R-EP** was found to stabilize better within the internal cavities of both **5.1-R** and **5.2-R** cages than its *S*-enantiomer, and the **5.2-R+R-EP** shows a highest relative binding energy value of 21.1 among all, as evident from the nature and strengths of its non-classical interactions (Figures A24- A5.25 and Table 5.1). Nevertheless, the suboptimal size of both *R* and *S* enantiomers of **EP** causes them to preferentially stabilize near the cage window, causing an easy diffusion of the **EP** guests in and out of the cage cavity.

Table 5.1. UV-Visible titration derived selective association constants (K [M^{-1}]) and binding selectivity (ζ) and the HPLC chiral separation studies of chiral hosts resolved by 5.1-R.

Guest	5.1-R				5.2-R			
	Recognition		ΔE_{pref}	Separation (%ee)			ΔE_{pref}	Separation (%ee)
	K_{11}	ζ			K_{11}	ζ		
	[M^{-1}]	(selective)			[M^{-1}]	(selective)		
R-SO	951.6	1.77 (R)	3.52	9	116617.9	88.51 (R)	73.57	98.2
S-SO	537.6				1317.6			
R-EP	519.7	3 R)	2.12	65.7	254.0	26.46 (R)	21.12	86.8
S-EP	173.1				9.6			
R-DO	1550.9	5.85 (R)	3.94	71.2	5220.7	11.74 (R)	6.40	80.3
S-DO	265.2				444.6			

For the **DO** system, due to the larger size of the guest molecules, both enantiomers were stabilized at the external cavities of the cages in the energy-optimized host-guest complexes. The **5.2-R+R-DO** complex primarily exhibited N-H $\cdots$ F hydrogen bonding interactions between the N-H group of the oxazole ring of **R-DO** and the anilate F atoms. Additionally, a non-classical C-H $\cdots$ F interaction between the oxazole ring's C-H and the anilate F atoms further stabilized the **5.2-R+R-DO** complex. In contrast, the energy-optimized structure of **5.2-R+S-DO** demonstrated only a C-H $\cdots$ π interaction. In the case of **5.1-R+R-DO**, two non-classical hydrogen bonding interactions were observed, along with a C-H $\cdots$ π interaction between the C-H group of the oxazole ring and the phenyl group of the cage. However, the **5.1-R+S-DO** complex exhibited only two non-classical C-H $\cdots$ Cl interactions between the host and guest molecules. The binding energies of each of these host-guest pairs were consistent with the chiral recognition patterns observed in UV-Visible titration studies (Figures A5.26- A5.27 and Table 5.1, Supporting Information), with the most favourable host-guest systems displaying a higher number of stronger interactions.

5.3.6 Chiral separation Studies

Driven by the **5.1-R** and **5.2-R** cages' effective binding attributes, we investigated their chiral separation capabilities for the enantiomers of **SO**, **EP**, and **DO** guests. We employed the crystallization inclusion method where the racemic mixture of the desired guest molecule is mixed in excess with the host **5.1-R** and **5.2-R** separately in chloroform, and the solution is left to crystallize at room temperature. The excess guest molecules were removed from the crystalline residue by repeatedly washing it in cold diethyl ether, in which the cage is insoluble, followed by solvent evaporation. $^{31}\text{P}\{^1\text{H}\}$ -NMR and representative mass spectra of the precipitate show that the cage is stable and that the host-guest assembly is forming after the crystallization inclusion procedure. Upon their extraction with methanol, the liberated guest molecules were subjected to an analysis using the High-performance liquid chromatography (HPLC) technology.

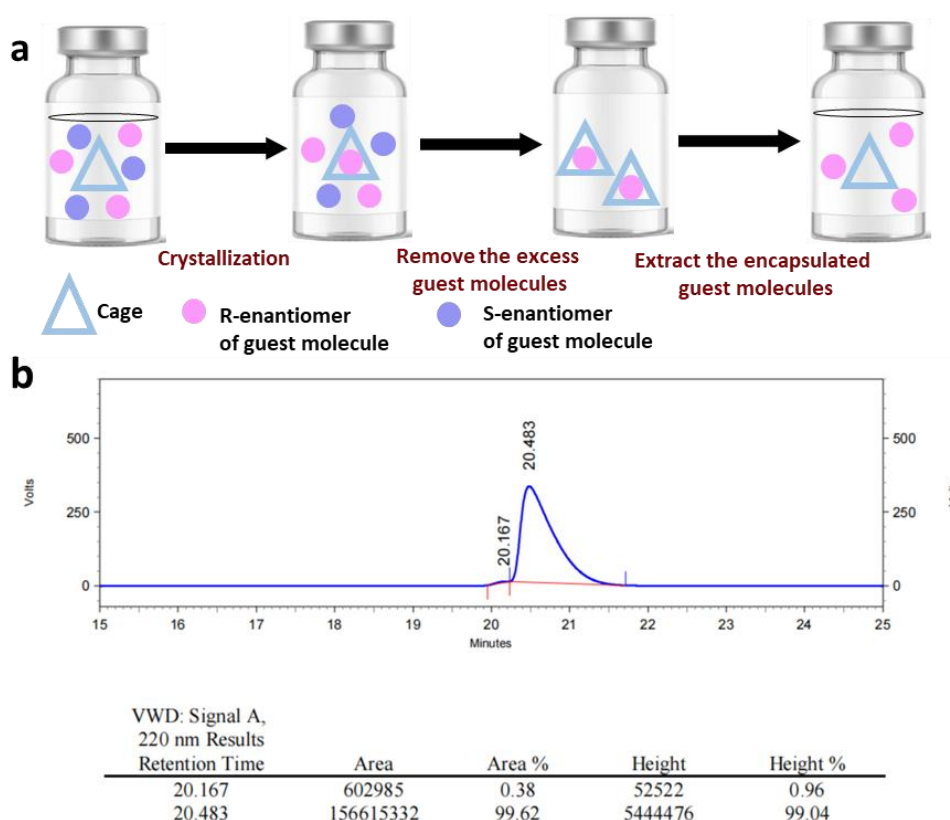


Figure 5.3. a) Schematic representation of crystallisation inclusion method for chiral separation, b) HPLC chromatogram and analysis plot showing the resolved peaks for separation of rac-**SO**.

The highest percentage enantiomeric value of 98% was obtained for **SO** desorbed from **5.2-R** for its *R*-isomer, as can be seen from the HPLC profiles (Figures A5.28- A5.43 and Table 5.1). In contrast, the **5.1-R** displayed a notably low %*ee* value of 6.8, which is also consistent with earlier observations of a 7% enantiomeric excess. Furthermore, for the **5.1-R** and **5.2-R** cages, respectively, the **R-EP** enantiomers had comparatively high %*ee* values of 65 and 86. For **5.1-R+R-DO** and **5.2-R+R-DO**, respectively, moderate %*ee* values of 71 and 80 were found. There is a good qualitative correlation between the obtained binding selectivity (ζ) data of these guest molecules and the observed trends in the %*ee*. Furthermore, from the separation efficiency data, it is evident that the size and specificity of interactions are more crucial in yielding high %*ee* values. The improved chiral separation abilities of the **5.2-R** could be attributed to the tighter packing and reduced external cavity volumes that maximize the interaction of the moderately sized guests with the chiral centers in the cage interiors and exteriors. Moreover, the improved portal diameters of **5.2-R** provide a synergy between the intrinsic and extrinsic pores of the cage for efficient recognition of the guest molecules. Also, **5.2-R** is the first self-assembled system to separate the enantiomers of **SO** with a remarkably high %*ee* value of 98% using the non-HKR protocol. The control experiments carried out only with chiral phosphoramidate ligands remained ineffective in resolving the enantiomers of the examined substrates under identical conditions.³⁸ These studies summarize that the precise internal cavities of the chiral cage assembly **5.2-R** provide an ideal platform for the enantioselective separation of oxiranes.

5.4 Conclusion

In summary, the enantioselective recognition and separation capabilities of the tetrahedral cages **5.1-R** and **5.2-R**, with the formula $[(\text{Pd}_3[\text{PO}(\text{N}(\text{*CH}(\text{CH}_3)\text{Ph})_3])_4(\text{C}_6\text{O}_4\text{X}_2)_6]$, where X = Cl or F, were systematically investigated against guest molecules such as styrene oxide (**SO**), epichlorohydrin (**EP**) and 4-benzyl-2-oxazolidinone (**DO**). These cages possess slight variations in functional groups and portal dimensions, which significantly influenced their performance in enantioselective applications. The highest 1:1 binding selectivity of 88 was observed for **R-SO** over its enantiomer **S-SO** with the **5.2-R** cage. Notably, an enantiomeric excess (%*ee*) of 98% was achieved for **R-SO**, which is among the highest %*ee* reported for any supramolecular cage system. The trends in binding selectivity and separation efficiency are driven by the optimal size of the guest molecules relative to the cage cavity, as well as the functional groups within the host that offer multiple interaction sites for incoming guest molecules. This study demonstrates that substituting Cl with F in the cage structure can

enhance enantioselective separation efficiency by up to 16-fold, as the **5.2-R** cage with fluorine substitution offers an improved portal dimension, tighter packing, and increased hydrogen bonding capacity. Finally, neutral Pd(II) cages supported by chiral imido-trianions offer an attractive platform for the recognition and separation of chiral molecules, highlighting their potential for diverse enantioselective applications.

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Appendix

Spectral, thermal, optical, and structural data

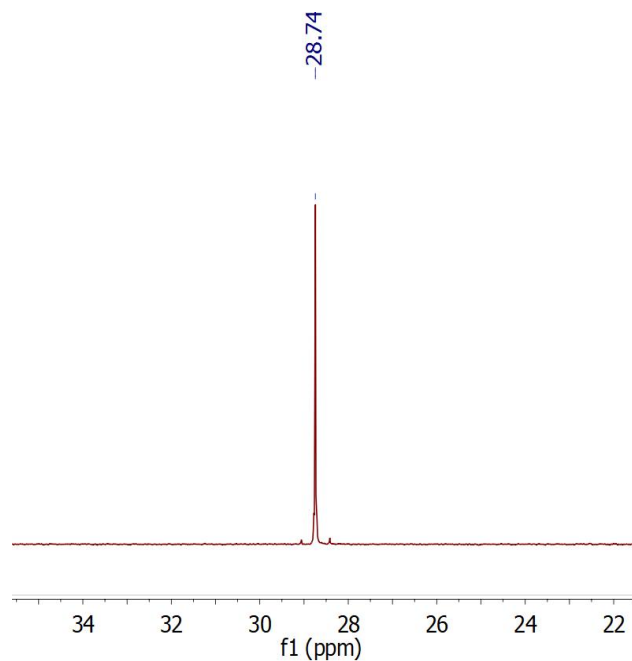


Figure A2.1. ^{31}P NMR spectra of a) **2.1-R**

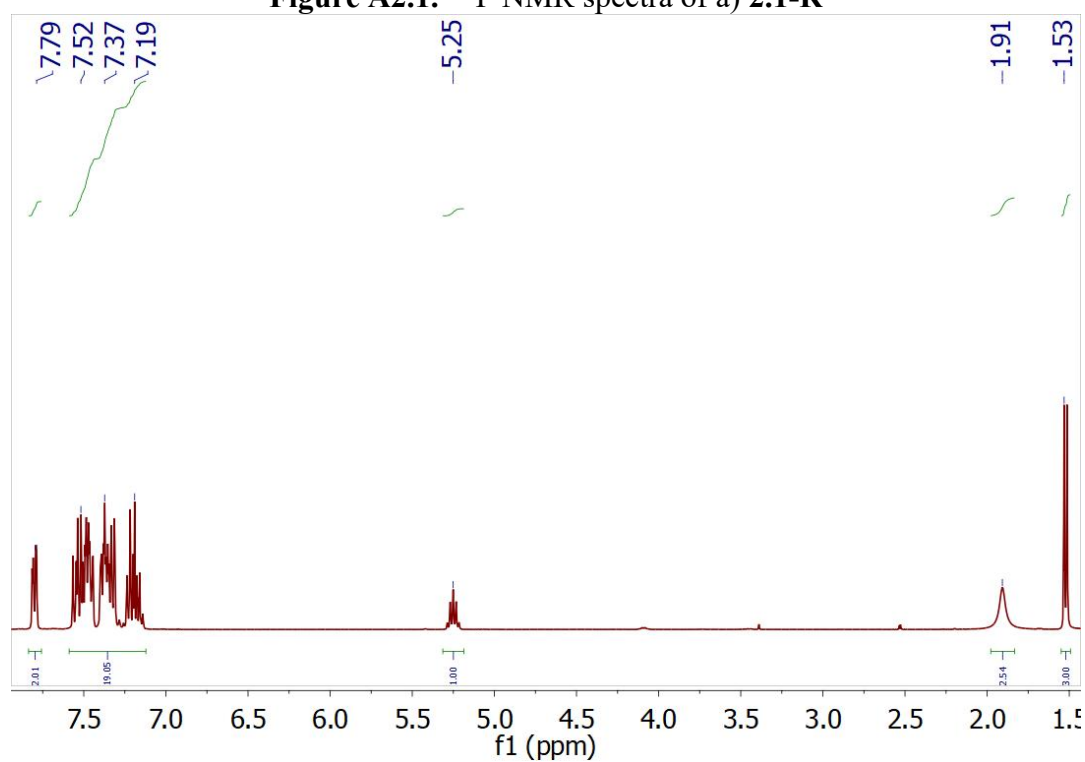
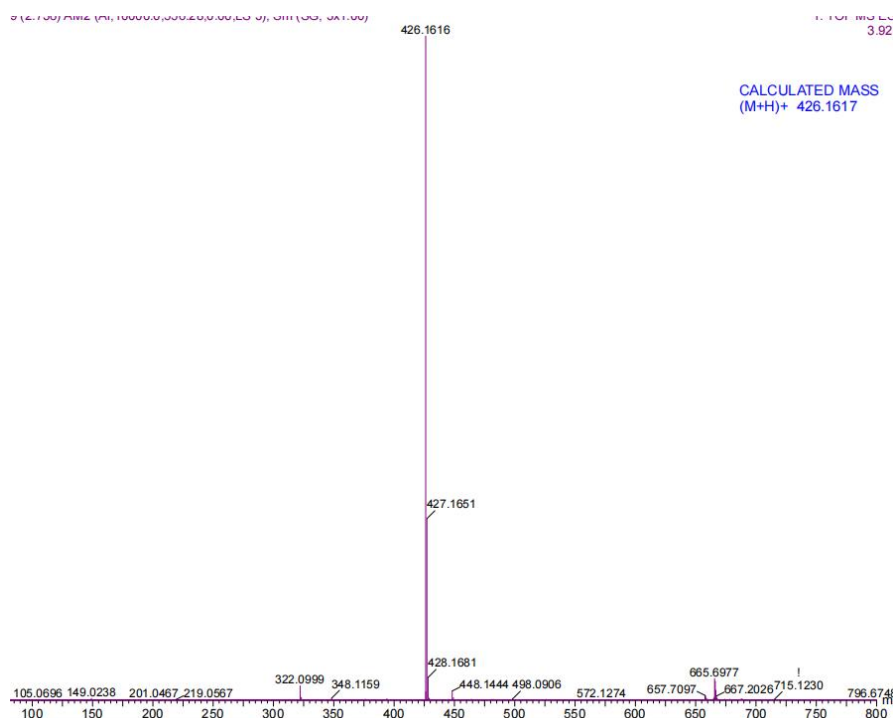
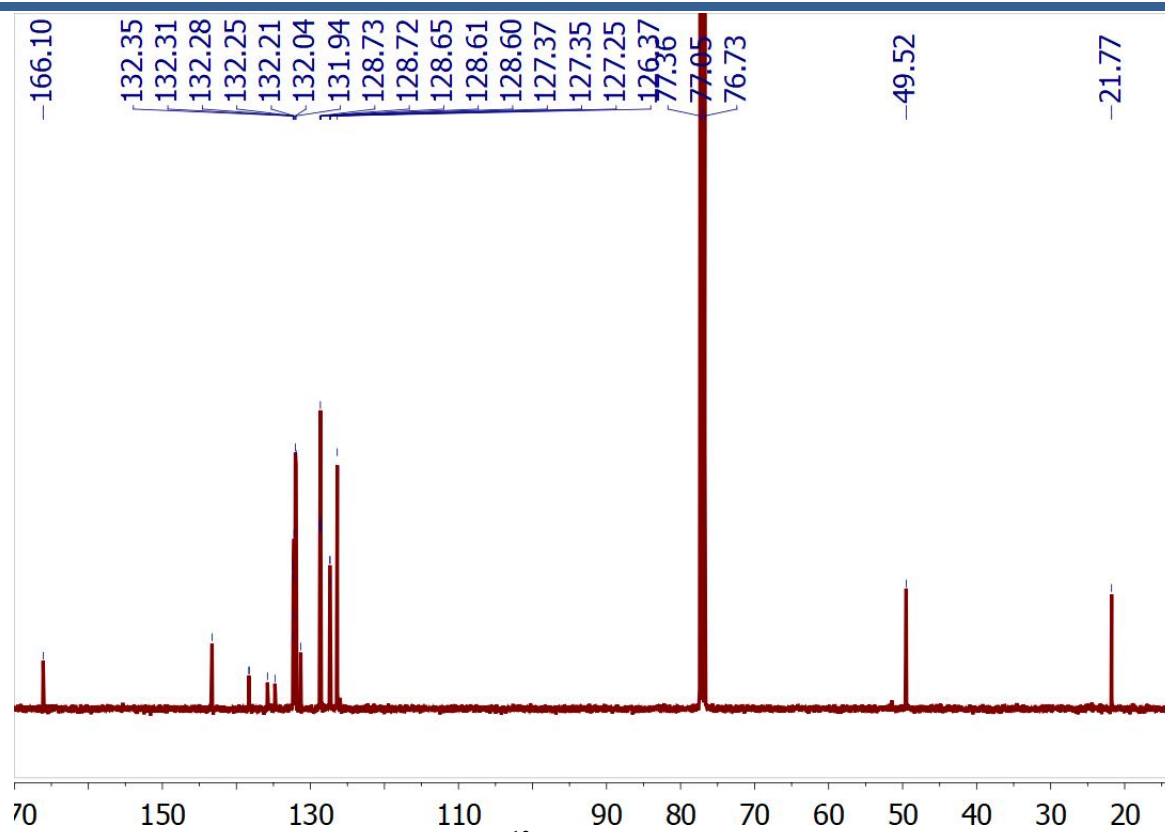


Figure A2.2. ^1H NMR spectrum of **2.1-R**.



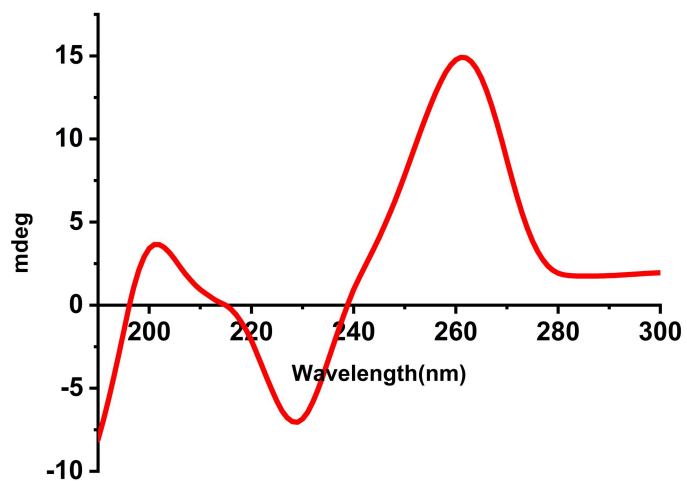


Figure A2.5. CD spectra of 2.1-R.

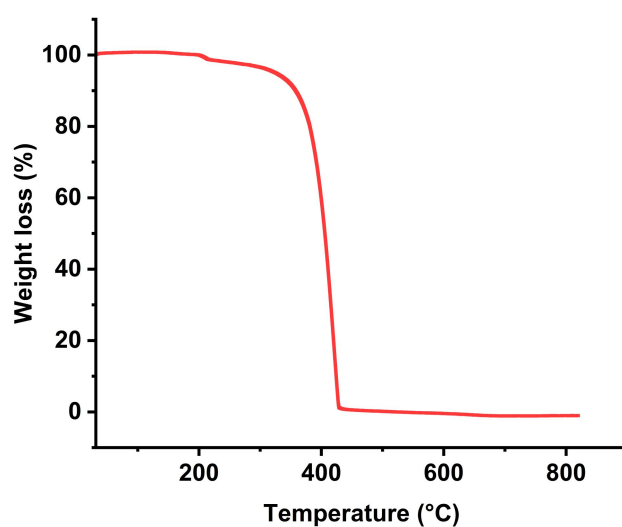


Figure A2.6. TGA graphs of 2.1-R.

Crystallographic information

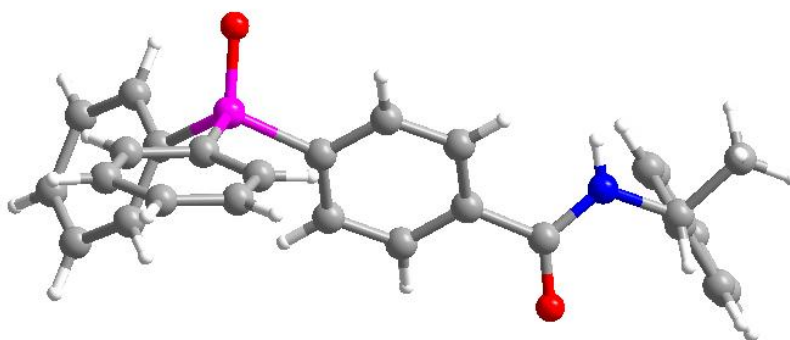


Figure A2.7. SCRXD structures of 2-R.

Table A2.1. Crystallographic Data for **2.1-R**.

Compound	2.1-R
Chemical formula	C ₂₇ H ₂₄ N O ₂ P
Formula weight	425.44
Temperature	150(2) K
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁
a (Å); α(°)	8.952(4); 90
b (Å); β(°)	11.094(5); 92.367(11)
c (Å); γ (°)	11.052(5); 90
V (Å ³); Z	1096.8(9)
ρ (calc.) mg m ⁻³	1.288
μ(Mo Kα) mm ⁻¹	0.150
2θ _{max} (°)	56.774
Flack parameter	-0.01(3)
R(int)	0.0553
Data / param.	5442/281
GOF	1.045
R1 [F>4σ(F)]	0.0312
wR2 (all data)	0.0805
Max. peak/hole(e.Å ⁻³)	0.296/-0.323

Table A2.2. Selected bond lengths [Å] and bond angles [°] for **2.1-R**.

Bond length		Bond angles	
P(1)-O(2)	1.5038(14)	O(2)-P(1)-C(31)	112.12(9)
P(1)-C(31)	1.793(2)	O(2)-P(1)-C(21)	112.71(8)
P(1)-C(21)	1.802(2)	C(31)-P(1)-C(21)	106.73(9)
P(1)-C(11)	1.807(2)	O(2)-P(1)-C(11)	110.54(9)
N(1)-C(1)	1.347(2)	C(31)-P(1)-C(11)	107.77(9)
N(1)-C(2)	1.464(2)	C(21)-P(1)-C(11)	106.68(9)
N(1)-H(1)	0.8800	C(1)-N(1)-C(2)	119.82(16)
O(1)-C(1)	1.236(2)	C(1)-N(1)-H(1)	120.1
		C(2)-N(1)-H(1)	120.1
		O(1)-C(1)-N(1)	122.77(18)
		O(1)-C(1)-C(14)	119.83(18)
		N(1)-C(1)-C(14)	117.39(16)
		N(1)-C(2)-C(3)	111.62(17)
		N(1)-C(2)-C(10)	109.64(17)
		C(3)-C(2)-C(10)	110.35(18)
		N(1)-C(2)-H(2)	108.4
		C(3)-C(2)-H(2)	108.4
		C(10)-C(2)-H(2)	108.4

Chiral recognition studies using ^1H -NMR titrations

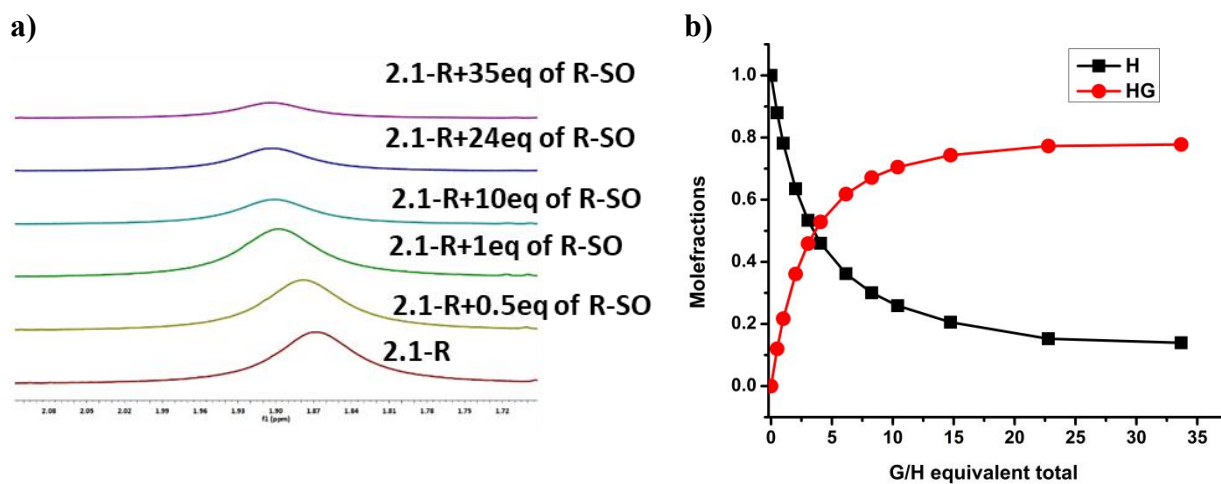


Figure A2.8. Stacked ^1H NMR plots for (a) Proton of **2.1-R** upon sequential addition of **R-SO** (b) Bind fit plots for **2.1-R+R-EP**.

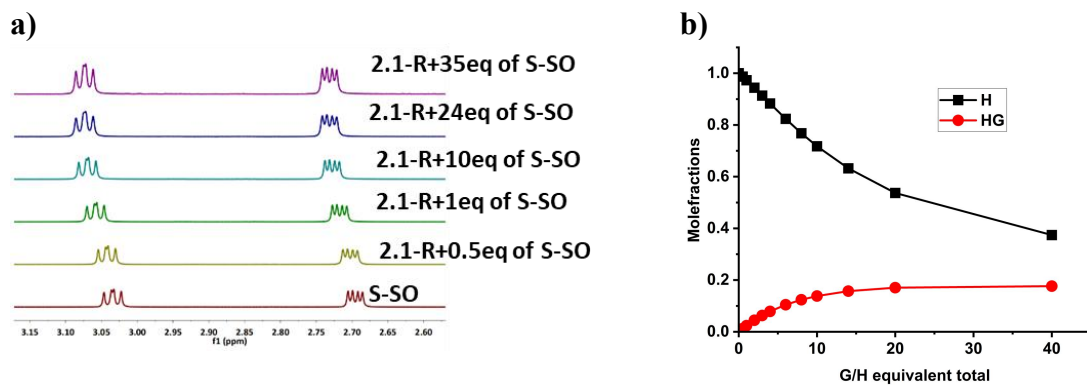


Figure A2.9. Stacked ^1H NMR plots for (a) Proton of **2.1-R** upon sequential addition of **S-SO** (b) Bind fit plots for **2.1-R+S-SO**.

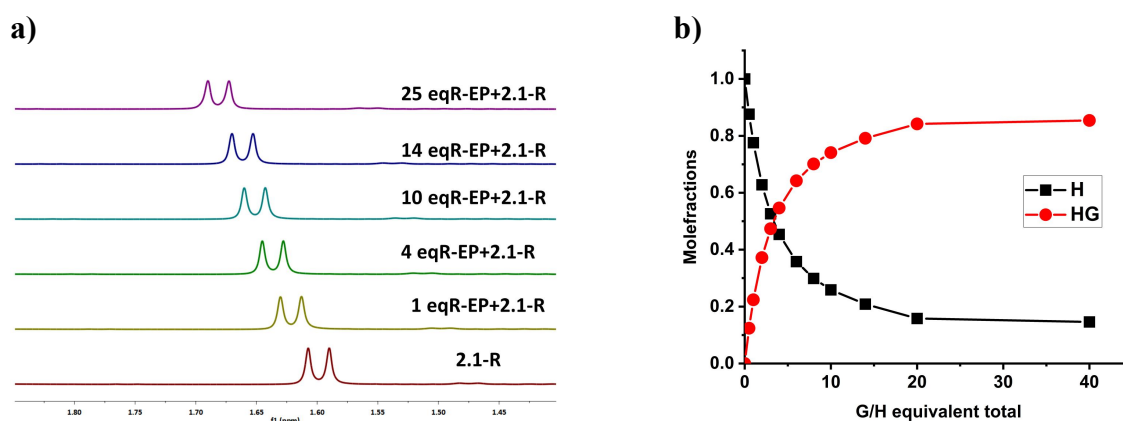


Figure A2.10. Stacked ^1H NMR plots for (a) Proton of **2.1-R** upon sequential addition of **R-EP** (b) Bind fit plots for **2.1-R + R-EP**.

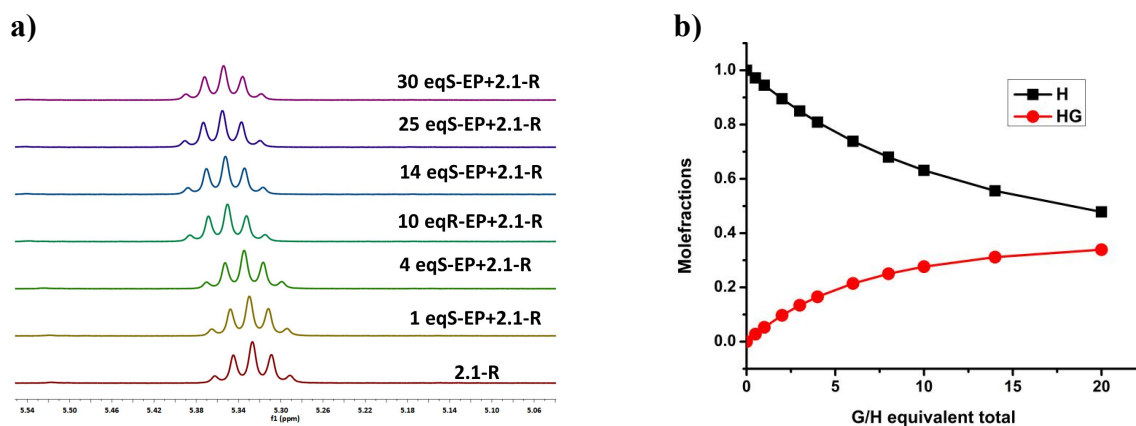


Figure A2.11. Stacked ^1H NMR plots for (a) Proton of **2.1-R** upon sequential addition of **S-EP** (b) Bind fit plots for **2.1-R + S-EP**.

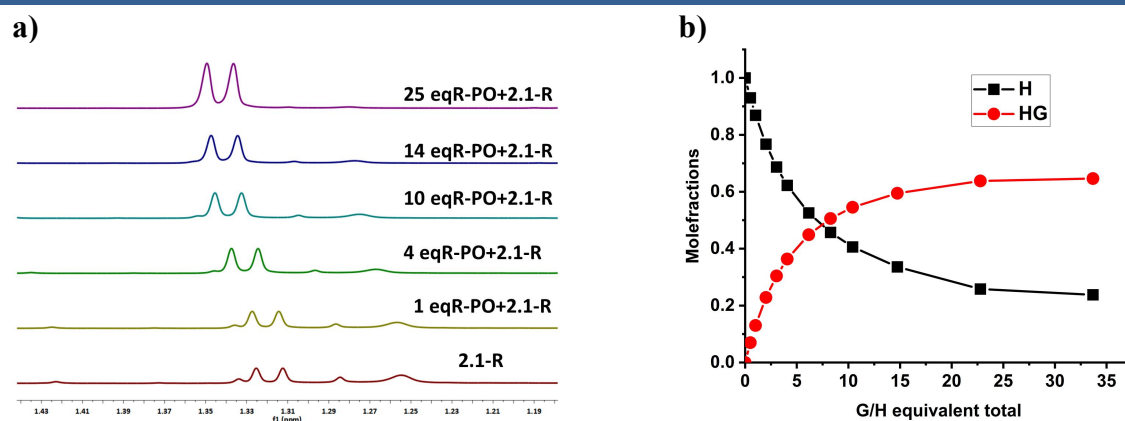


Figure A2.12. Stacked ^1H NMR plots for (a) Proton of **2.1-R** upon sequential addition of **R-PO** (b) Bind fit plots for **2.1-R+R-PO**.

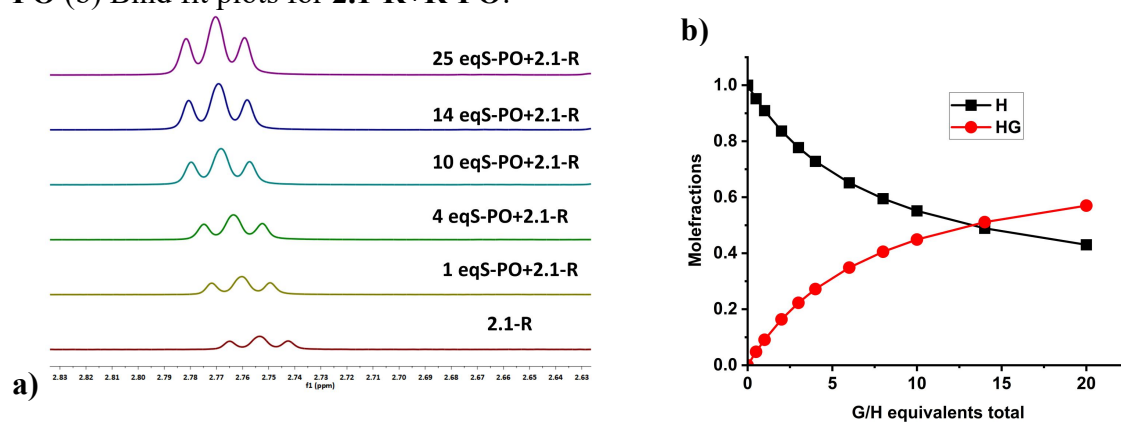


Figure A2.13. Stacked ^1H NMR plots for (a) Proton of **2.1-R** upon sequential addition of **S-PO** (b) Bind fit plots for **2.1-R+S-PO**.

^{31}P NMR spectra of 2.1-R

The ^{31}P NMR spectra of **2.1-R** before and after the addition of 1eq **R-PO**, **R-EP**, **R-SO** and **R-BO** guests showed significant downfield shifts (with δ - δ values 0.53, 0.41, 0.35, and 0.26 ppm) for their respective host guest mixtures of **2.1-R+R-PO**, **2.1-R+R-EP**, **2.1-R+R-SO** and **2.1-R+R-BO**.

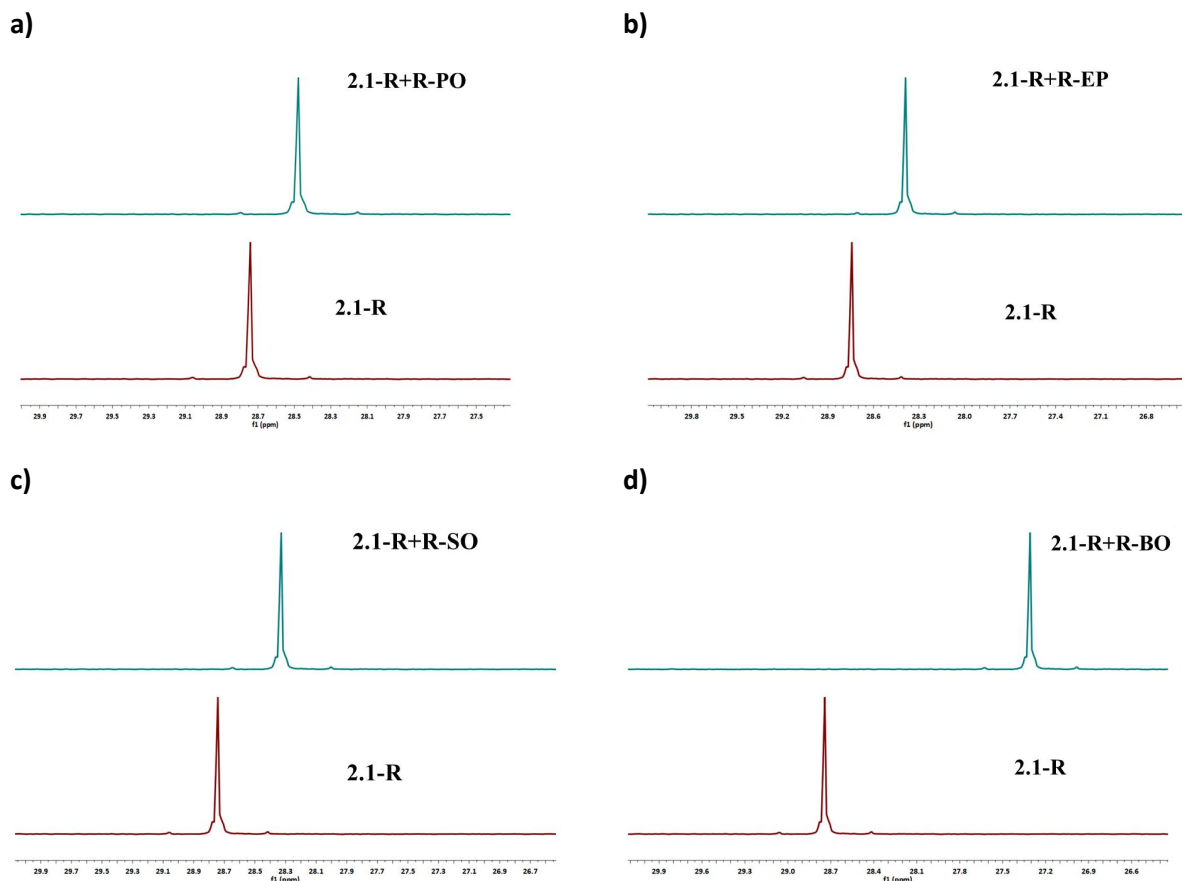


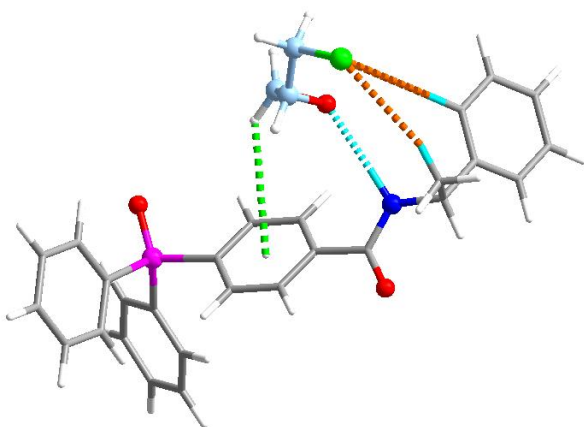
Figure A2.14. ^{31}P -NMR stacked spectra of **2.1-R** and host guest pairs: a) **2.1-R+R-PO**, b) **2.1-R+R-EP**, c) **2.1-R+R-SO**, and d) **2.1-R+R-BO**

Optimised structures of the host-guest Complexes and their binding energy calculations

Table A2.3. Gas phase binding energy for chiral phosphazene (**2.1-R**) host-guest complexes.

Host+Guest	Binding Energy, E (kcal/mol)	$\Delta E_{\text{pref.}}$ (kcal/mol)
2.1-R+ R-BO	-49.2	29.8
2.1-R+S-BO	-19.4	
2.1-R+ R-SO	-37.4	18.1
2.1-R+ S-SO	-19.3	
2.1-R+R-EP	-29.8	16.4
2.1-R+S-EP	-7.4	
2.1-R+R-PO	-19.8	7.01
2.1-R+S-PO	-12.79	

a)



b)

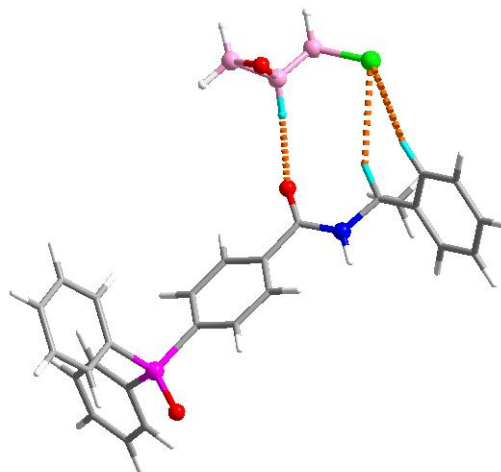


Figure A2.15. DFT optimised structures for host-guest complexes of (a) **2.1-R+R-EP** and (b) **2.1-R+S-EP**, N blue; O red; Cl green; H white. The non-classical interactions ($X=N, O$) are shown in dotted lines: cyan $N-H\cdots X$, purple $\pi\cdots\pi$, green $C-H\cdots\pi$, and orange polar $X-H\cdots\pi$.

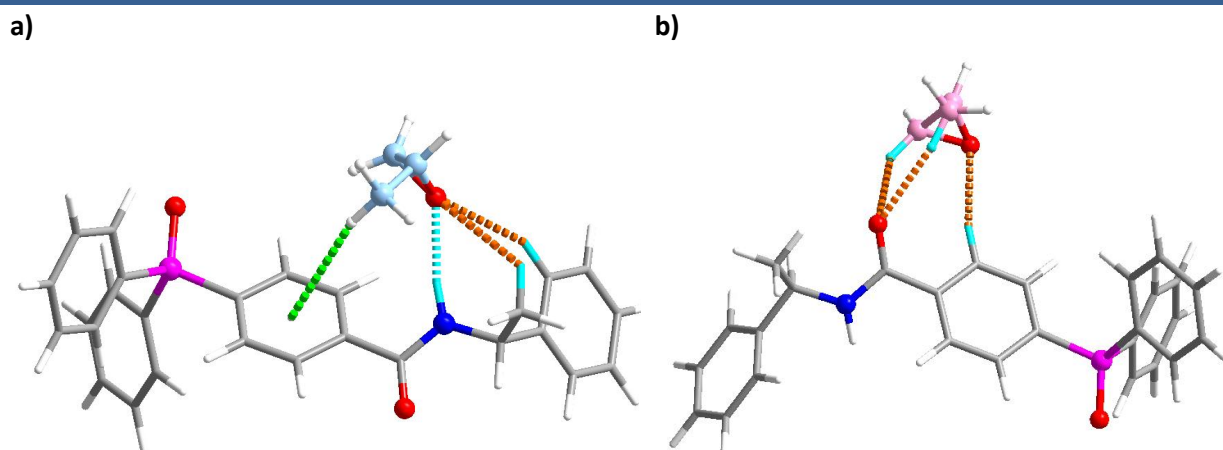


Figure A2.16 DFT optimised structures for host-guest complexes of (a) **2.1-R+R-PO** and (b) **2.1-R+S-PO**, N blue; O red; Cl green; H white. The non-classical interactions (X=N, O) are shown in dotted lines: cyan N-H $\cdots$ X, purple $\pi\cdots\pi$, green C-H $\cdots\pi$, and orange polar X-H $\cdots\pi$.

Table A2.4. Bond length and bond angles for the host-guest complexes of the chiral phosphazene.

Host + Guest	Interactions(D-H $\cdots$ A)	d(H $\cdots$ A)	d(D $\cdots$ A)	<DHA	Type of Interaction
2.1-R+R-EP	C29-H46 $\cdots$ Cl40	3.8055	4.8247	156.95(3)	Weak H-Bond
	C24-H34 $\cdots$ Cl40	3.1731	4.2332	163.14(5)	Weak H-Bond
	N4-H32 $\cdots$ O37	2.1570	3.1506	165.54(2)	H-Bond
	C36-H64 $\cdots\pi$	3.5323	4.3468	132.90(9)	CH- π
2.1-R+S-EP	C23-H50 $\cdots$ Cl64	3.2916	4.1926	141.00(5)	Weak H-Bond
	C11-H33 $\cdots$ Cl64	3.0841	4.0771	151.40(6)	Weak H-Bond
	C56-H59 $\cdots$ O3	2.2510	3.3336	172.05(3)	Weak H-Bond
2.1-R+R-PMO	C49-H56 $\cdots$ O2	2.5888	3.5226	143.45(6)	Weak H-Bond
	C43-H55 $\cdots$ O2	2.4003	3.4617	161.93(1)	Weak H-Bond
	C5-H71 $\cdots$ O38	3.0606	3.5373	107.20(3)	Weak H-Bond
	N4-H32 $\cdots$ O38	2.1369	3.1423	169.868	H-Bond
	C29-H75 $\cdots$ O38	2.7350	3.7734	159.65(6)	Weak H-Bond
	C24-H35 $\cdots$ O38	3.1143	3.8737	126.95(7)	Weak H-Bond
2.1-R+S-PMO	C8-H54 $\cdots$ O38	2.2916	3.3699	170.58(4)	Weak H-Bond

	C37-H74...O2	2.5308	3.2460	122.38(6)	Weak H-Bond
	C39-H45...O2	2.5255	3.2509	123.16(6)	Weak H-Bond
	C23-H44... π	3.2889	4.3207	158.78(2)	CH- π
2.1-R+R-PO	C29-H48...O58	2.5719	3.5787	153.54(4)	Weak H-Bond
	C24-H34...O58	3.0589	3.8011	125.45(6)	Weak H-Bond
	N4-H32...O58	2.0424	3.0388	165.92(8)	H-Bond
	C62-H65... π	3.5948	4.6331	159.01(9)	CH- π
2.1-R+S-PO	C16-H50...O65	2.3412	3.4089	167.18(5)	Weak H-Bond
	C58-H61...O3	2.5270	3.5362	152.94(9)	Weak H-Bond
	C62-H64...O3	2.4504	3.3949	144.37(7)	Weak H-Bond
2.1-R+R-SO	C29-H56...O38	2.6027	3.6285	156.93(3)	Weak H-Bond
	C24-H34...O38	2.9887	3.7730	128.75(7)	Weak H-Bond
	N4-H32...O38	2.1428	3.1292	163.57(3)	H-Bond
	C67-H71...O2	2.3650	3.4216	163.30(7)	Weak H-Bond
2.1-R+R-SO	C10-H53...O61	2.2854	3.3283	160.06(3)	Weak H-Bond
	C56-H57...O2	2.4862	3.2251	124.14(9)	Weak H-Bond
	C59-H60...O2	2.5617	3.2807	122.68(9)	Weak H-Bond

Spectral, thermal, optical, and structural data

a)

b)

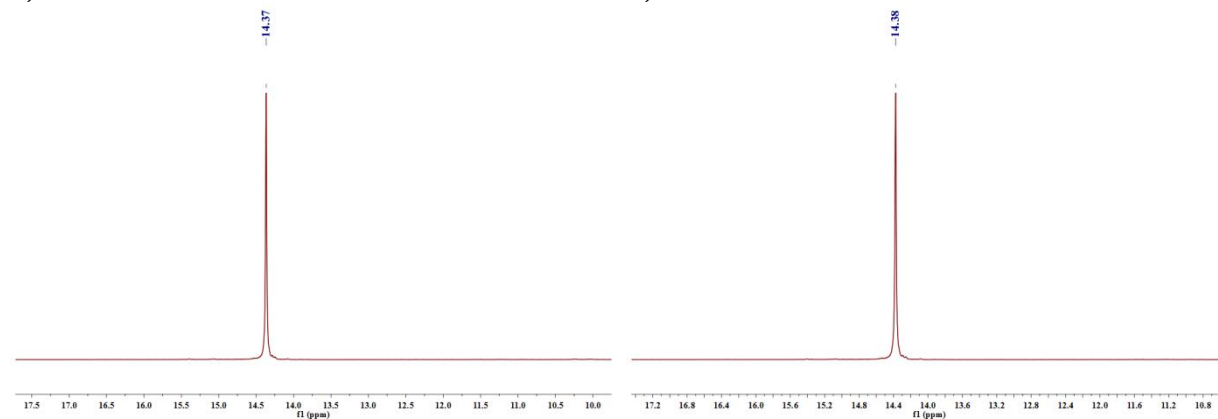


Figure A3.1: ^{31}P NMR spectra of a) **3.1-R** and b) **3.2-S**

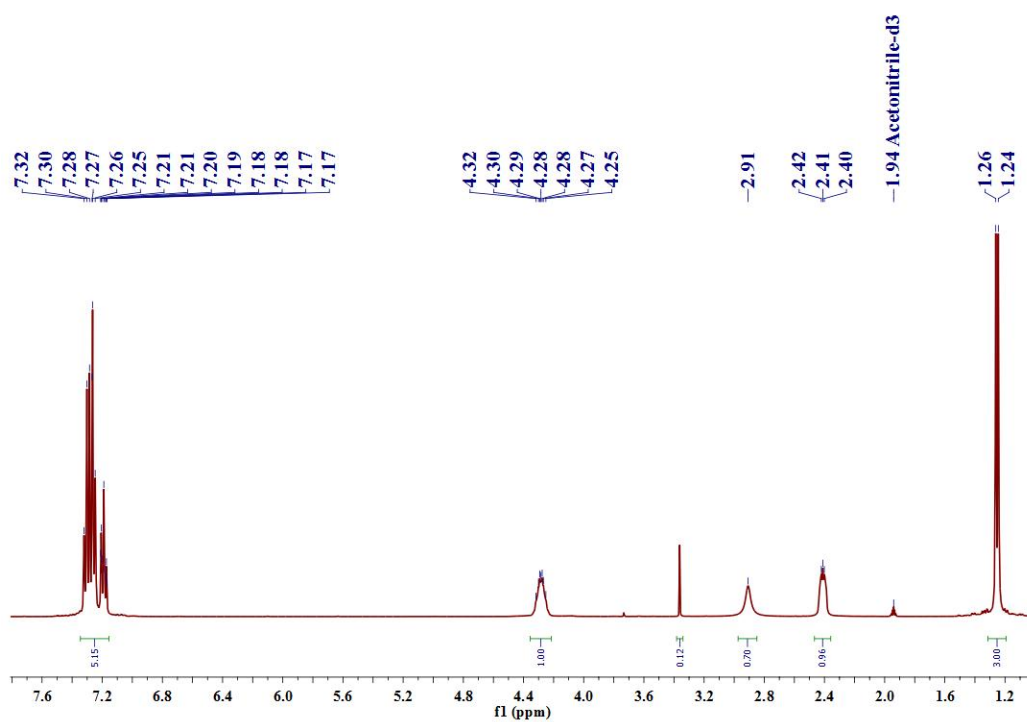


Figure A3.2: ^1H NMR spectrum of **3.1-R**.

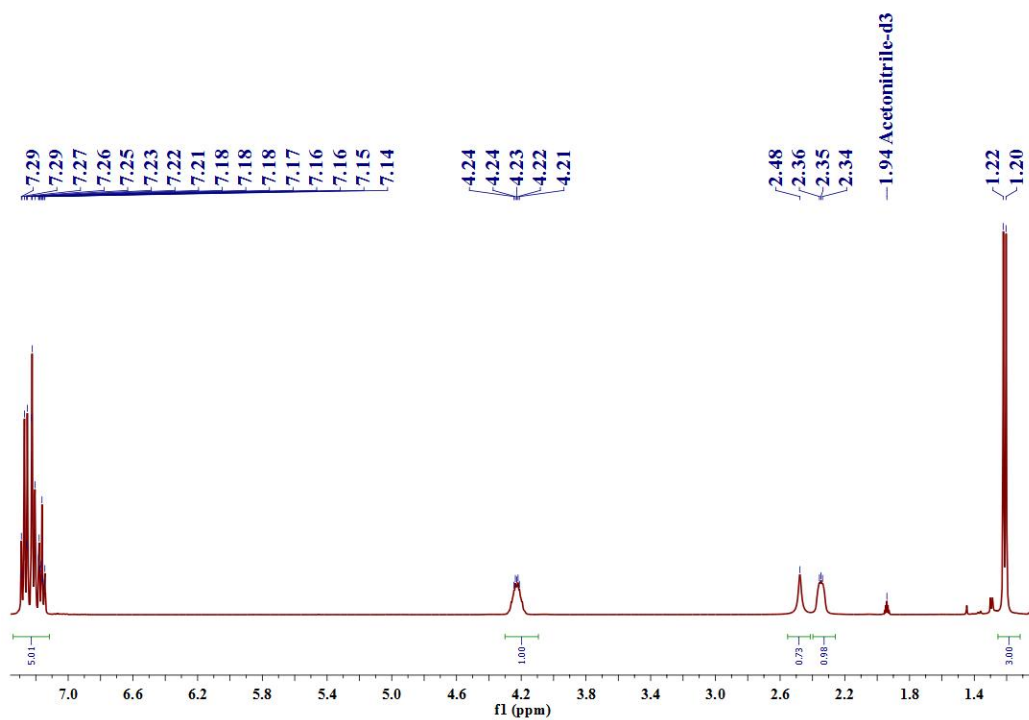


Figure A3.3: ¹H NMR spectrum of **3.1-S**.

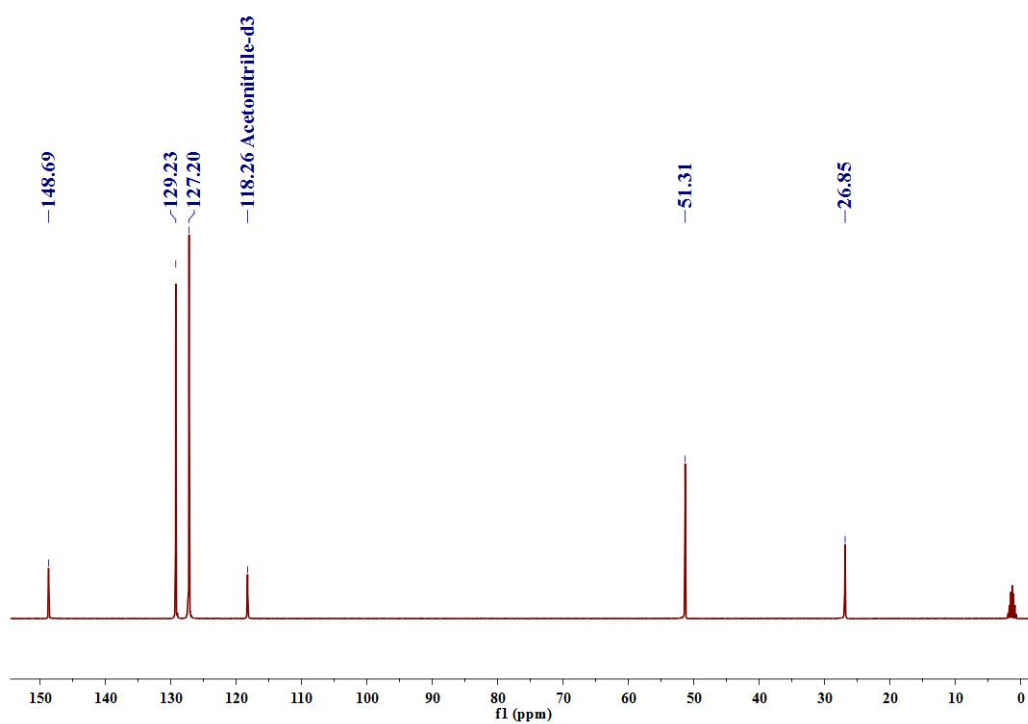


Figure A3.4: ¹³C NMR spectra of **3.1-R**.

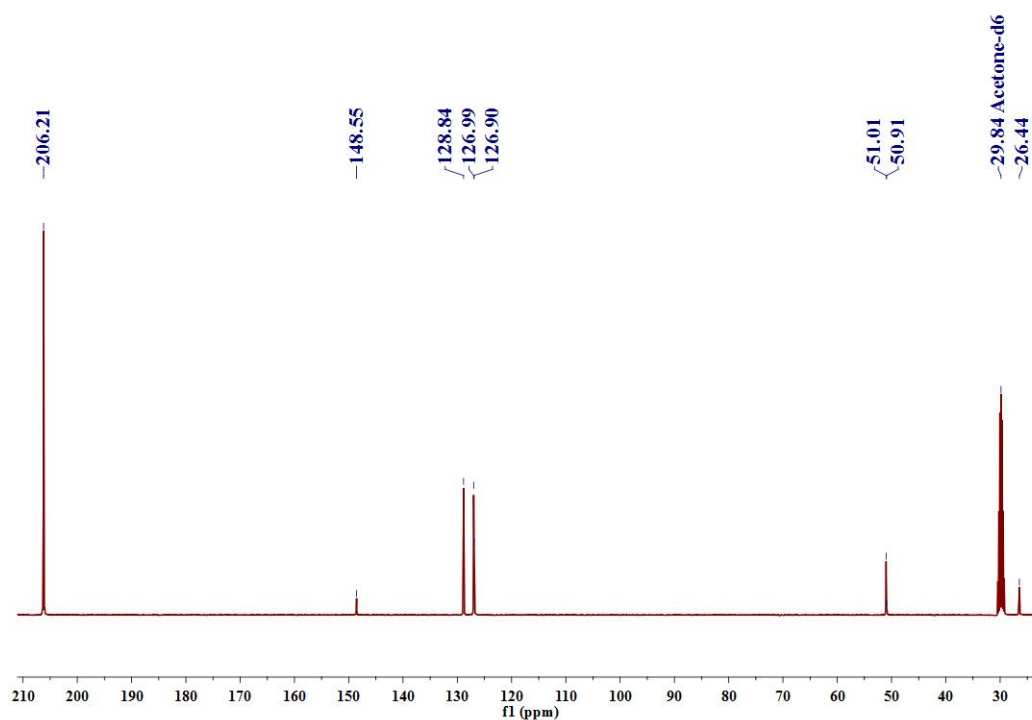


Figure A3.5: ¹³C NMR spectra of 3.1-S.

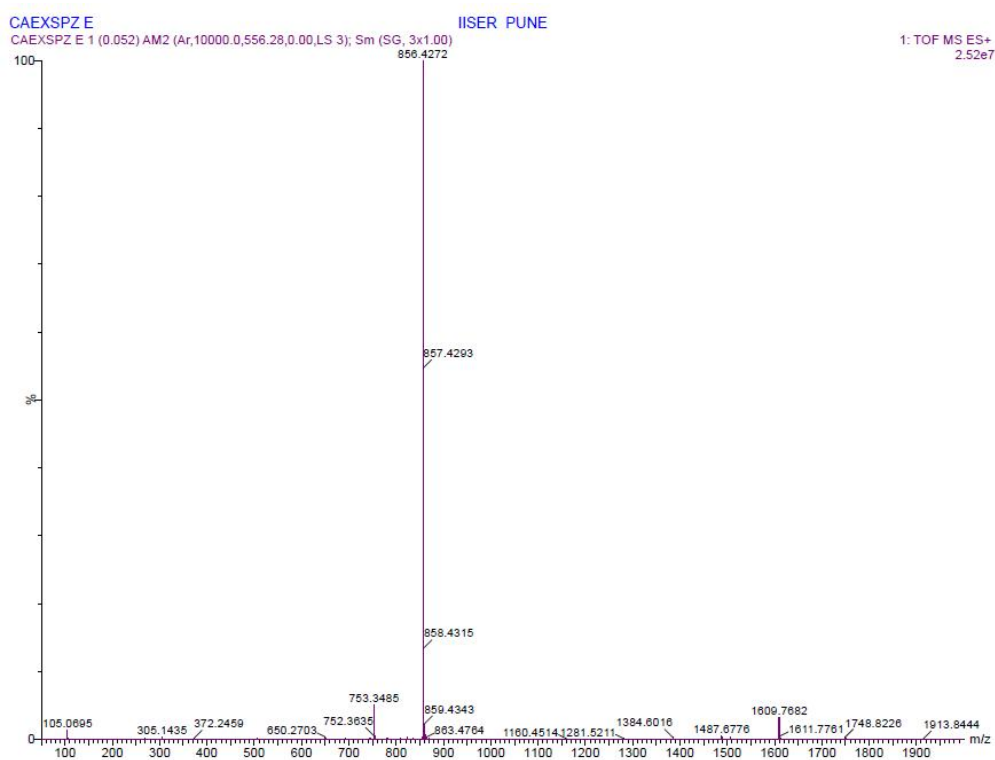


Figure A3.6: ESI-MS (+) mass spectrum of 3.1-R.

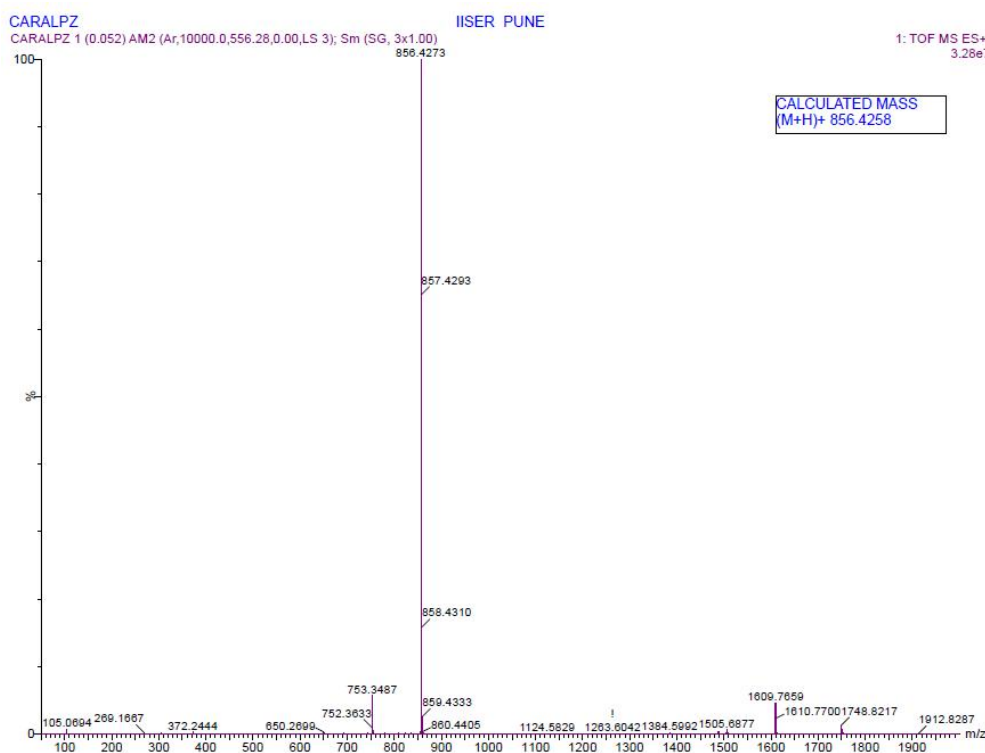


Figure A3.7: ESI-MS (+) mass spectrum of 3.1-S.

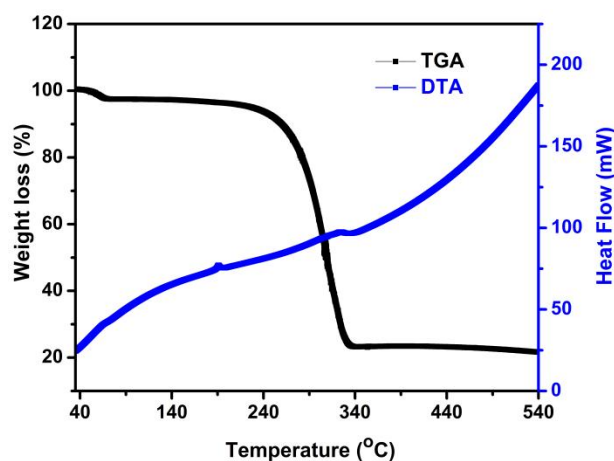
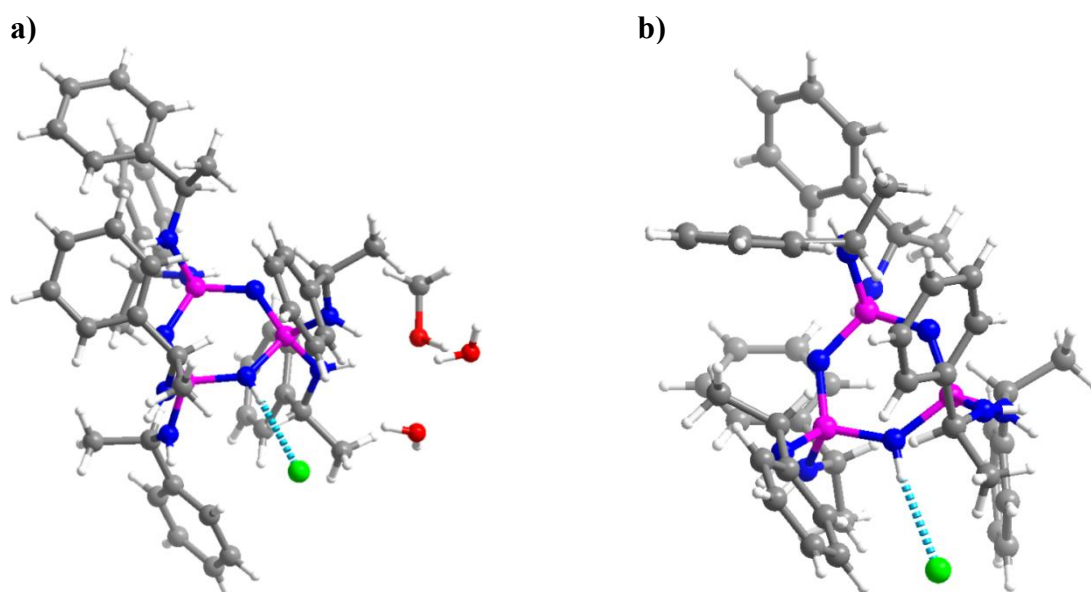


Figure A3.8: TGA graphs of 3.1-R.

Table S1: Specific rotation (α_D) values for cages 3.1-R and 3.1-S.

Compounds	Specific rotation (α_D)
3.1-R	+111
3.1-S	-119

Crystallographic information**Figure A3.9:** SCRXD structures of a) **3.2-R** and b) **3.2-S**.**Table S2:** Crystallographic Data for **3.2-R** and **3.2-S**.

Compound	3.2-R	3.2-S
Chemical formula	C ₄₉ H ₆₉ Cl N ₉ O ₃ P ₃	C ₄₈ H ₆₁ Cl N ₉ P ₃
Formula weight	960.49	892.41
Temperature	150(2) K	150(2) K
Crystal system	Monoclinic	Monoclinic
Space group	<i>P</i> 2 ₁	<i>P</i> 2 ₁
a (Å); α(°)	14.0663(19); 90	13.051(6); 90
b (Å); β(°)	11.2190(15); 96.890(4)	9.790(4); 105.887(9)
c (Å); γ (°)	16.280(2); 90	20.262(8); 90
V (Å ³); Z	2550.6(6)	2490.0(18)
ρ (calc.) mg m ⁻³	1.251	1.190
μ(Mo Kα) mm ⁻¹	0.219	0.215
2θ _{max} (°)	56.774	50.09
Flack parameter	-0.01(2)	0.2(3)
R(int)	0.0579	0.1629
Data / param.	12733/607	8712/456
GOF	1.013	1.145
R1 [F > 4σ(F)]	0.0452	0.1186
wR2 (all data)	0.1121	0.3166
Max. peak/hole(e.Å ⁻³)	1.301/-0.687	1.444/-0.761

Table S3: Selected bond lengths [Å] and bond angles [°] for **3.2-R**.

Bond length	Bond angles
P(1)-N(1)	N(1)-P(1)-N(3)
P(1)-N(3)	N(1)-P(1)-N(11)
P(1)-N(11)	N(3)-P(1)-N(11)
P(1)-N(12)	N(1)-P(1)-N(12)
N(1)-P(2)	N(3)-P(1)-N(12)
P(2)-N(22)	N(11)-P(1)-N(12)
P(2)-N(21)	P(2)-N(1)-P(1)
P(2)-N(2)	N(1)-P(2)-N(22)
N(2)-P(3)	N(1)-P(2)-N(21)
N(2)-H(2)	N(22)-P(2)-N(21)
P(3)-N(3)	N(1)-P(2)-N(2)
P(3)-N(32)	N(22)-P(2)-N(2)
P(3)-N(31)	N(21)-P(2)-N(2)
	P(2)-N(2)-P(3)
	P(2)-N(2)-H(2)
	P(3)-N(2)-H(2)
	N(3)-P(3)-N(32)
	N(3)-P(3)-N(31)
	N(32)-P(3)-N(31)
	N(3)-P(3)-N(2)
	N(32)-P(3)-N(2)
	N(31)-P(3)-N(2)
	P(3)-N(3)-P(1)

Chiral recognition studies using ^1H -NMR titrations

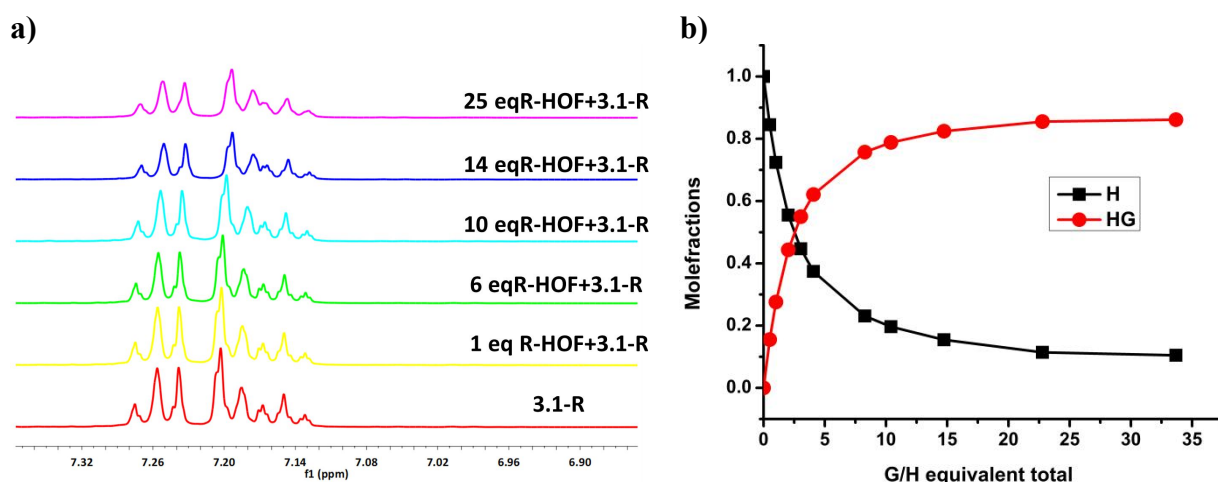


Figure A3.10: Stacked ^1H NMR plots for (a) Proton of **3.1-R** upon sequential addition of **R-HOF** (b) Bind fit plots for **3.1-R + R-HOF**.

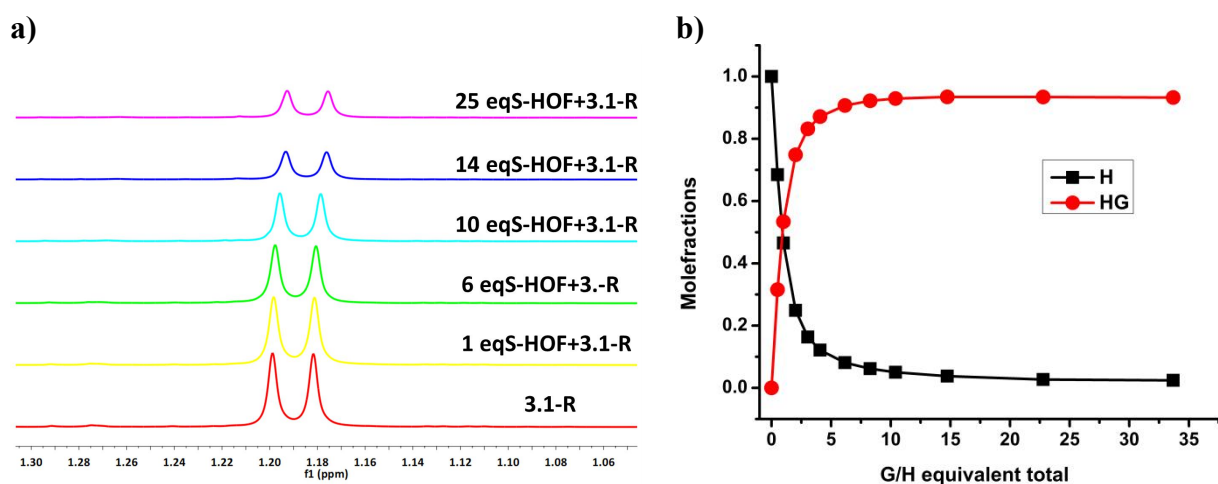


Figure A3.11: Stacked ^1H NMR plots for (a) Proton of **3.1-R** upon sequential addition of **S-HOF** (b) Bind fit plots for **3.1-R + S-HOF**.

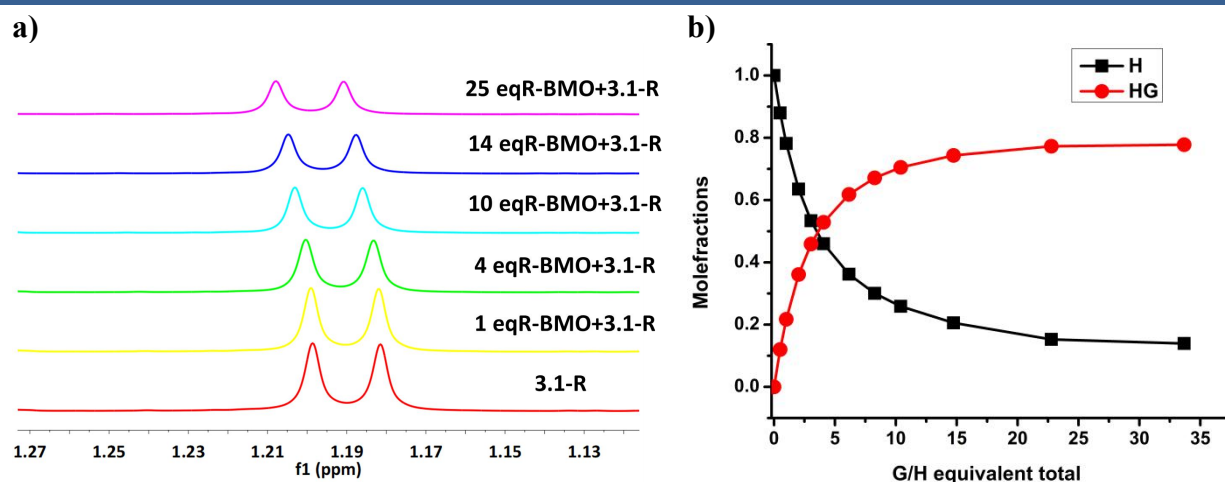


Figure A3.12: Stacked ^1H NMR plots for (a) Proton of **3.1-R** upon sequential addition of **R-BMO** (b) Bind fit plots for **3.1-R+R-BMO**.

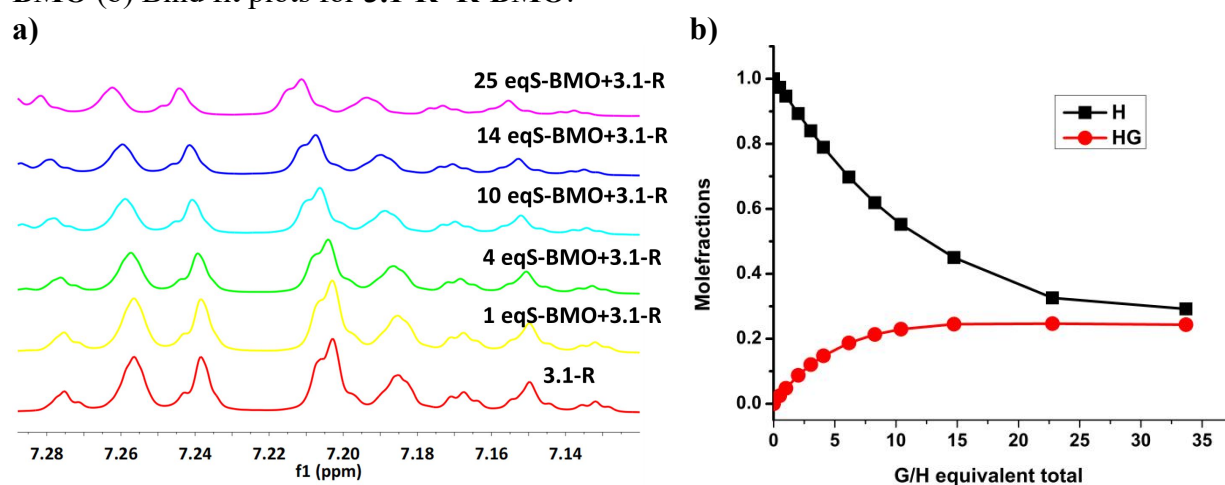


Figure A3.13: Stacked ^1H NMR plots for (a) Proton of **3.1-R** upon sequential addition of **S-BMO** (b) Bind fit plots for **3.1-R+S-BMO**.

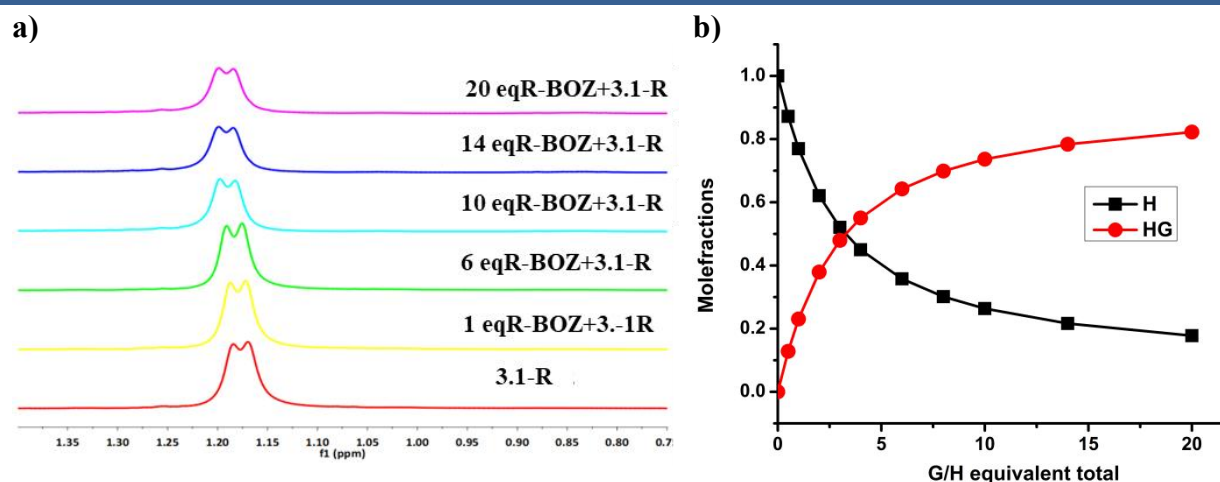


Figure A3.14: Stacked ^1H NMR plots for (a) Proton of **3.1-R** upon sequential addition of **R-BOZ** (b) Bind fit plots for **3.1-R+R-BOZ**.

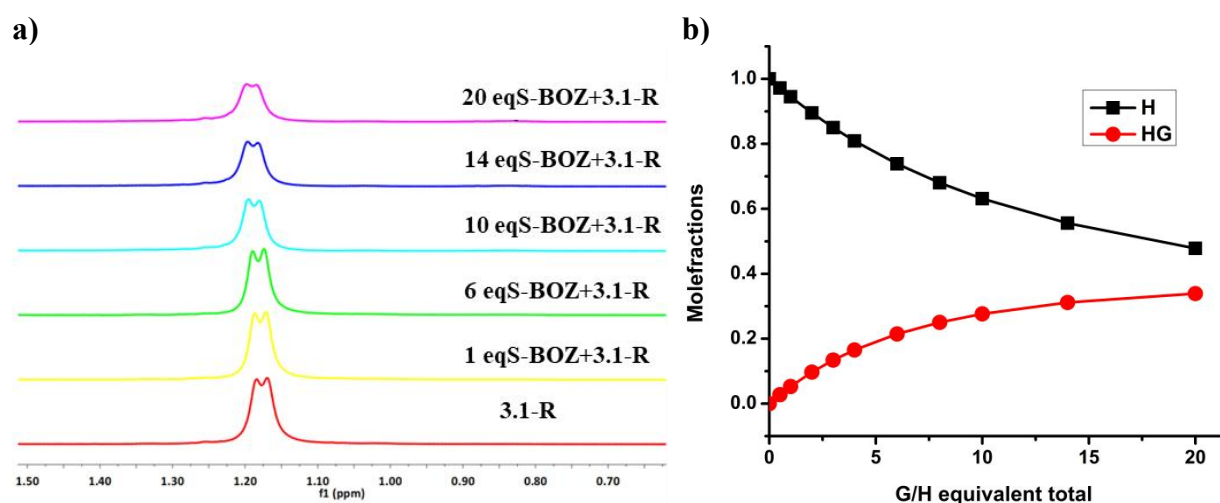


Figure A3.15: Stacked ^1H NMR plots for (a) Proton of **3.1-R** upon sequential addition of **S-BOZ** (b) Bind fit plots for **3.1-R+S-BOZ**.

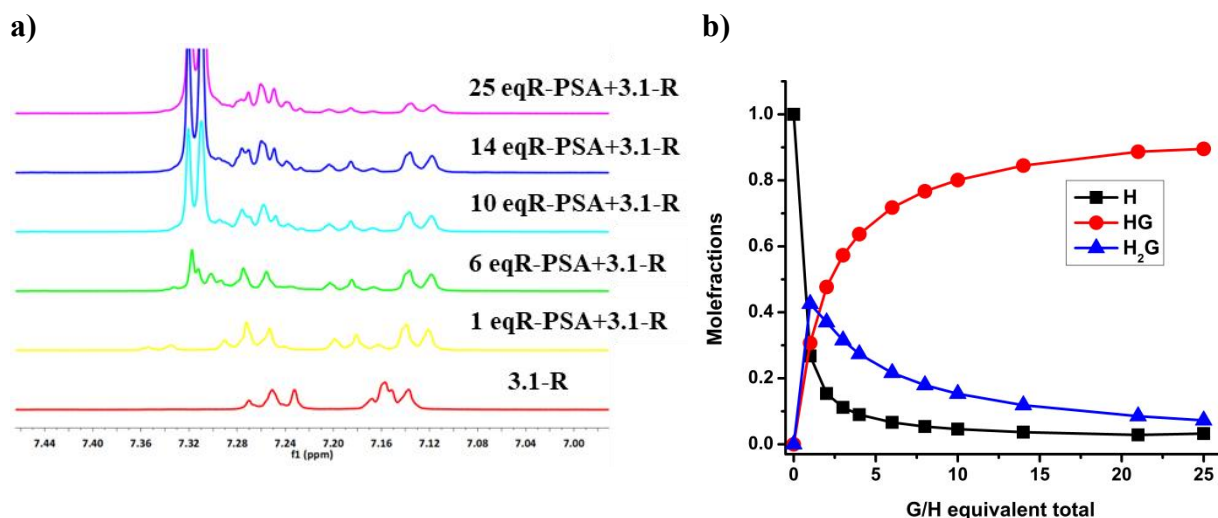


Figure A3.16: Stacked ^1H NMR plots for (a) Proton of **3.1-R** upon sequential addition of **R-PSA** (b) Bind fit plots for **3.1-R+R-PSA**.

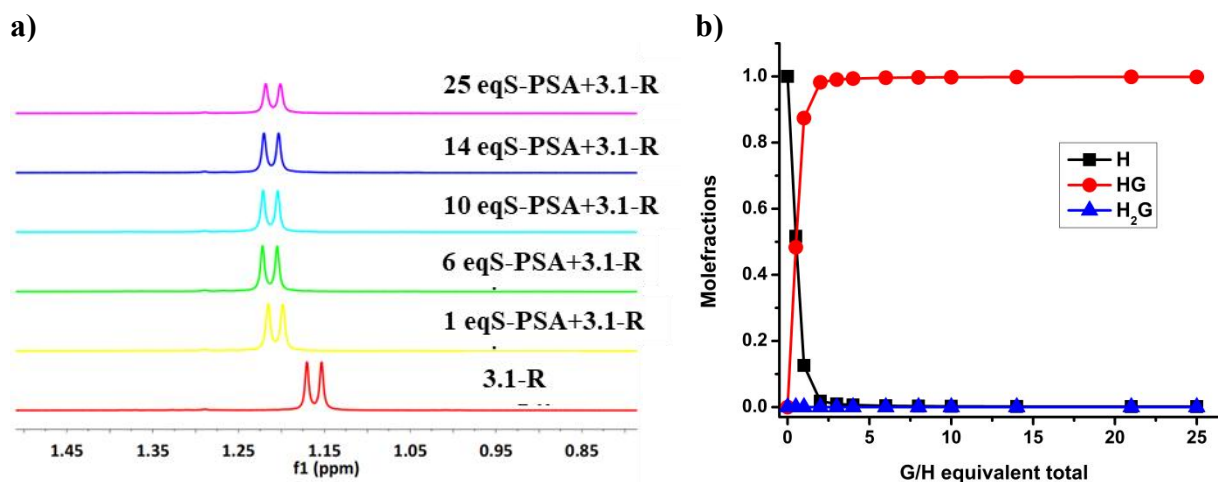


Figure A3.17: Stacked ^1H NMR plots for (a) Proton of **3.1-R** upon sequential addition of **S-PSA** (b) Bind fit plots for **3.1-R+S-PSA**.

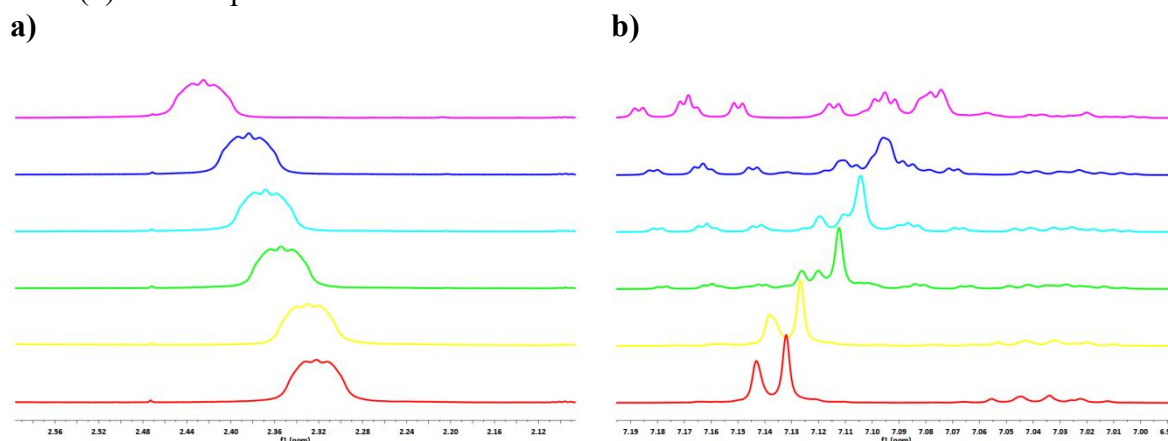
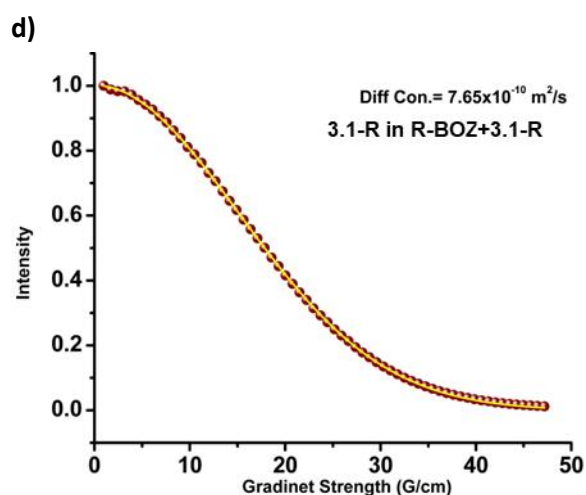
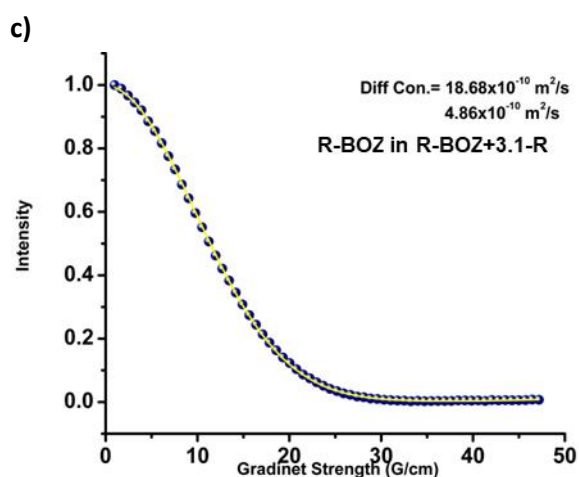
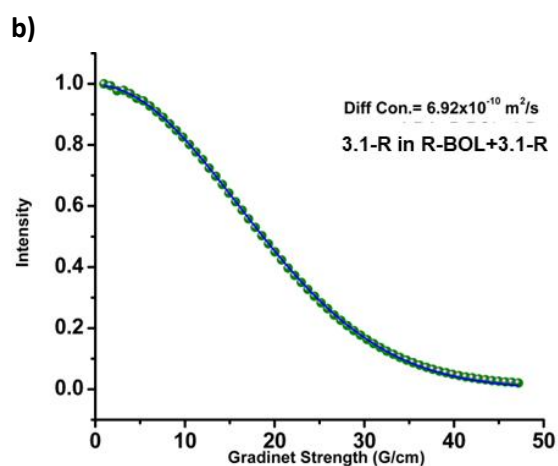
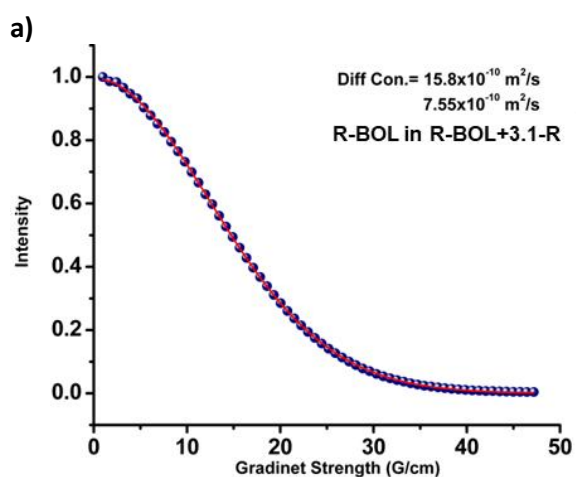


Figure A3.18: ^1H -NMR titration plots **3.1-R+Rac-BOL** showing shifts in the a) N-H protons and b) C-H and Me-H protons of the alpha-methylbenzylamino substituents of **3.1-R**.

Characterizations data for host-guest complexes: DOSY NMR data

Table S4: Diffusion coefficients as obtained from the DOSY experiment for host and different guests in the studied host-guest systems.

1+Guest	Diffusion Coefficient ($\text{E}^{-10} \text{ m}^2/\text{s}$)		
	Guest		Host
	Free	Bound	Bound
BOL	15.8(7)	7.5(5)	6.9(2)
BOZ	18.6(8)	4.8(6)	7.6(5)
PSA	16.1(1)	7.0(8)	7.2(7)



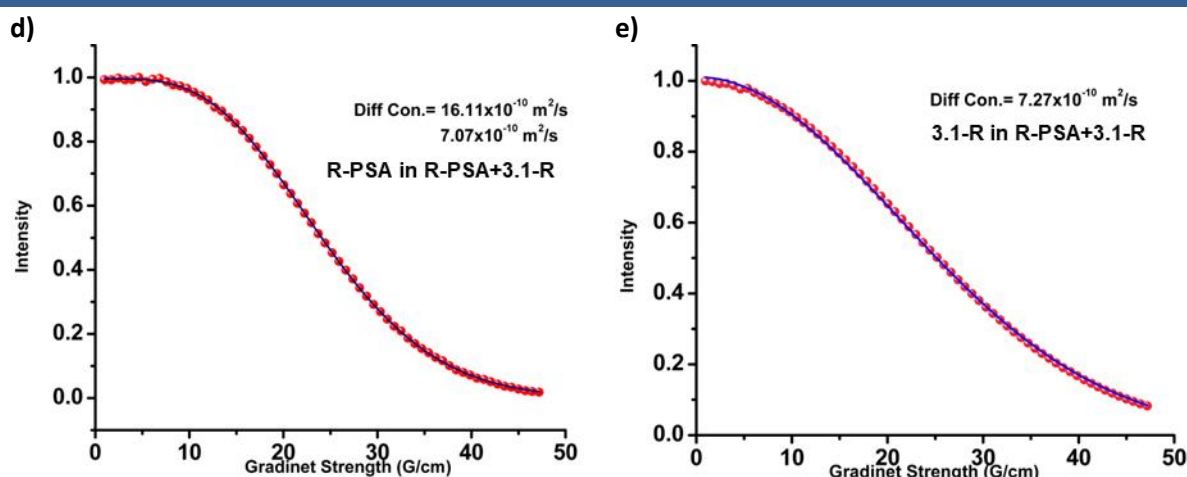
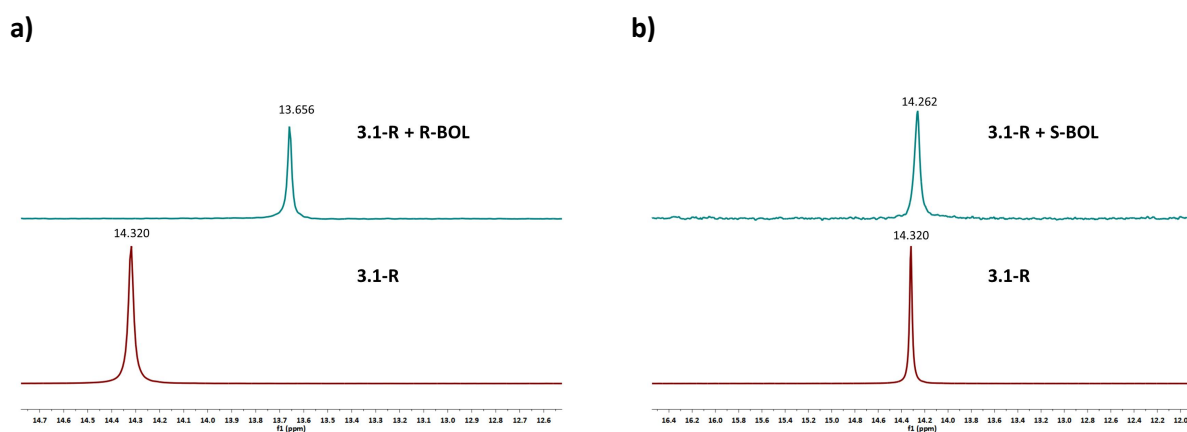


Figure A3.19: DOSY NMR data (298K) for the host-guest events of **3.1-R+R-BOL**, **3.1-R+R-BOZ**, and **3.1-R+R-PSA**. Integral decay profile of guest protons (left), and host protons (right) in the host-guest system plotted as a function of gradient strength. Diffusion coefficients obtained for free and bound guest molecules, a) **3.1-R+R-BOL**, c) **3.1-R+R-BOZ**, and e) **3.1-R+R-PSA**. Diffusion coefficients obtained for **3.1-R** in the host-guest mixtures of b) **3.1-R+R-BOL**, d) **3.1-R+R-BOZ**, and f) **3.1-R+R-PSA**. All the DOSY NMR data were fit either to biexponential (in a, c, e) and mono-exponential (b, d, f) decay curves. The dots represent experimental data, and the solid lines show the best fits in all figures (a-f).

³¹P NMR spectra of 3.1-R

The ³¹P NMR spectra of **3.1-R** before and after the addition of 1eq **R-BOL**, **R-PSA** and **R-BOZ** guests showed significant downfield shifts (with δ - δ values 0.664, 0.315 0.243 ppm) for their respective host guest mixtures of **3.1-R+R-BOL**, **3.1-R+R-PSA** and **3.1-R+R-BOZ** (Figure A3.18.). Whereas, for the corresponding **3.1-R+S-BOL**, **3.1-R+S-PSA** and **3.1-R+S-BOZ** mixtures, only negligible shifts have been observed. This signifies the definitive host-guest formation of **3.1-R** with the R-isomers of the guest molecules.



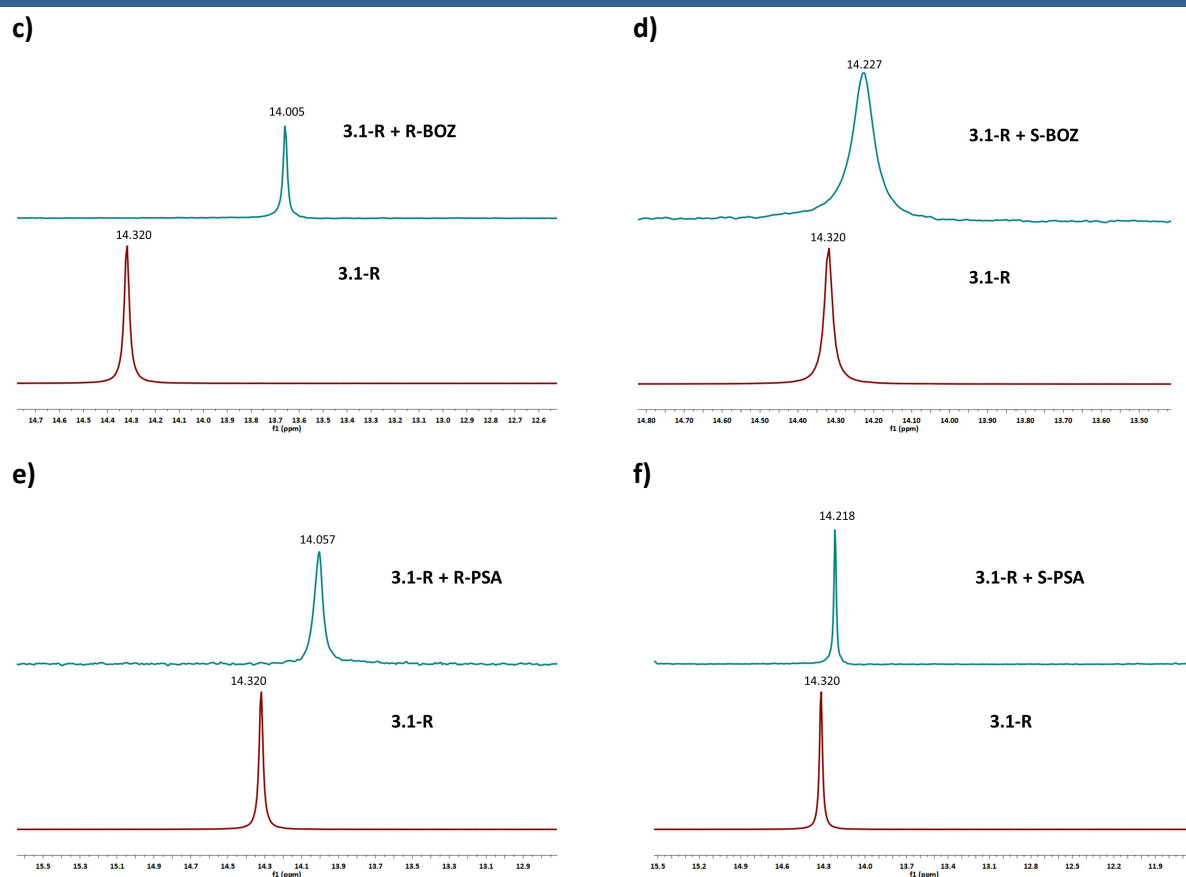


Figure A3.20: ^1H -NMR stacked spectra of **3.1-R** and host guest pairs: a) **3.1-R+R-BOL**, b) **3.1-R+S-BOL**, c) **3.1-R+R-BOZ**, d) **3.1-R+S-BOZ**, e) **3.1-R+R-PSA** and f) **3.1-R+S-PSA**

Optimised structures of the host-guest Complexes and their binding energy calculations

Table S5: Gas phase binding energy for chiral phosphazene (**3.1-R**) host-guest complexes.

Host+Guest	Binding Energy, E (kcal/mol)	$\Delta E_{\text{pref.}}$ (kcal/mol)
3.1-R+ R-BOL	-18.75	14.51
3.1-R+S-BOL	-4.24	
3.1-R+ R-BOZ	-58.79	10.42
3.1-R+ S-BOZ	-48.37	
3.1-R+R-HOF	-29.86	7.6
3.1-R+S-HOF	-22.26	
3.1-R+R-BMO	-15.26	2.37
3.1-R+S-BMO	-12.89	
3.1-R+R-PSA	-58.1	18.8
3.1-R+S-PSA	-39.3	

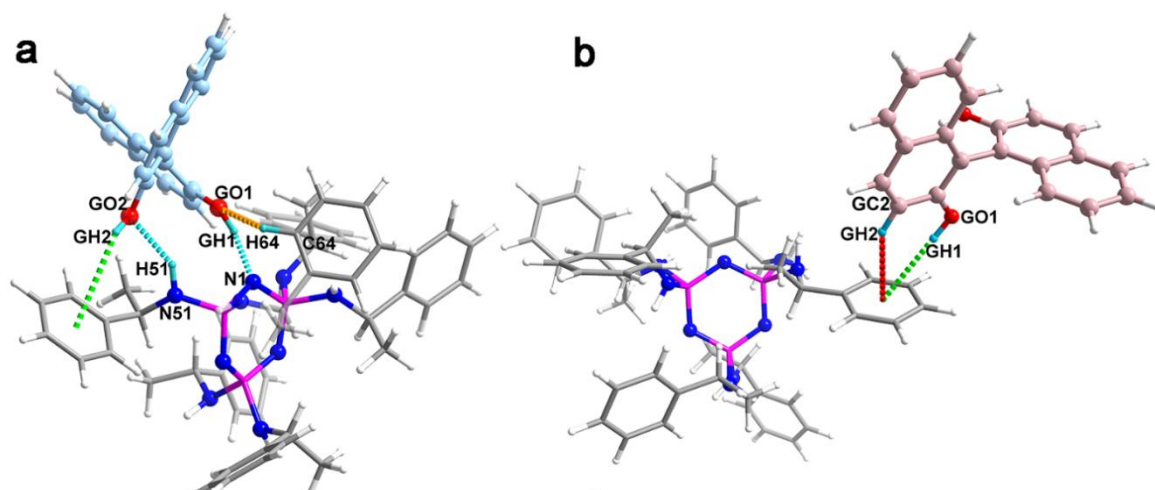


Figure A3.21: DFT optimised structures for host-guest complexes of (a) **3.1-R+R-BOL** and (b) **3.1-R+S-BOL**, N blue; O red; Cl green; H white. The non-classical interactions ($X=N, O$) are shown in dotted lines: green $O-H\cdots X$, yellow $C-H\cdots X$ and blue $C-H\cdots \pi$.

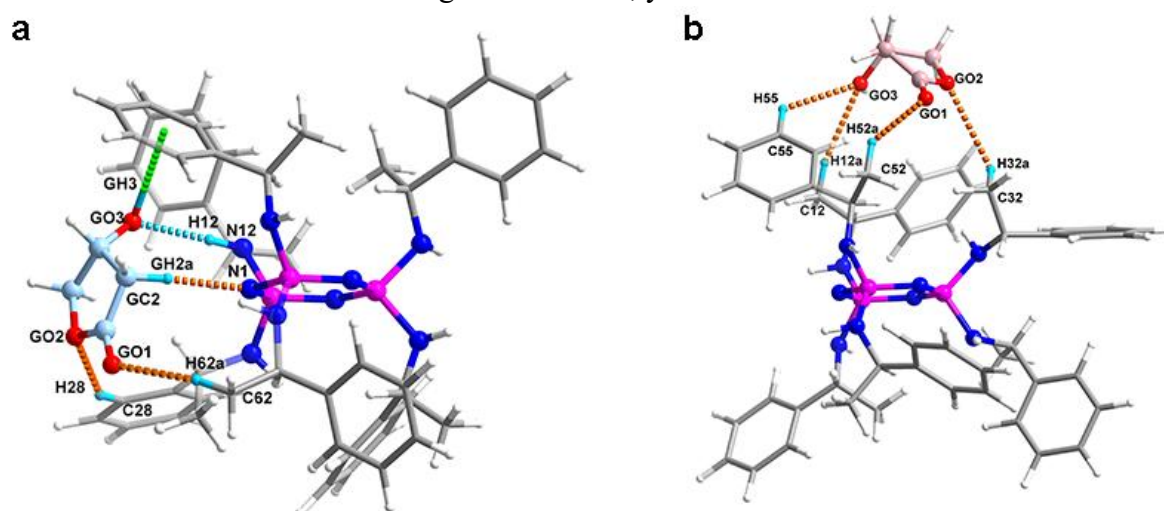


Figure A3.22: DFT optimised structures for host-guest complexes of (a) **3.1-R+R-HOF[#]** and (b) **3.1-R+S-HOF[#]**, N blue; O red; Cl green; H white. The non-classical interactions ($X=N, O$) are shown in dotted lines: green $O-H\cdots X$, yellow $C-H\cdots X$ and blue $C-H\cdots \pi$.

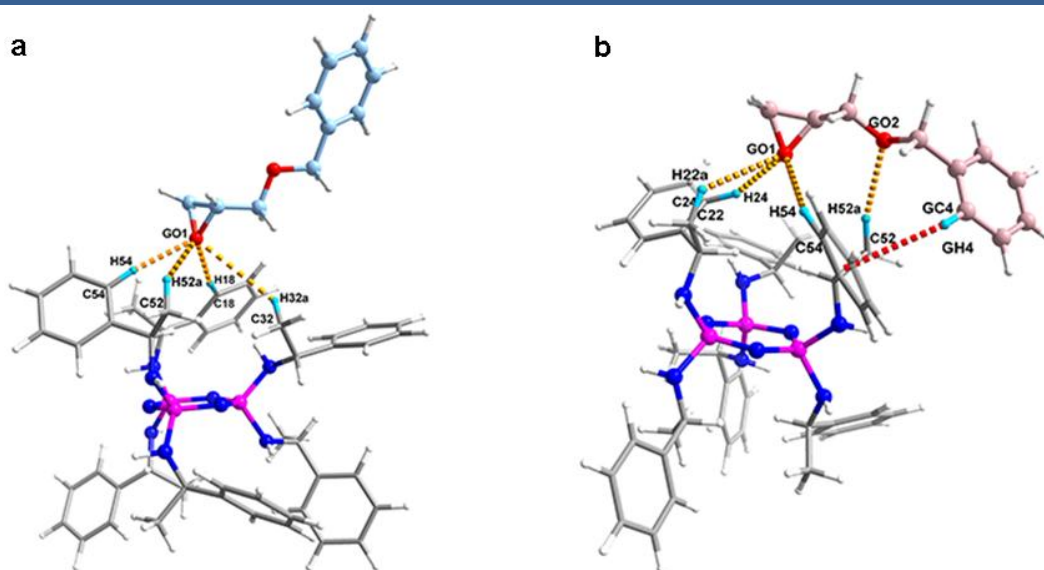


Figure A3.23: DFT optimised structures for host-guest complexes of (a) **3.1-R+R-BMO*** and (b) **3.1-R+S-BMO***, N blue; O red; Cl green; H white. The non-classical interactions (X=N, O) are shown in dotted lines: green O-H...X, yellow C-H...X and blue C-H... π .

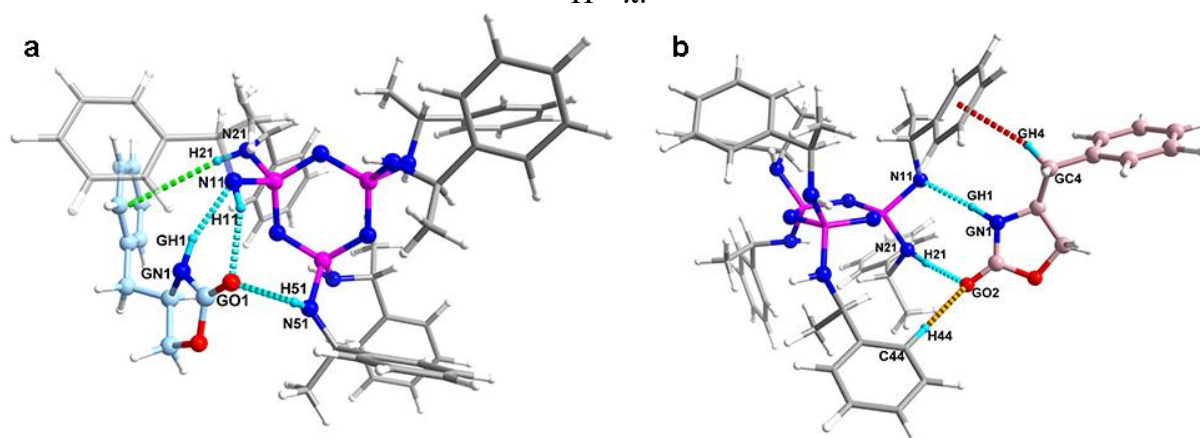


Figure A3.24: DFT optimised structures for host-guest complexes of (a) **3.1-R+R-BOZ** and (b) **3.1-R+S-BOZ**, N blue; O red; Cl green; H white. The non-classical interactions (X=N, O) are shown in dotted lines: green O-H...X, yellow C-H...X and blue C-H... π .

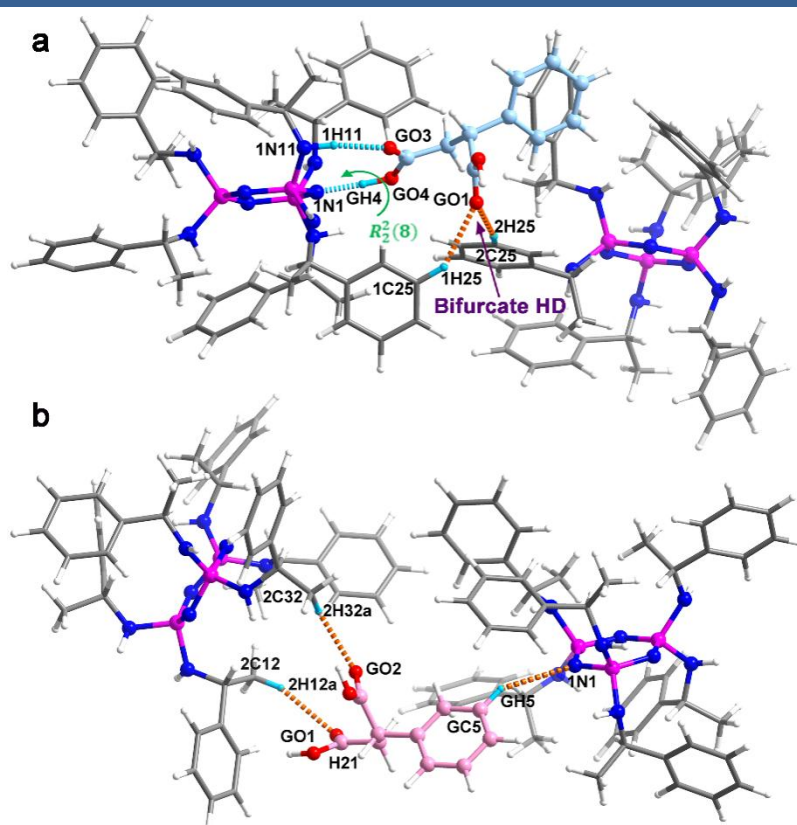


Figure A3.25: DFT optimised structures for host-guest complexes of (a) **3.1-R+R-PSA**, and (b) **3.1-R+S-PSA**, N blue; O red; Cl green; H white. The non-classical interactions (X=N, O) are shown in dotted lines: green O-H...X, yellow C-H...X and blue C-H... π .

* **R-BMO** and **S-BMO** were found to interact with **3.1-R** at the exterior of pocket *A* via non-classical C-H...O interactions involving the epoxide oxygen atoms. A comparison of the energy-optimized structures of **3.1-R+R-BMO** and **3.1-R+S-BMO** assemblies indicates a clear difference in the orientations of the benzyl group of the **BMO**. In the **3.1-R+R-BMO** complex, it is bent towards the phosphazene and engages in C-H... π interactions with two of the benzyl substituents of **3.1-R** (C18-H18...GO1 and C54-H54...GO1). This orientation provides an additional C-H...O interaction involving the ether oxygen of the **R-BMO** (C32-H32a...GO1 and C52-H52a...GO1). In contrast, similar interactions were found in the **3.1-R+S-BMO** assembly (C22-H22a...GO1, C24-H24...GO1, C54-H54a...GO1), owing to the flipped-up orientation of the **S-BMO** benzyl group an additional C52-H52a...GO2 interaction was also found in **3.1-R+S-BMO** complex. Nevertheless, a low ΔE_{pref} of only 2.3 was observed for the selective binding of **R-BMO**, suggesting a less pronounced difference in the binding of these enantiomers with **3.1-R**. Notably, both these assemblies showed no strong H-bonding interactions involving the phosphazene amino groups and the N-atoms of the P_3N_3 ring, which corroborates the overall poor binding energy values for their optimised host-guest assemblies and corresponding low experimental K_a values.

The interaction of **R-HOF** with **3.1-R** takes place again in the pocket *C* with a classical N12-H12...GO3 and a non-classical GC2-GH2a...N1_(ring) H-bonds serving as the primary force. In addition, other interactions GO3-G H3... π and C62-H62a...GO1 and C28-H28...GO2 have also been found to exist in the **3.1-R+R-HOF** system. Whereas the **S-HOF** interacts with **3.1-R** at the exterior of pocket *A* via C-H...O contacts involving benzyl ring C-

H and Me-H protons of **3.1-R** (C52-H52a $\cdots$ GO1, C32-H32a $\cdots$ GO2, C12-H12a $\cdots$ GO3 and C55-H55 $\cdots$ GO3). It is evident that the steric crowding at the *A*-sites provides hindered access to the guest molecules, making the host-guest interactions weaker for the **3.1-R+S-HOF** system. The variations in the strengths of these interactions have resulted in a ΔE_{pref} of ~ 7.6 in favour of the **3.1-R+R-HOF** complex

Table S6: Bond length and bond angles for the host-guest complexes of the chiral phosphazene.

Host + Guest	Interactions(D-H $\cdots$ A)	d(H $\cdots$ A)	d(D $\cdots$ A)	<DHA	Type of Interaction
3.1-R+R-BOL	C(GC10)-H(GH10) $\cdots$ N(N11)	2.945	4.014	168.2	Weak H-Bond
	C(C64)-H(H64) $\cdots$ O(GO1)	2.624	3.464	133.8(5)	Weak H-Bond
	C(C52)-H(H52a) $\cdots$ O(GO2)	2.800	3.632	128.6(1)	Weak H-Bond
	O(GO1)-H(GH1) $\cdots$ N(N1)	1.781	2.736	159.0(3)	H-Bond
	N(N51)-H(H51) $\cdots$ O(GO1)	2.536	3.250	126.7(4)	H-Bond
	N(N51)-H(H51) $\cdots$ O(GO2)	2.194	3.086	145.0(5)	H-Bond
	C(C52)-HC52a) $\cdots\pi$	3.245	4.065	131.7(7)	CH- π
3.1-R+S-BOL	O(GO2)-H(GH2) $\cdots\pi$	3.379	4.071	129.8(9)	Polar- π
	C(GC2)-H(GH2) $\cdots\pi$	3.1172	4.070	147.6(4)	CH- π
3.1-R+R-BOZ	O(GO1)-H(GH1) $\cdots\pi$	2.800	3.810	177.8(4)	Polar- π
	N(N51)-H(H51) $\cdots$ O(GO1)	2.323	3.181	154.3(6)	H-Bond
	N(N11)-H(H11) $\cdots$ O(GO1)	2.198	3.141	152.1(2)	H-Bond
	N(GN1)-H(GH1) $\cdots$ N(N11)	2.174	3.073	146.0(9)	H-Bond
	N(GN1)-H(GH1) $\cdots$ N(N21)	3.636	4.600	160.2(8)	H-Bond
3.1-R+S-BOZ	N(N21)-H(N21) $\cdots\pi$	3.321	4.329	176.9(9)	Polar- π
	C(GC4)-H(GH4) $\cdots\pi$	2.895	3.714	131.5(7)	CH- π
	N(GN1)-H(GH1) $\cdots$ N(11)	2.189	3.200	169.8(7)	H-Bond
	N(GN1)-H(GH1) $\cdots$ N(1)	3.443	4.192	131.5(9)	H-Bond
	N(N21)-H(H21) $\cdots$ O(GO2)	1.924	2.945	173.4(4)	H-Bond
3.1-R+R-HOF	C(C44)-H(H44) $\cdots$ O(GO2)	2.571	3.523	179.3(8)	Weak H-Bond
	C(C28)-H(H28) $\cdots$ O(GO2)	2.677	3.655	149.0(1)	Weak H-Bond
	C(C62)-H(H62a) $\cdots$ O(GO1)	2.641	3.727	170.0(1)	Weak H-Bond
	C(GC2)-H(GH2a) $\cdots$ N(N1)	2.256	3.353	174.0(3)	Weak H-Bond
	N(N12)-H(H12) $\cdots$ O(GO3)	2.177	3.188	168.7(9)	H-Bond
3.1-R+S-HOF	O(GO3)-H(GH3) $\cdots\pi$	2.616	3.500	155.8(8)	Polar- π
	C(C32)-H(H32a) $\cdots$ O(GO2)	3.225	4.083	135.7(8)	Weak H-Bond
	C(C52)-H(H52a) $\cdots$ O(GO1)	2.714	3.619	139.8(2)	Weak H-Bond

	C(C55)-H(H55a)···O(GO3)	2.883	3.623	125.4(9)	Weak H-Bond
	C(C12)-H(H12)···O(GO3)	2.939	3.972	157.5(6)	Weak H-Bond
3.1-R+R-BMO	C(C18)-H(H18)···O(GO1)	2.508	3.566	163.0(1)	Weak H-Bond
	C(C32)-H(H32a)···O(GO1)	3.375	4.377	131.2(8)	Weak H-Bond
	C(C52)-H(C52a)···O(GO1)	2.969	3.810	133.9(7)	Weak H-Bond
	C(C54)-H(H54)···O(GO1)	2.522	3.599	170.1(9)	Weak H-Bond
3.1-R+S-BMO	C(C24)-H(H24)···O(GO1)	2.492	3.471	149.1(4)	Weak H-Bond
	C(C22)-H(H22a)···O(GO1)	3.017	3.853	133.5(8)	Weak H-Bond
	C(C54)-H(H54)···O(GO1)	2.564	3.627	165.7(2)	Weak H-Bond
	C(C52)-H(H52a)···O(GO1)	3.236	4.043	131.3(6)	Weak H-Bond
	C(C52)-H(H52a)···O(GO2)	2.600	3.661	163.3(8)	Weak H-Bond
	C(GC4)-H(GH4)··· π	3.139	4.071	144.2(6)	CH- π
3.1-R+R-PFA	C(2C25)-H(2H25)···O(GO1)	2.500	3.600	163.0(1)	Weak H-Bond
	C(1C25)-H(1H25)···O(GO1)	2.500	3.400	146.0(2)	Weak H-Bond
	C(1C24)-H(1H24)···O(GO3)	3.000	4.001	150.0(1)	Weak H-Bond
	N(1N11)-H(1H11)···O(GO3)	2.00	3.000	165.0(1)	H-Bond
	O(GO4)-H(GH4)···N(1N1)	1.600	2.600	171.0(2)	H-Bond
3.1-R+S-PFA	C(2C32)-H(2H32a)···O(GO3)	2.500	3.400	138.0(1)	Weak H-Bond
	C(1C12)-H(2H12)···O(GO1)	2.600	3.700	161.0(2)	Weak H-Bond
	C(GC5)-H(GH5)···N(1N1)	3.700	4.000	151.0(1)	Weak H-Bond

Characterizations data for host-guest complexes: NOESY NMR data

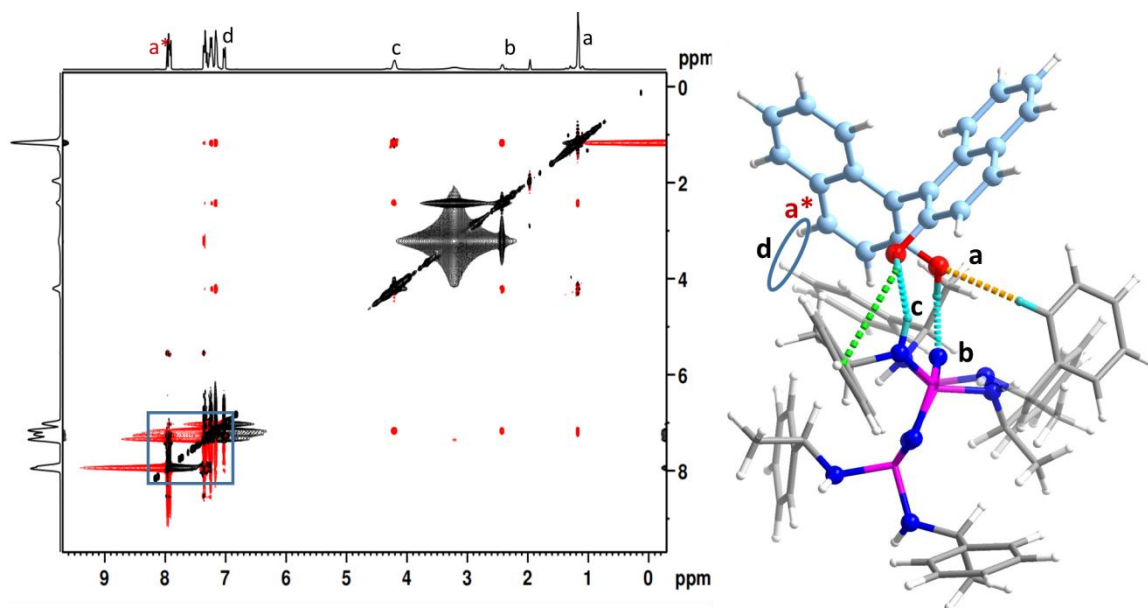


Figure A3.26: ^1H -2D-NOESY NMR data (298K) for the mixture **3.1-R+R-BOL**.

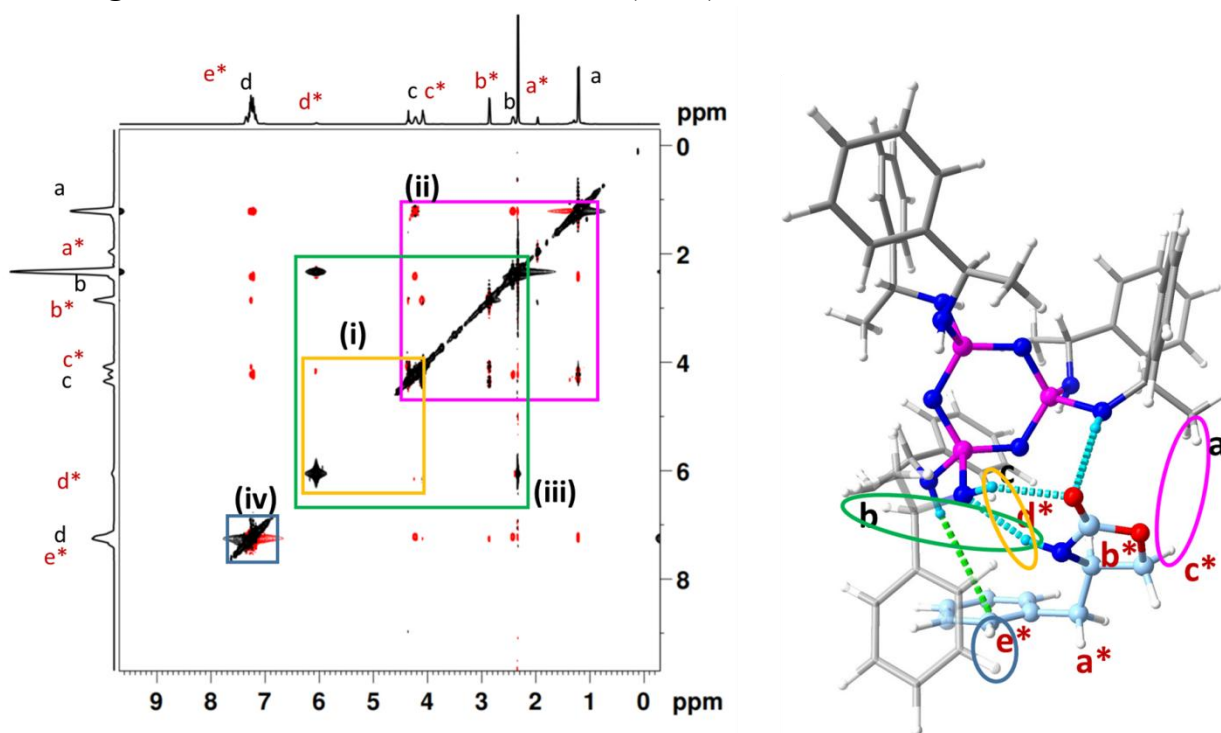


Figure A3.27: ^1H -2D-NOESY NMR data (298K) for the mixture **3.1-R+R-BOZ**.

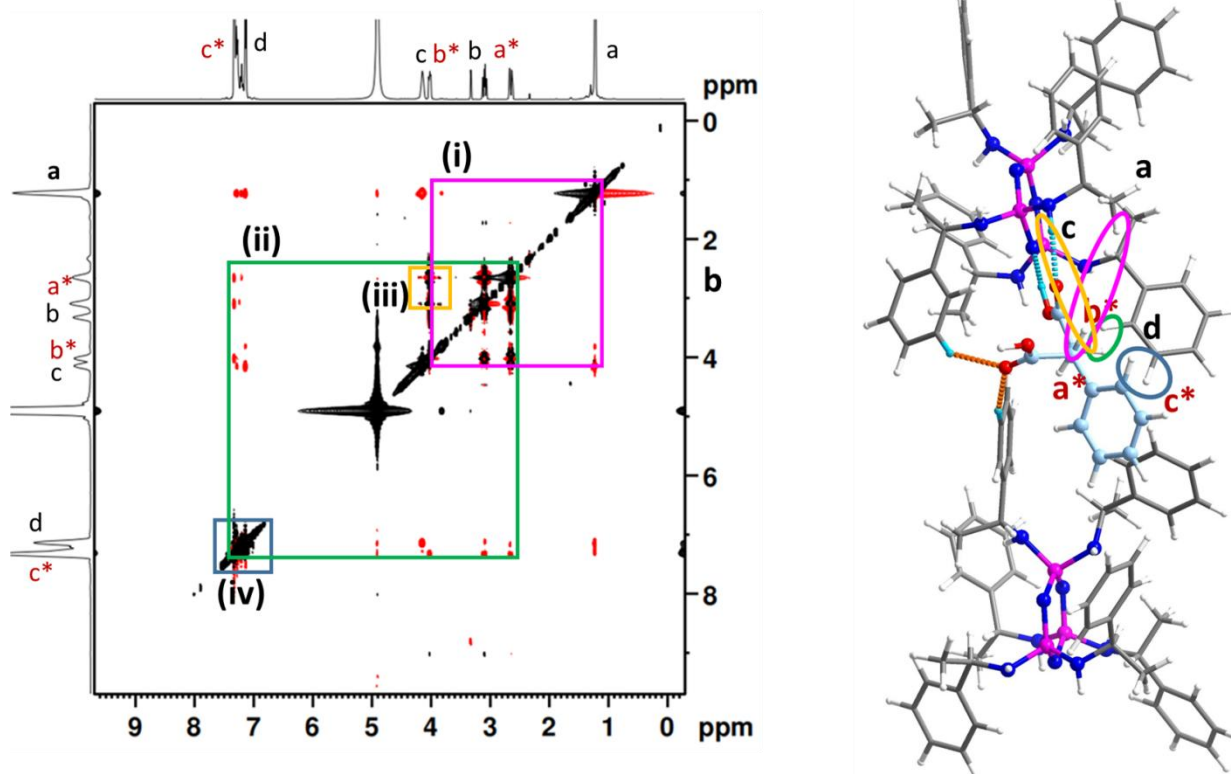


Figure A3.28: ^1H -2D-NOESY NMR data (298K) for the mixture **3.1-R+R-PSA**.

Characterization data for host-guest complexes: ^1H -NMR and mass spectra

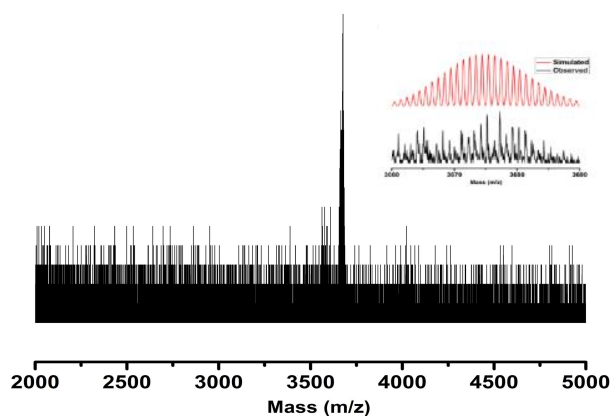


Figure A4.1. MALDI-TOF (Reflector mode) spectrum of **4.1-R**

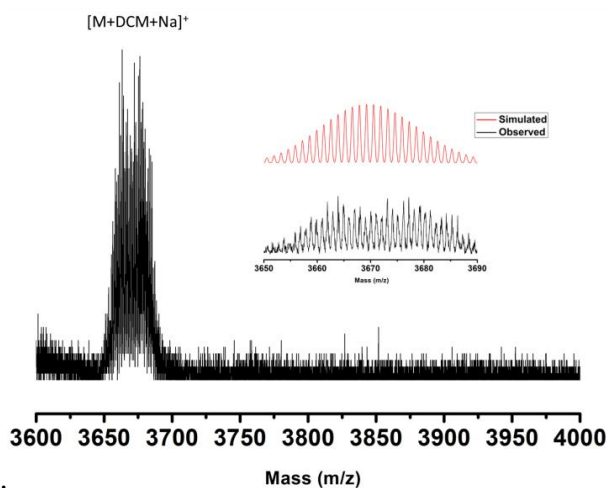


Figure A4.2. MALDI-TOF (Reflector mode) spectrum of **4.1-S**.

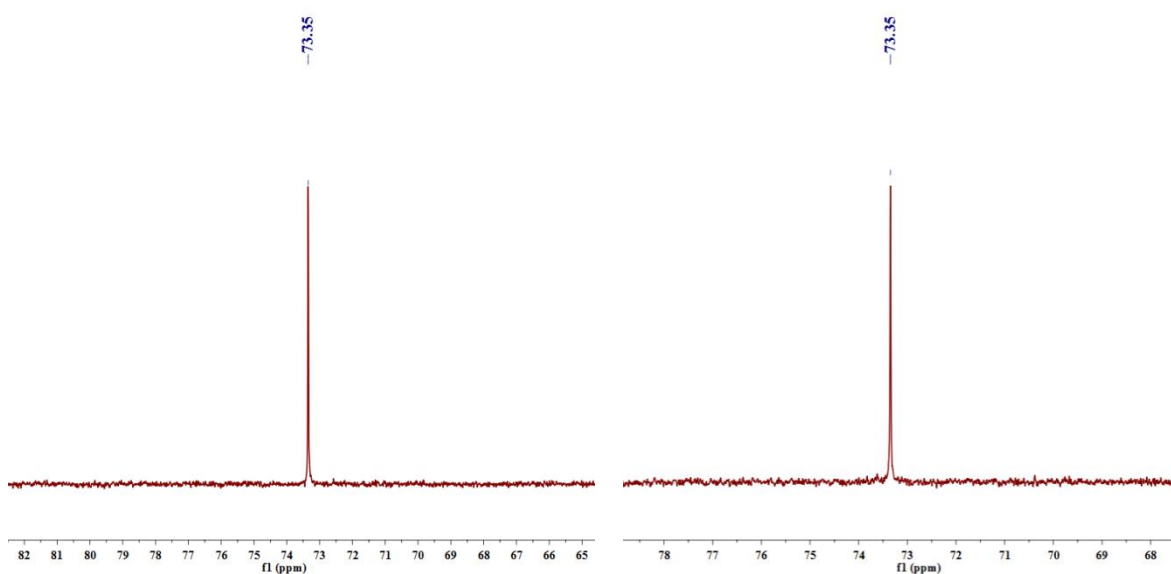


Figure A4.3. ^{31}P NMR spectra of **4.1-R** (left) and **4.1-S** (right).

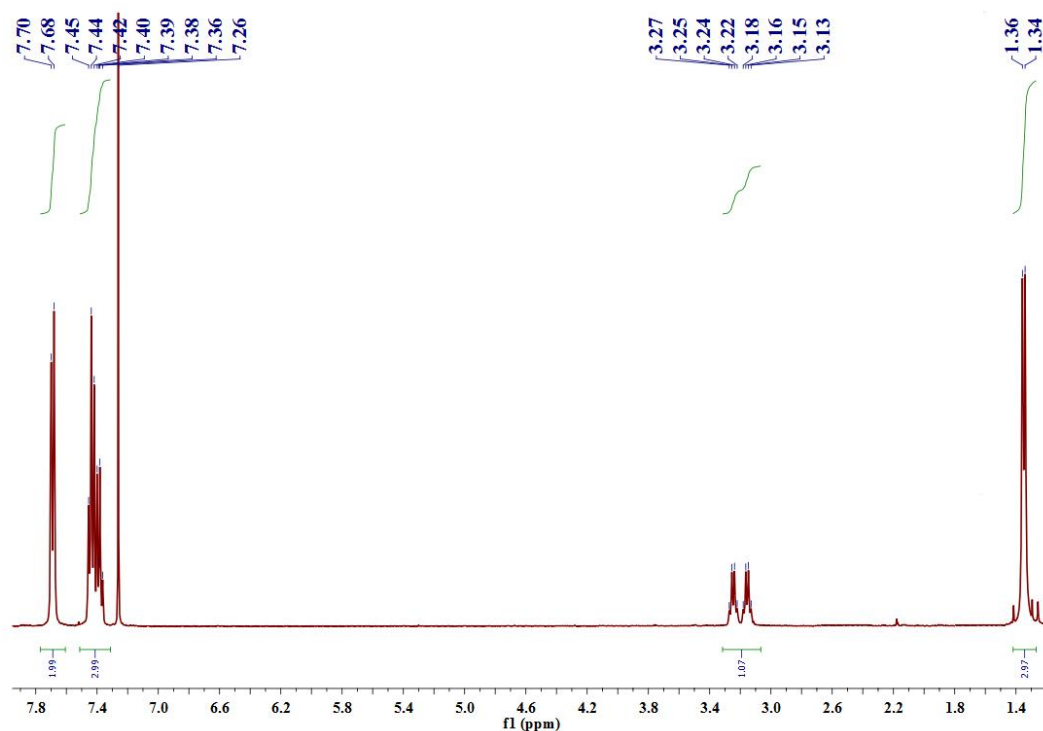


Figure A4.4. ¹H NMR spectrum of 4.1-R.

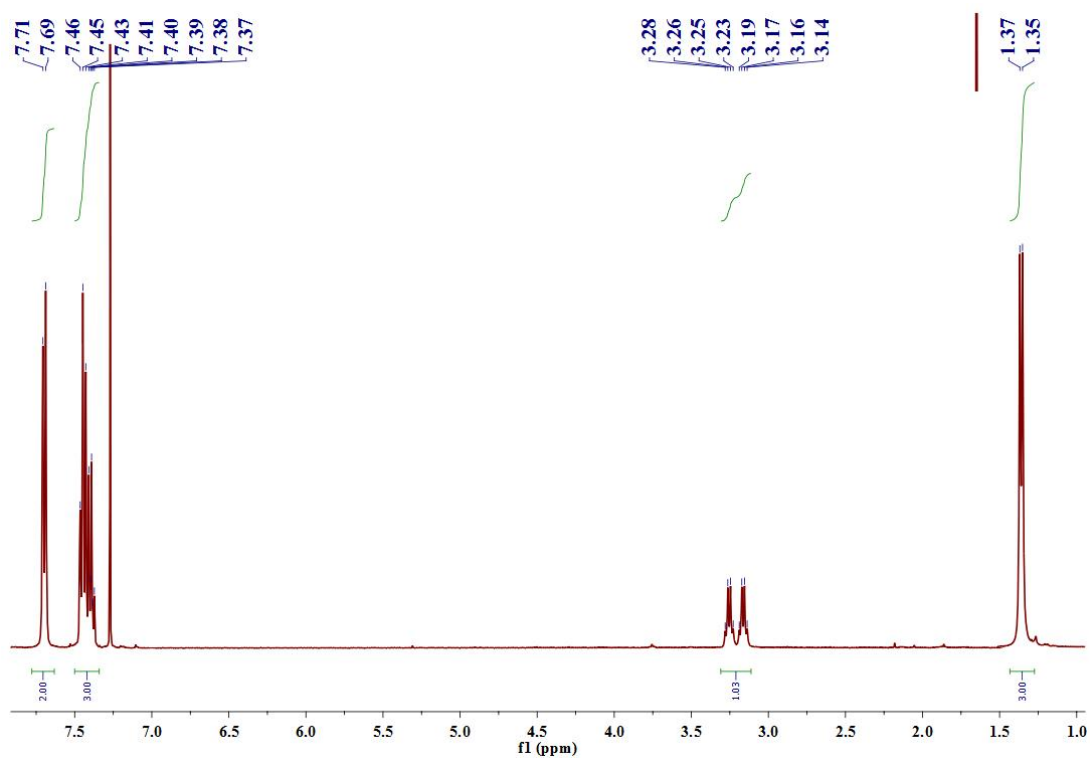


Figure A4.5. ¹H NMR spectrum of 4.1-S.

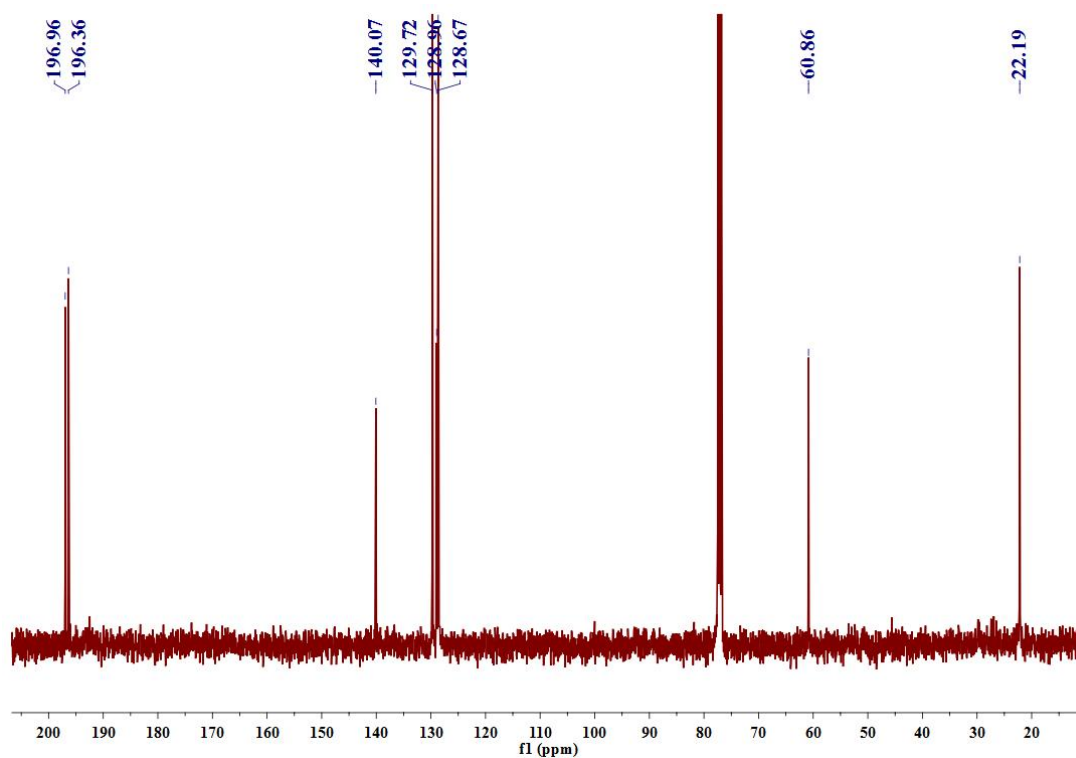


Figure A4.6. ¹³C NMR spectrum of 4.1-R.

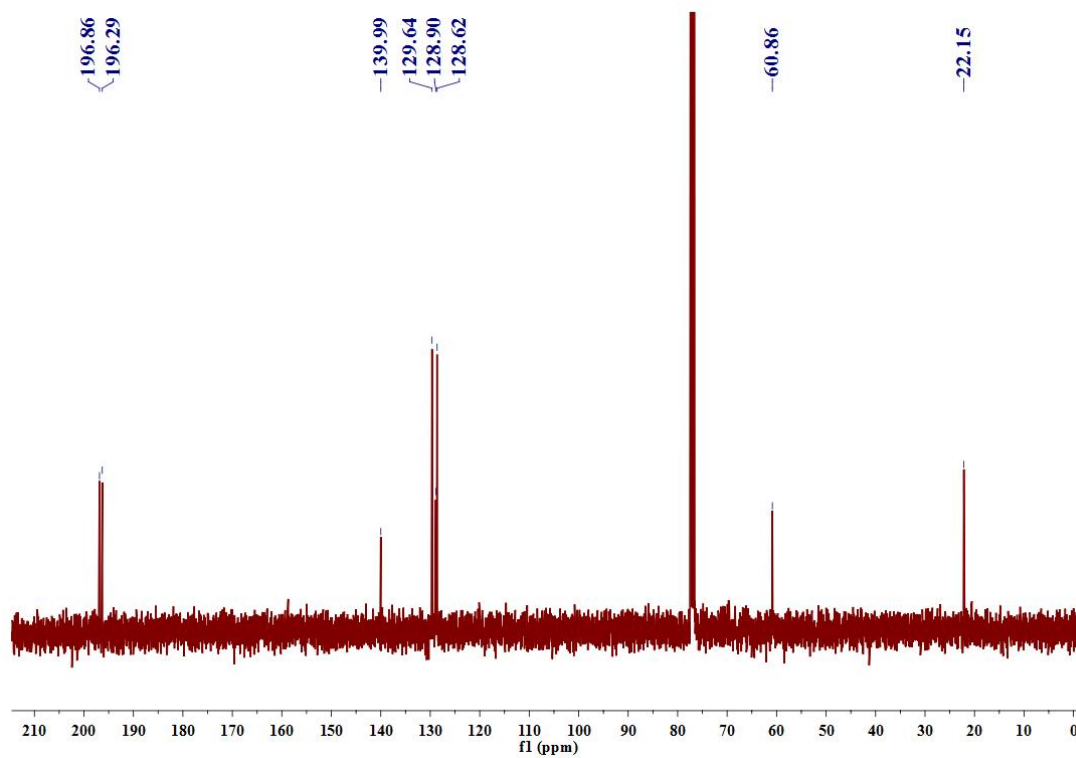


Figure A4.7. ¹³C NMR spectrum of 4.1-S.

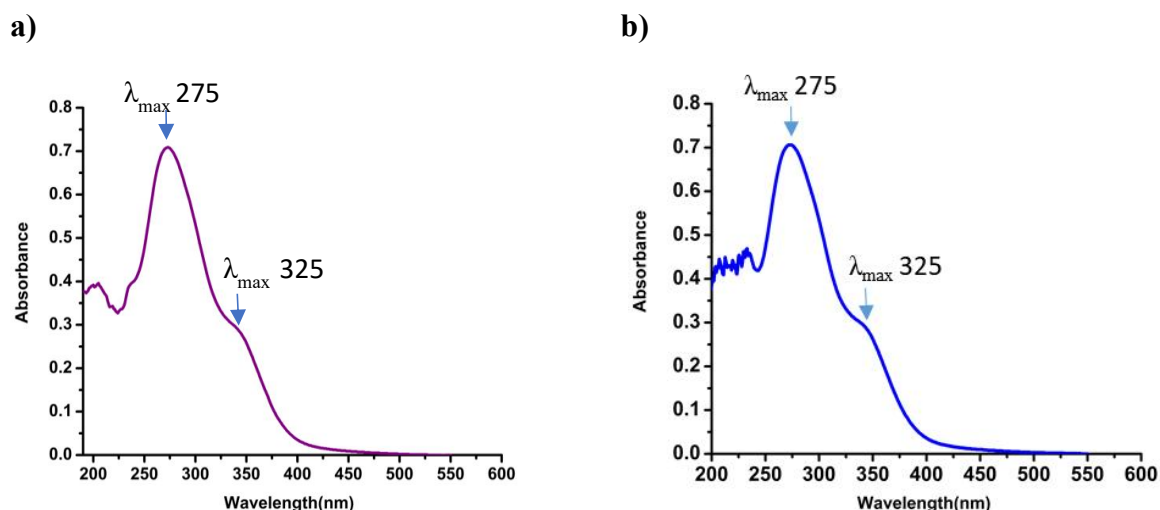


Figure A4.8. UV-Visible spectra (normalized) of **4.1-R** at milli-molar (a) and micro-molar (b) concentrations.

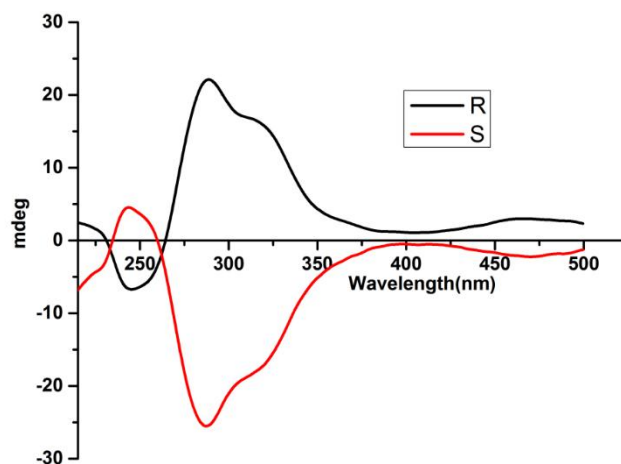


Figure A4.9. CD spectra of **4.1-R** and **4.1-S** in Chloroform.

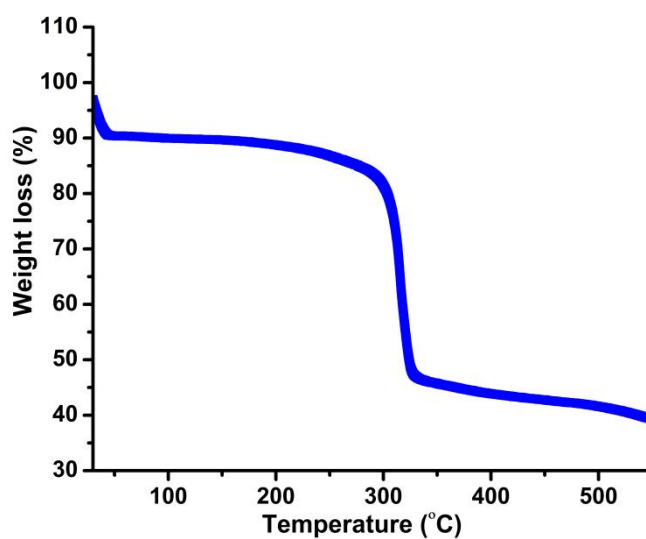


Figure A4.10. TGA profile of **4.1-R**.

Table S1. Specific rotation (α_D) values for cages **4.1-R** and **4.1-S** and the Ligands $L^{RRR}H_3$ and $L^{SSS}H_3$.

Compound	Specific rotation (α_D)
4.1-R	+671
4.1-S	-689
$L^{RRR}H_3$	+22
$L^{SSS}H_3$	-27

Crystallographic information

Table S2. Crystallographic Data for Cages **4.1-R** and **4.1-S**.

Compound	4.1-R	4.1-S
Chemical formula	$C_{120}H_{108}N_{12}O_{28}P_4Pd_{12}$	$C_{120}H_{108}N_{12}O_{28}P_4Pd_{12}$
Formula weight	3566.86	3566.86
Temperature	100(2) K	100(2) K
Crystal system	Cubic	Cubic
Space group	$F432$	$F432$
a (Å); $\alpha(^{\circ})$	34.898(6); 90	34.885(4); 90
b (Å); $\beta(^{\circ})$	34.898(6); 90	34.885(4); 90
c (Å); $\gamma(^{\circ})$	34.898(6); 90	34.885(4); 90
V (Å ³); Z	42501(22)	42452(14)
ρ (calc.) mg m ⁻³	1.115	1.116
μ (Mo K α) mm ⁻¹	1.064	1.066
2 θ max ($^{\circ}$)	44.994	45.014
Flack parameter	0.01(14)	0.02(4)
R(int)	0.0805	0.1491
Data / param.	2344/123	2348/91
GOF	1.289	1.146
R1 [F>4 σ (F)]	0.0266	0.0343
wR2 (all data)	0.0768	0.0942
Max. peak/hole(e.Å ⁻³)	0.359/-0.386	0.569/-0.421

Table S3. Selected bond lengths (Å) and bond angles ($^{\circ}$) for **4.1-R** and **4.1-S**.

CAGE	Bond Lengths	Bond Angles
4.1-R	Pd(1)-N(1) 1.993(11) Pd(1)-O(3) 2.029(9) Pd(1)-N(1) 2.046(10) Pd(1)-O(2) 2.058(9) Pd(1)-P(1) 2.7286(18)	N(1)-Pd(1)-O(3) 176.2(3) N(1)-Pd(1)-N(1) 77.1(2) O(3)#1-Pd(1)-N(1) 99.2(3) N(1)-Pd(1)-O(2) 99.9(3) O(3)#1-Pd(1)-O(2) 83.85(15) N(1)#2-Pd(1)-O(2) 176.0(3) P(1)-Pd(1)-Pd(1) 55.93(3) Pd(1)#2-Pd(1)-Pd(1) 60.0
4.1-S	Pd(01)-N(1) 2.014(14) Pd(01)-N(1) 2.031(14) Pd(01)-O(006) 2.038(12) Pd(01)-O(1) 2.046(13)	N(1)-Pd(01)-N(1) 77.2(3) N(1)-Pd(01)-O(006) 176.5(4) N(1)#1-Pd(01)-O(006) 99.3(4) N(1)-Pd(01)-O(1) 99.7(4) N(1)#1-Pd(01)-O(1) 176.2(4) O(006)-Pd(01)-O(1) 83.7(2) Pd(01)-Pd(01)-Pd(01) 60.0

Structural illustrations and analysis of the chiral tetrahedral cages

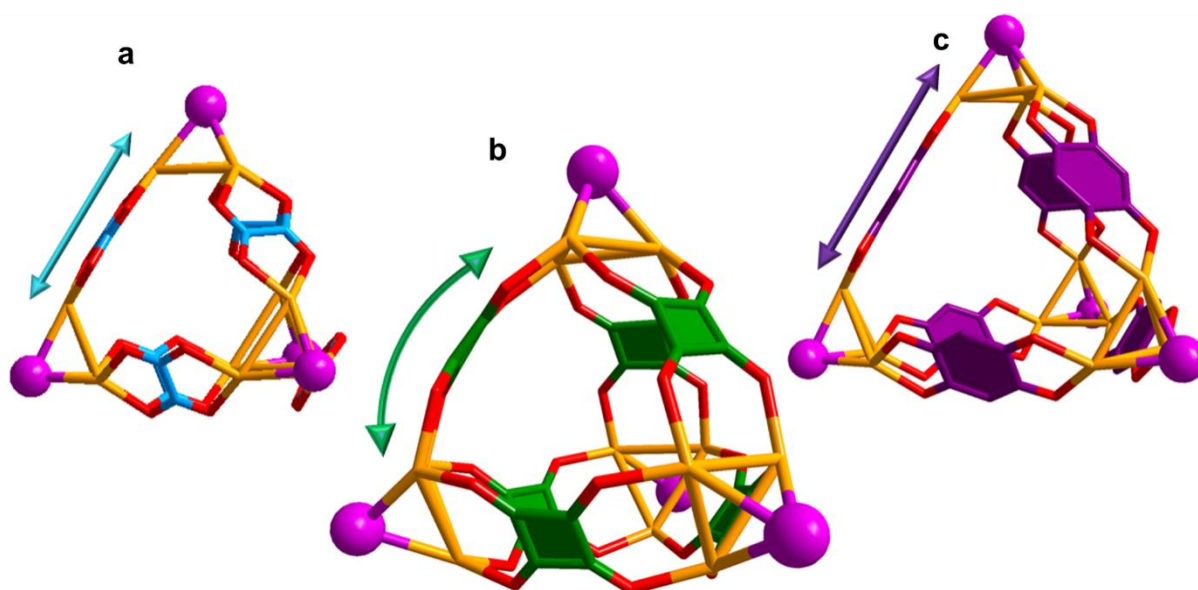


Figure A4.11. Structural comparison for **4.1-R** (**b**) with the previously reported oxalate¹ (**a**) and anilate.⁸ The Pd-Pd bonds are provided as a guide to the eye. (**c**) linker based chiral cages indicating the bent nature of the tetrahedral edges in case of **4.1-R**.

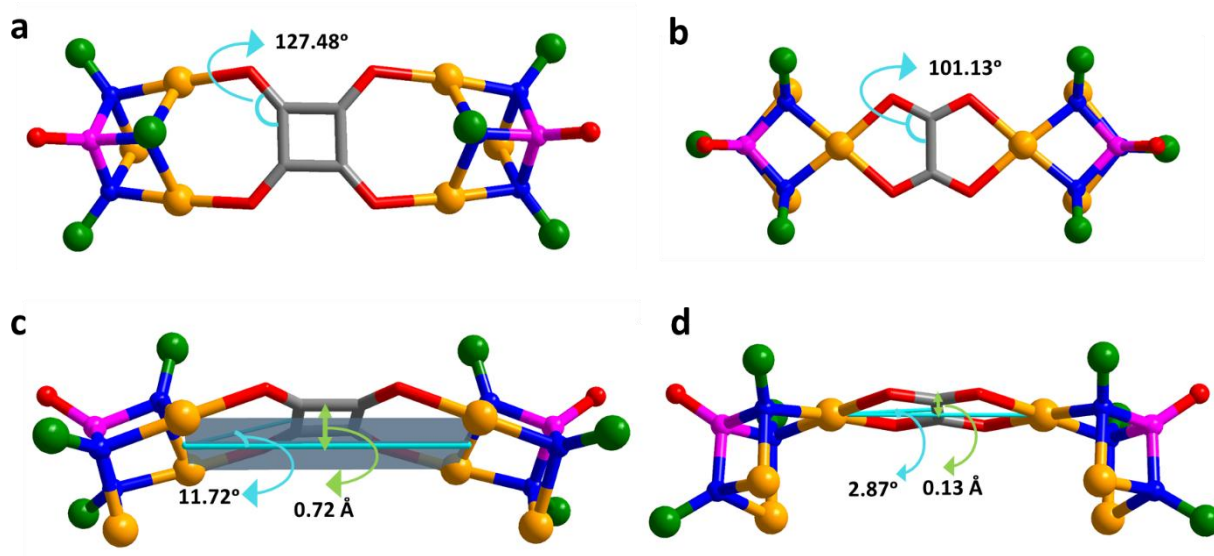


Figure A4.12. Comparison of average O-C-C angle in (**a**) **4.1-R** and (**b**) oxalate based cage and inclination angle along with distance in (**c**) **4.1-R** and (**d**) oxalate based cage.¹

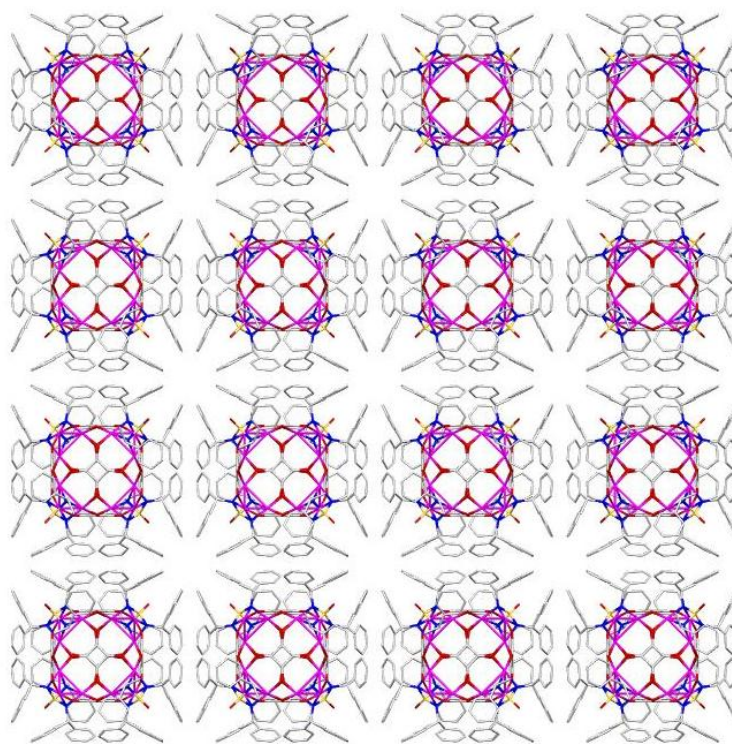


Figure A4.13. View of packing of the cage **4.1-R** along the c-axis.

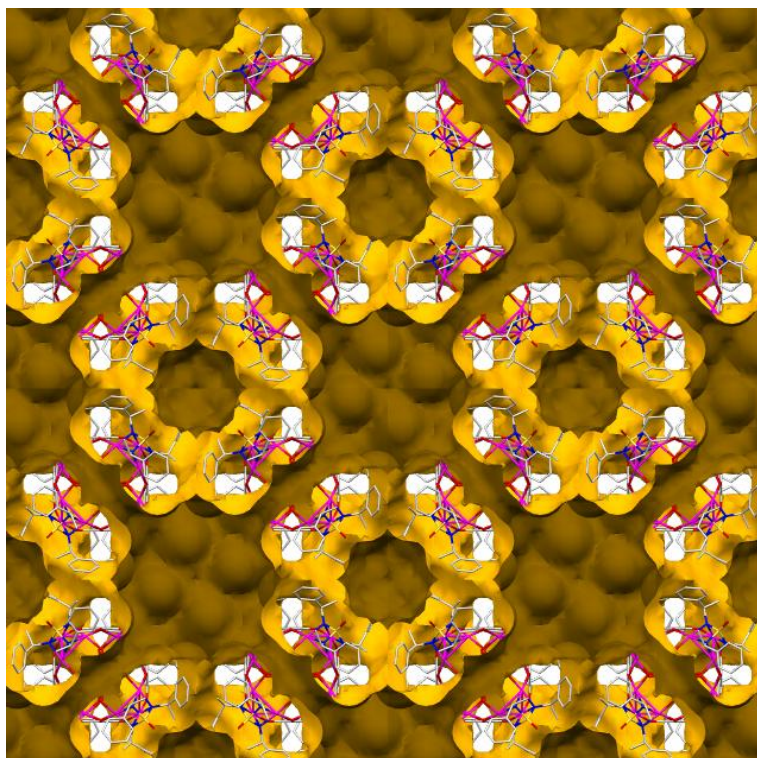


Figure A4.14. 2*2*2 packing structure of **4.1-R** along with its solvent accessible surface in cubic $F432$ phase.

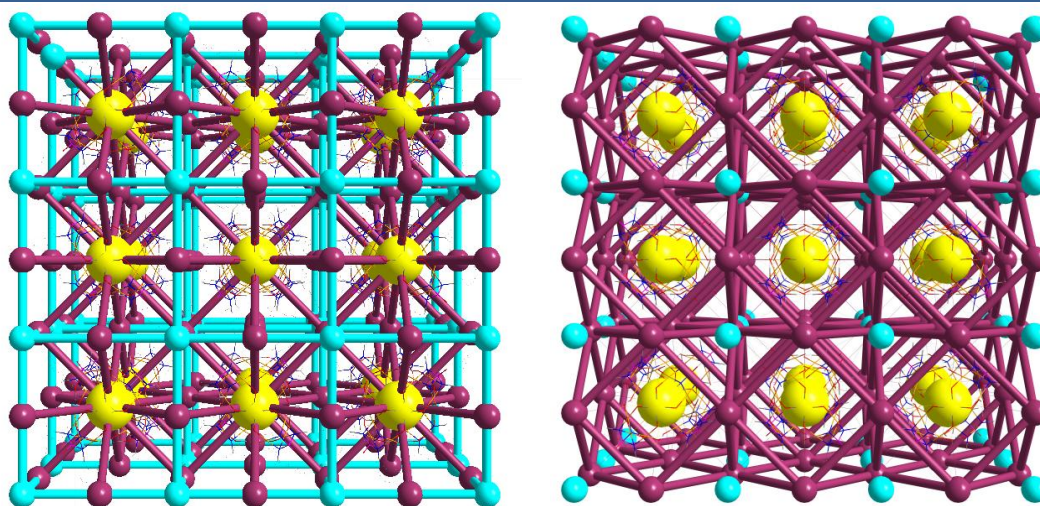


Figure A4.15. Packing Structure of **4.1-R** in $F432$ showing the Intrinsic and extrinsic cavities. The yellow spheres depict the intrinsic voids of the individual cages and red and blue spheres depict the extrinsic voids that lies in face and body center of the packing, respectively. The blue lines demonstrate the mode of connection between the body centered extrinsic cavity and the red lines demonstrate the mode of connection between the face centered extrinsic cavity (left). Only connection between the face centered extrinsic cavities are demonstrated (right).

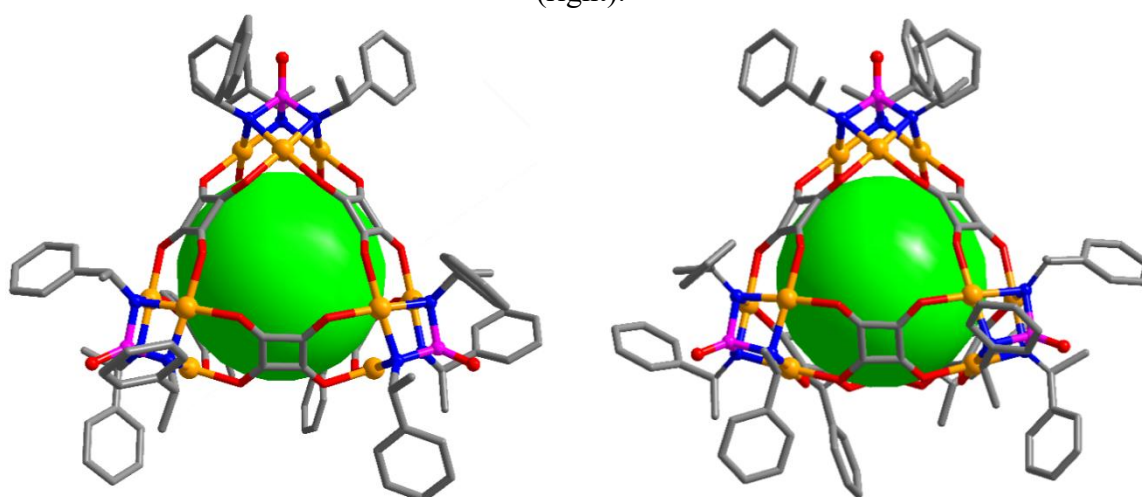


Figure A4.16. View of the intrinsic cavity surface present in **4.1-R** (right) and **4.1-S** (left) Green spheres represent the intrinsic voids of these cages.

Table S4. Cavity volume, window size and solvent accessible void volume comparison of oxalate- anilate- and squarate ligand based cages.

Cage	Cavity volume ($\text{\AA}^3$)	Window Size ($\text{\AA}$)	Solvent accessible voids volume ($\text{\AA}^3$)
Oxalate-Cage	86	4.5	13051 (51%)
Anilate-Cage	224	3.8	3000 (33%)
Squarate-cage 4.1-R	286	5.6	12134 (28%)

Characterization data for host-guest complexes: ^1H -NMR and mass spectra

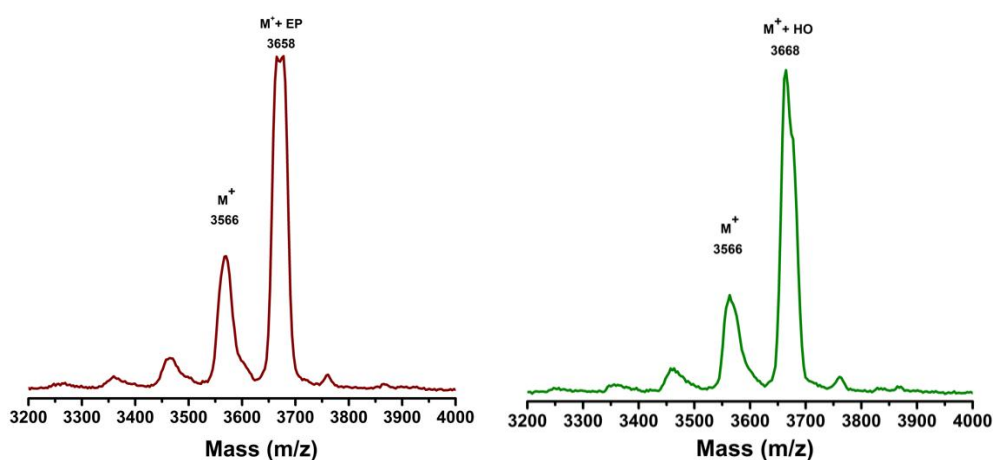


Figure A4.17. MALDI-TOF spectra of $\pm\text{EP}+4.1\text{-R}$ and $\pm\text{HO}+4.1\text{-R}$ in the linear mode.

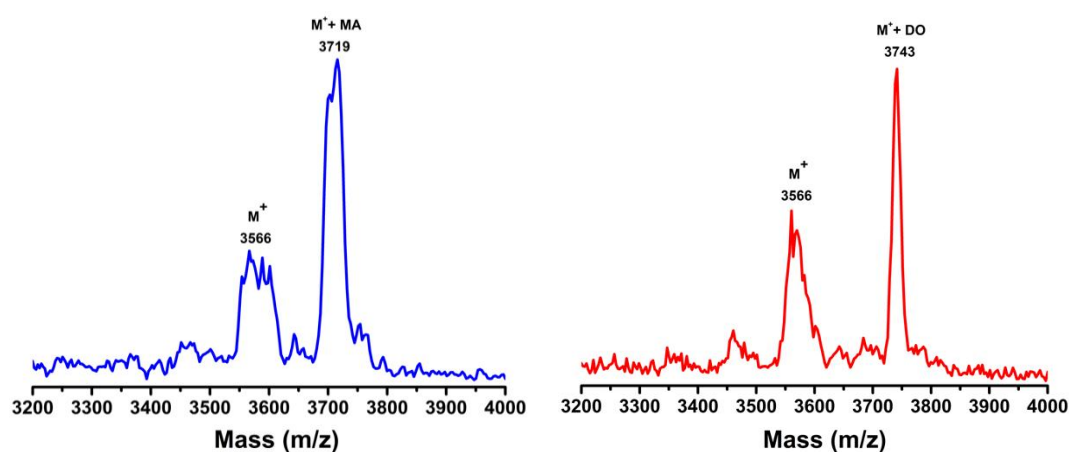


Figure A4.18. MALDI-TOF spectra of $\pm\text{MA}+4.1\text{-R}$ and $\pm\text{DO}+4.1\text{-R}$ in the linear mode.

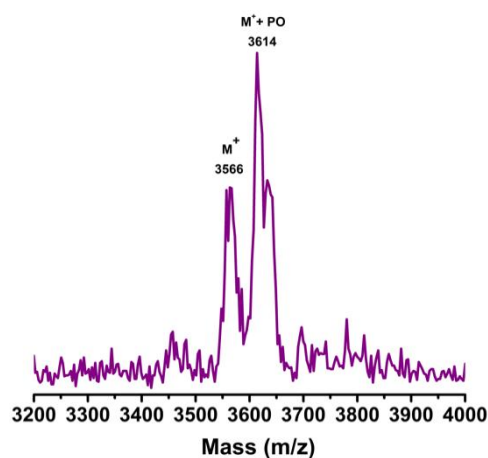


Figure A4.19. MALDI-TOF spectrum of $\pm\text{PO}+4.1\text{-R}$ in the linear mode.

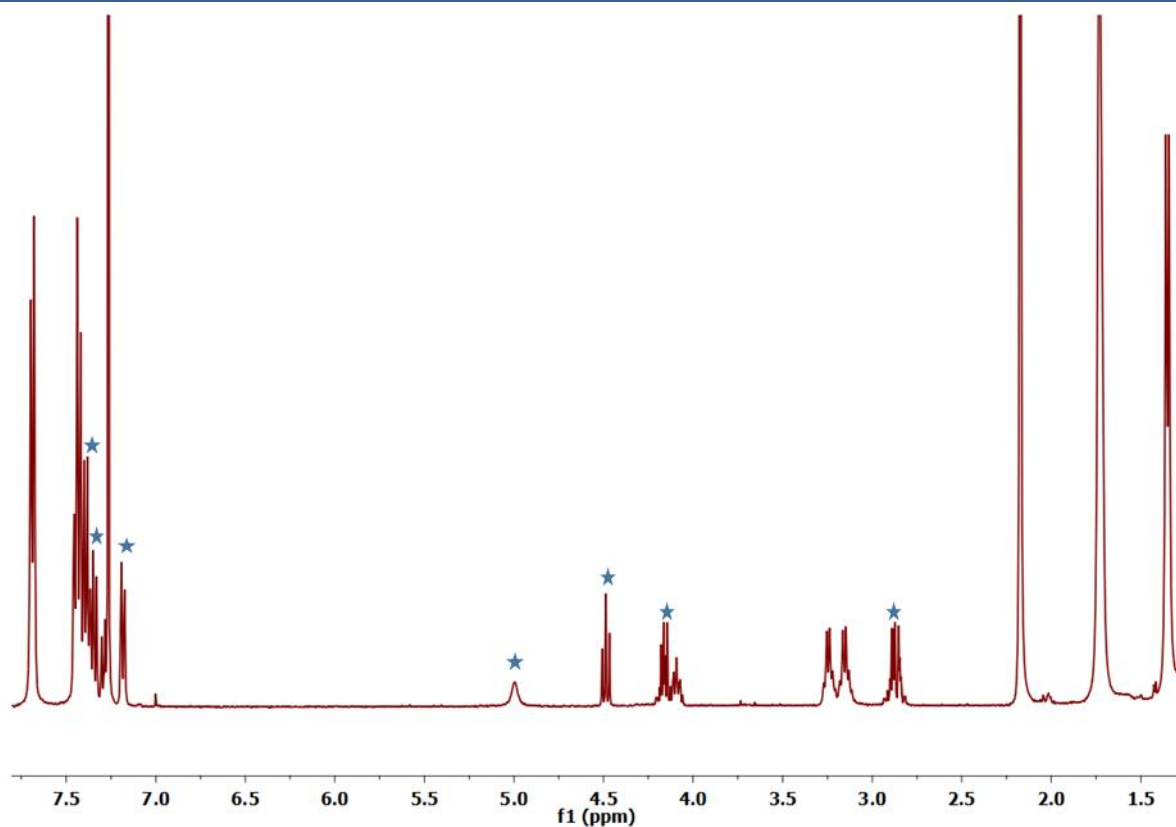


Figure A4.20. ^1H NMR spectrum of $\pm\text{DO}+4.1\text{-R}$. The symbol * indicate the peaks due to the encapsulated $\pm\text{DO}$ guests in the cage.

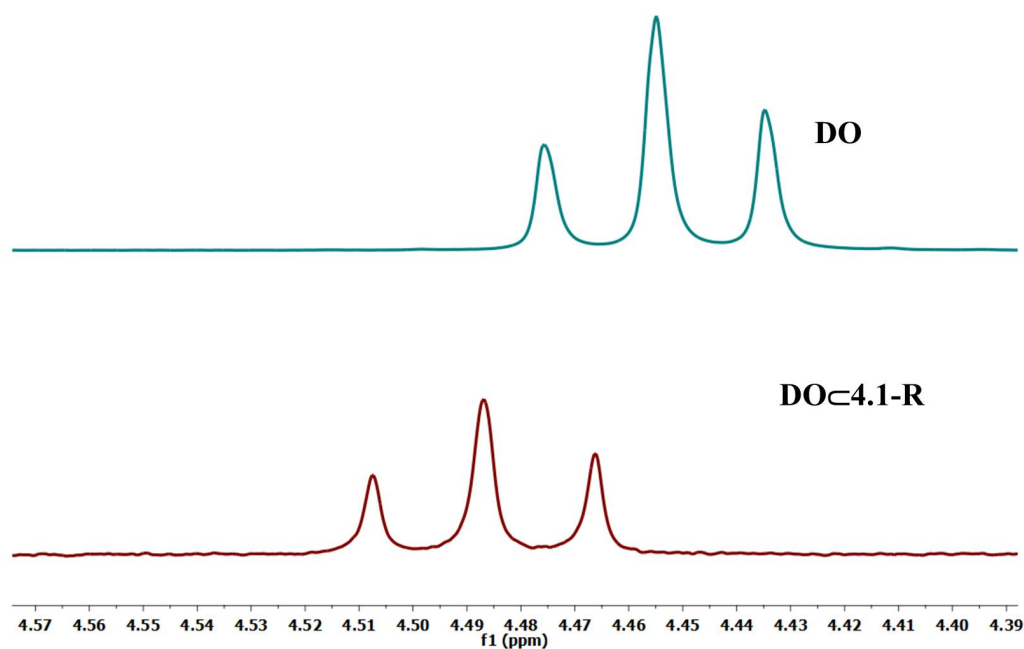


Figure A4.21. Comparative ^1H -NMR (CDCl_3 , 298K) spectra of free and encapsulated $\pm\text{DO}$ in **4.1-R**.

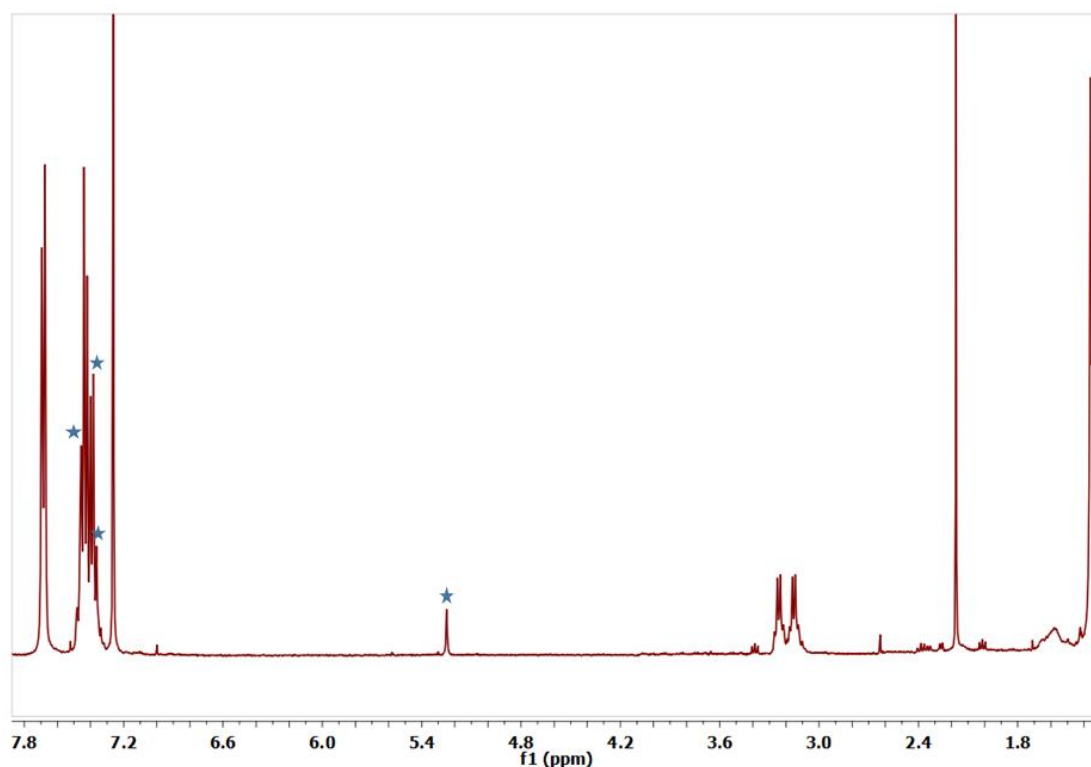


Figure A4.22. ^1H NMR spectrum of $\pm\text{MA}+4.1\text{-R}$. The symbol * indicate the peaks due to the encapsulated $\pm\text{MA}$ guests in the cage.

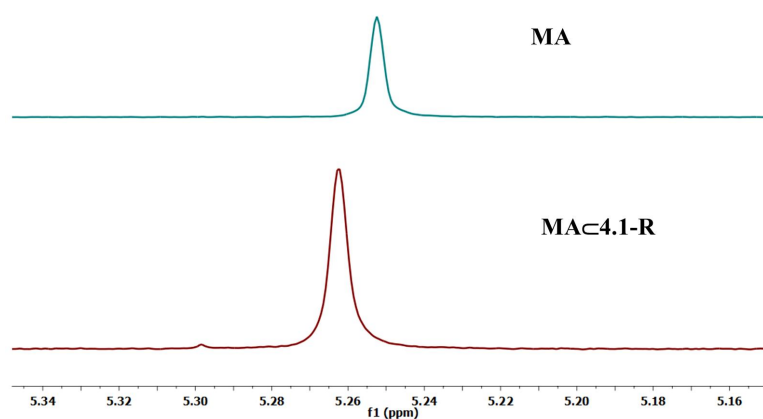


Figure A4.23. Comparative ^1H -NMR (CD_3OD , 298K) spectra of free and encapsulated $\pm\text{MA}$ in **4.1-R**.

Table S5. Value of chemical shifts of the guest molecules 4-benzyl-2-oxazolidinone and mandelic acid and their host-guest complexes.

Compound	δ (ppm)
$\pm\text{DO}$	4.455
4.1-R+$\pm\text{DO}$	4.487
$\pm\text{MA}$	5.252
4.1-R+$\pm\text{MA}$	5.262

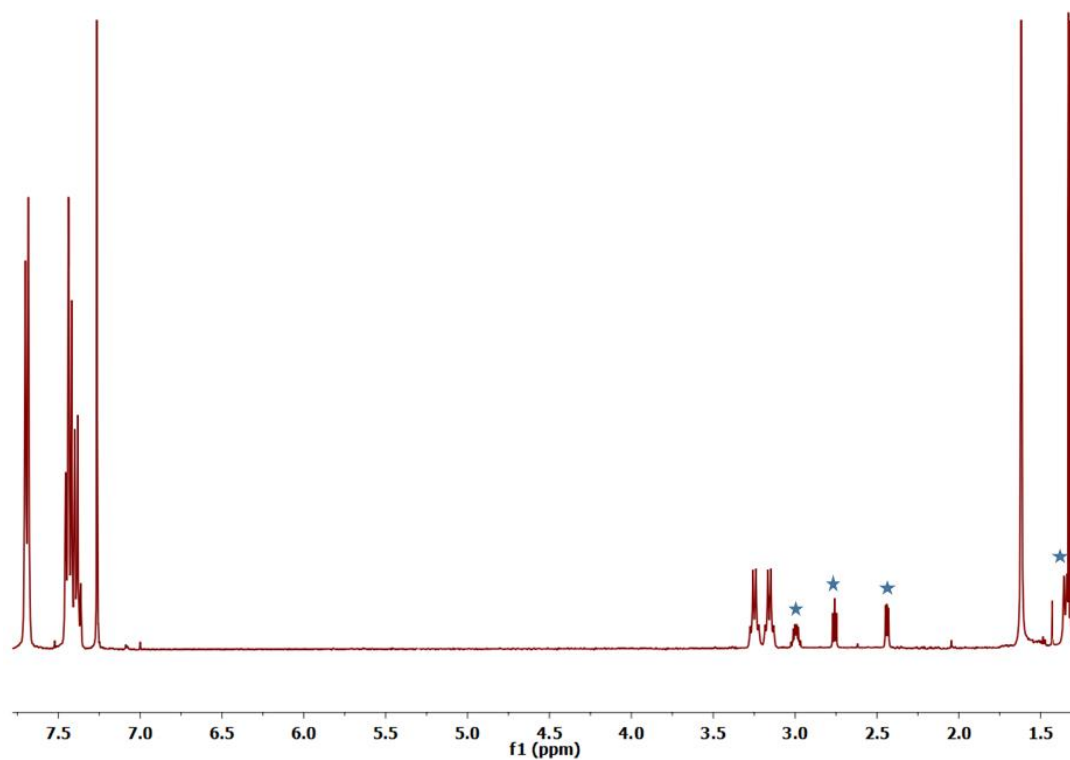


Figure A4.24. ^1H NMR spectrum of $\pm\text{PO}+4.1\text{-R}$. The symbol * indicate the peaks due to the encapsulated $\pm\text{PO}$ guests in the cage.

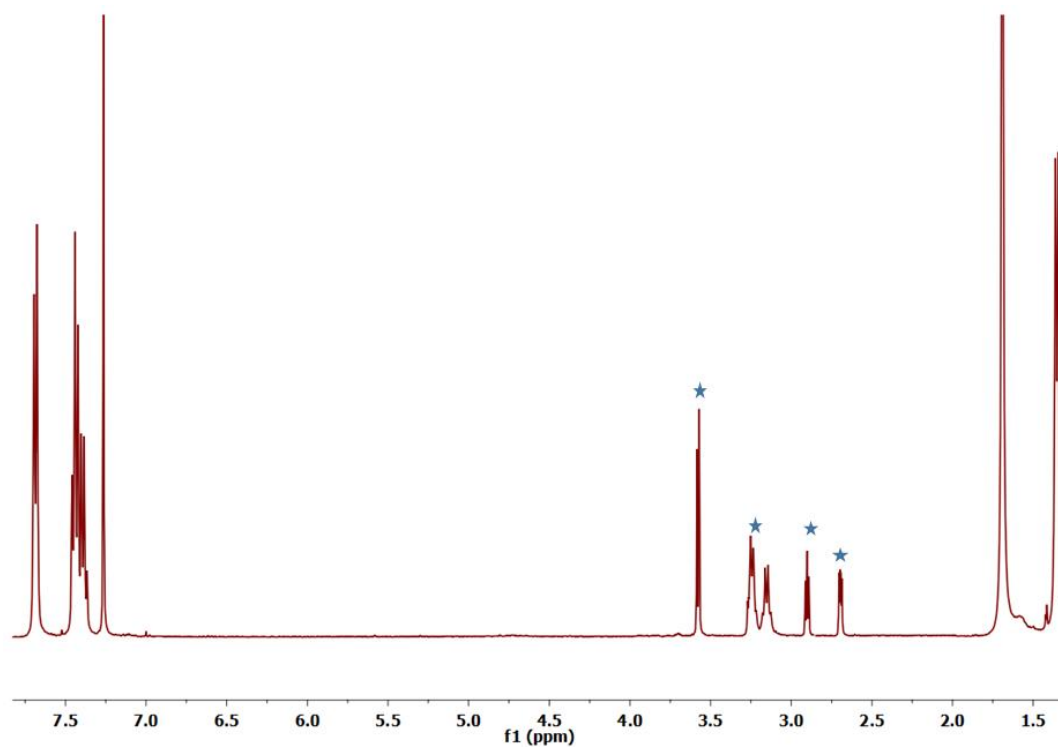


Figure A4.25. ^1H NMR spectrum of $\pm\text{EP}+4.1\text{-R}$. The symbol * indicate the peaks due to the encapsulated $\pm\text{EP}$ guests in the cage.

Characterization data for host-guest complexes: ^1H -2D-DOSY NMR data

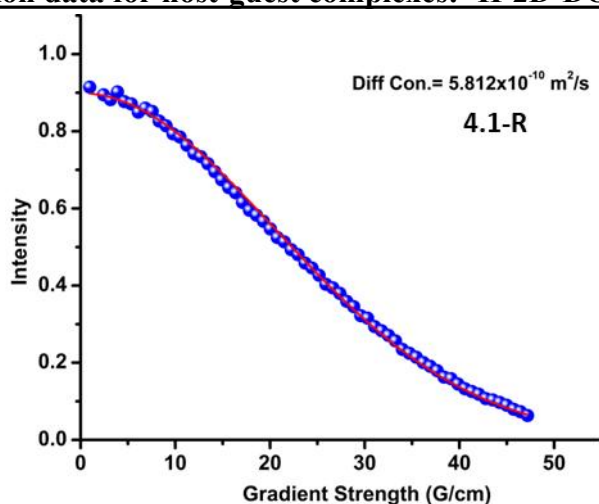
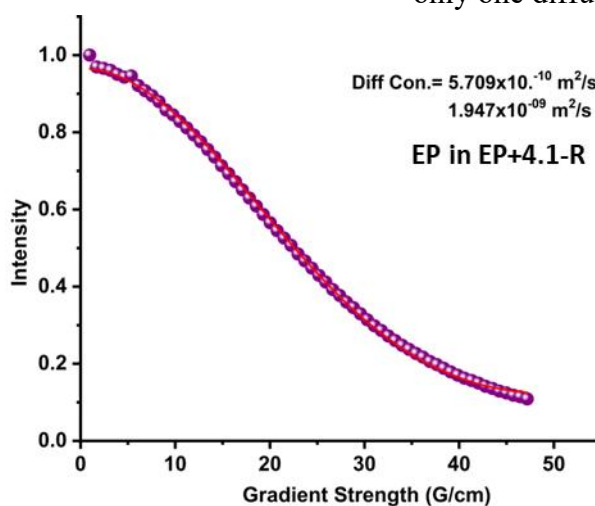
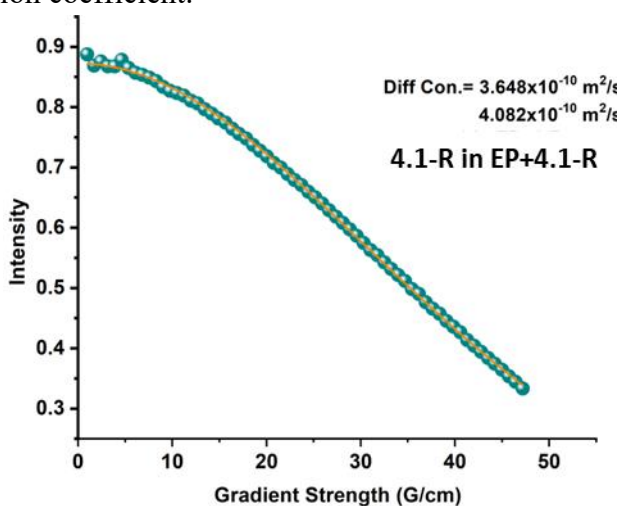


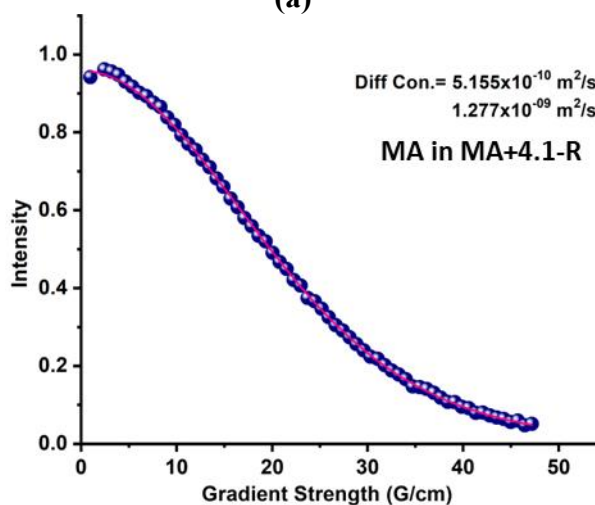
Figure A4.26. Integral decay profile of host proton of cages **4.1-R** (^1H -2D DOSY NMR performed in CDCl_3 at 298K) without any guest showing mono-exponential decay curve with only one diffusion coefficient.



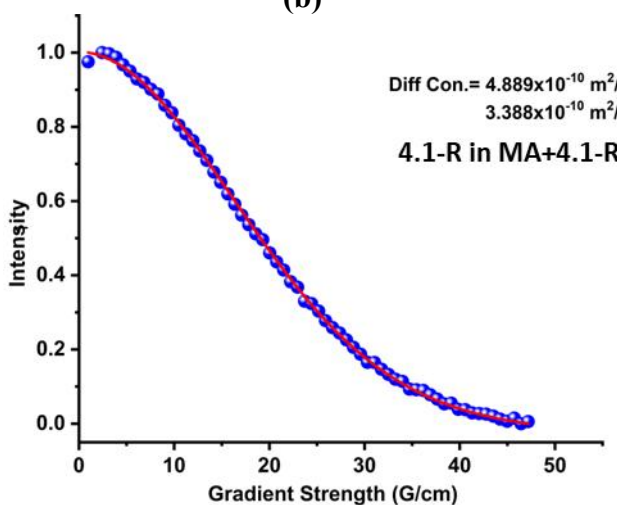
(a)



(b)



(c)



(d)

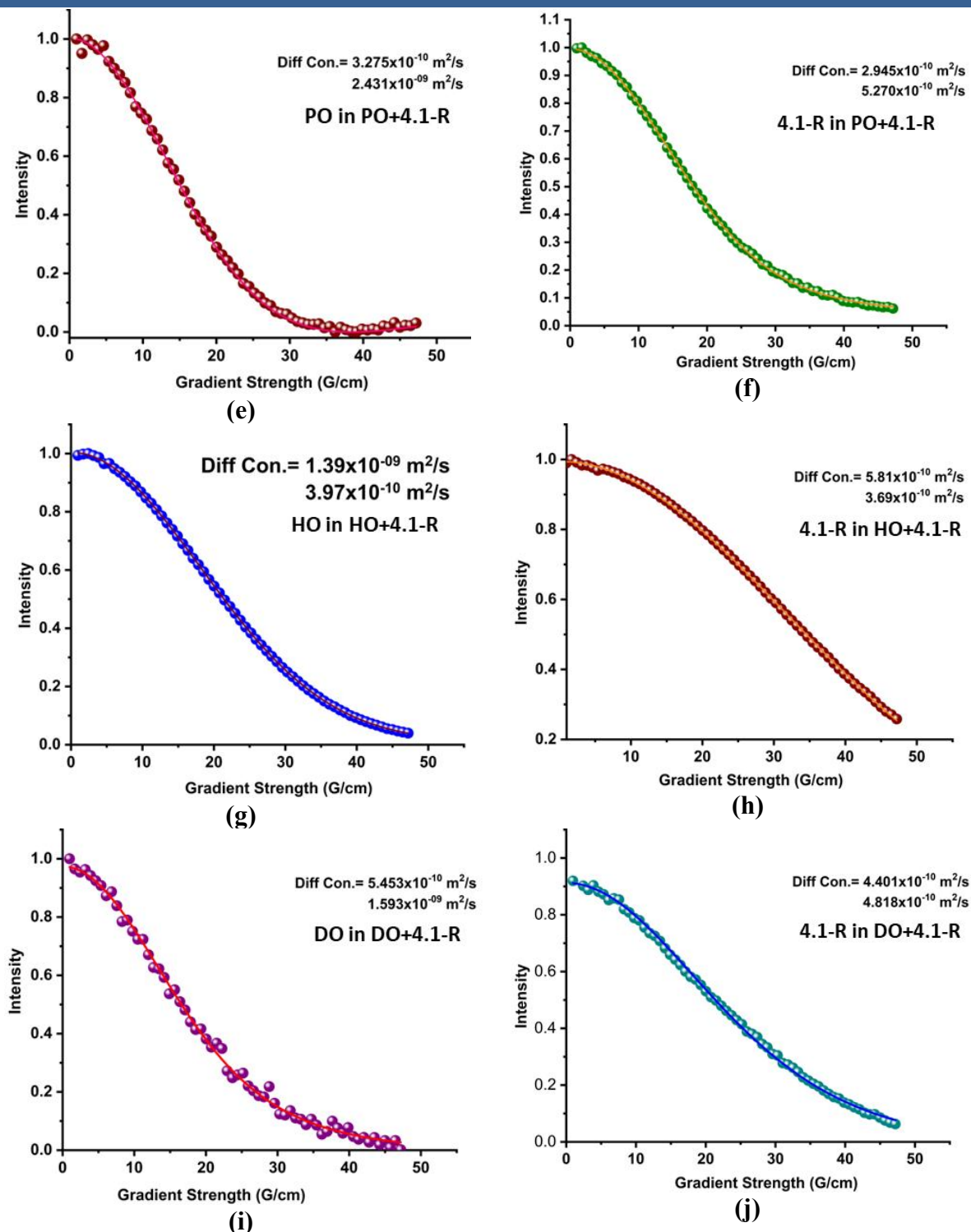


Figure A4.27. DOSY NMR data (CDCl_3 , 298K) for the successful host-guest events. Integral decay profile of guest protons (left), and host protons (right) in the host-guest system plotted as a function of gradient strength. All the DOSY NMR data were fit to bi-exponential decay curves wherein the dots represent experimental data and the solid-lines show the best fit using the equation 1. Diffusion coefficients obtained for free and bound guest molecules, a) $\pm\text{EP}$, c) $\pm\text{MA}$, e) $\pm\text{PO}$, g) $\pm\text{HO}$ and i) DO , and diffusion coefficients obtained for free and bound **4.1-R**, b) $\pm\text{EP}+4.1\text{-R}$, d) $\pm\text{MA}+4.1\text{-R}$, f) $\pm\text{PO}+4.1\text{-R}$, h) $\pm\text{HO}+4.1\text{-R}$ and j) $\pm\text{DO}+4.1\text{-R}$ are shown in the figures.

Table S6: Diffusion coefficients as obtained from the DOSY experiment for host and different guests in the studied host-guest systems.

1+Guest	Diffusion Coefficient ($\text{E}^{-10} \text{ m}^2/\text{s}$)			
	Guest		Host	
	Free	Bound	Free	Bound
$\pm\text{EP}$	19.47(5)	5.70(9)	4.08(2)	3.64(8)
$\pm\text{HO}$	13.99(8)	3.97(4)	5.81(2)	3.69(6)
$\pm\text{MA}$	12.77(7)	5.16(5)	4.88(8)	3.38(8)
$\pm\text{PO}$	24.31(3)	3.27(5)	5.27(1)	2.94(6)
$\pm\text{DO}$	15.91(3)	5.45(3)	4.82(8)	4.40(1)
4.1-R	5.81(2)			

Chiral recognition studies using UV-Visible titrations

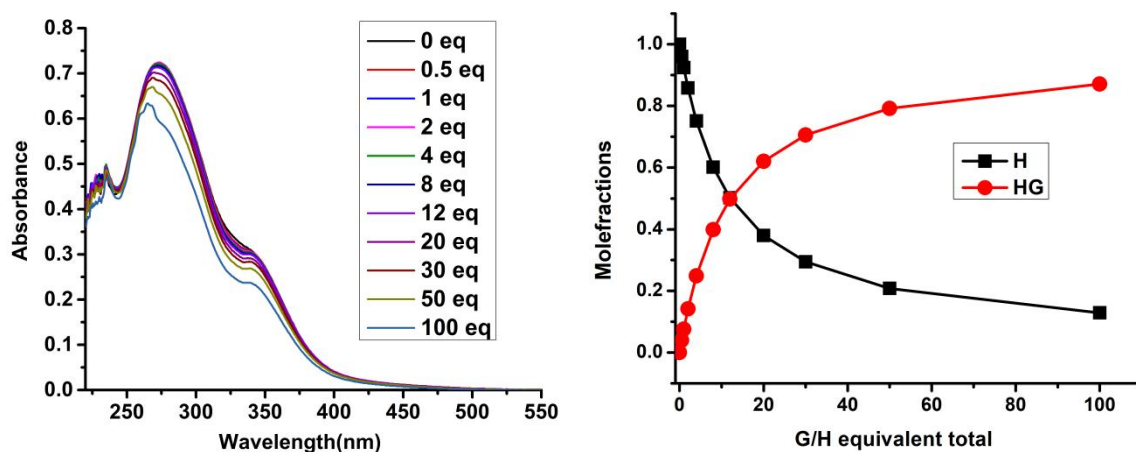


Figure A4.28. UV-Visible titration plots for the host-guest complex of **R-DO** upon addition to the **4.1-R** (left). Bind fit plot for **4.1-R** with **R-DO** (right).

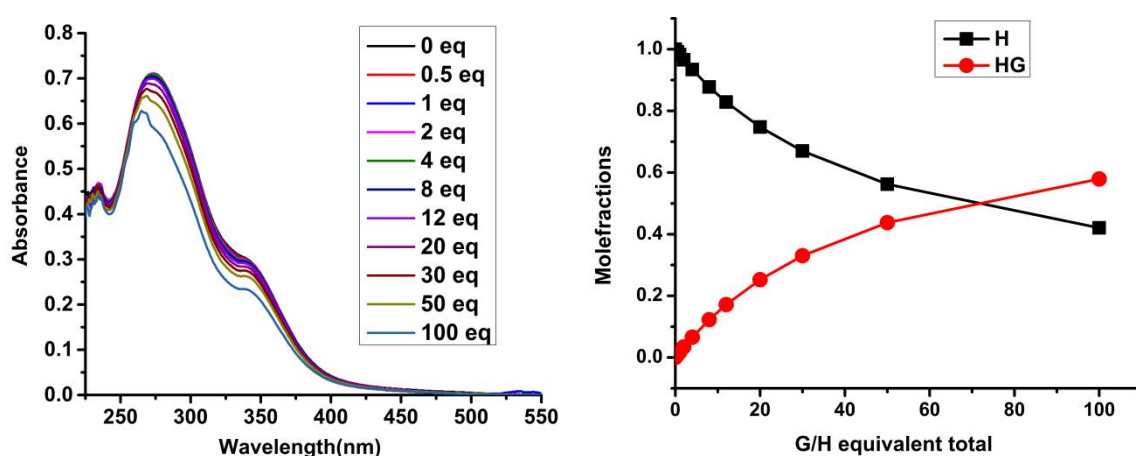


Figure A4.29. (a) UV-Visible titration plots for the host-guest complex of **S-DO** upon addition to the **4.1-R** (left). Bind fit plot for **4.1-R** with **S-DO** (right).

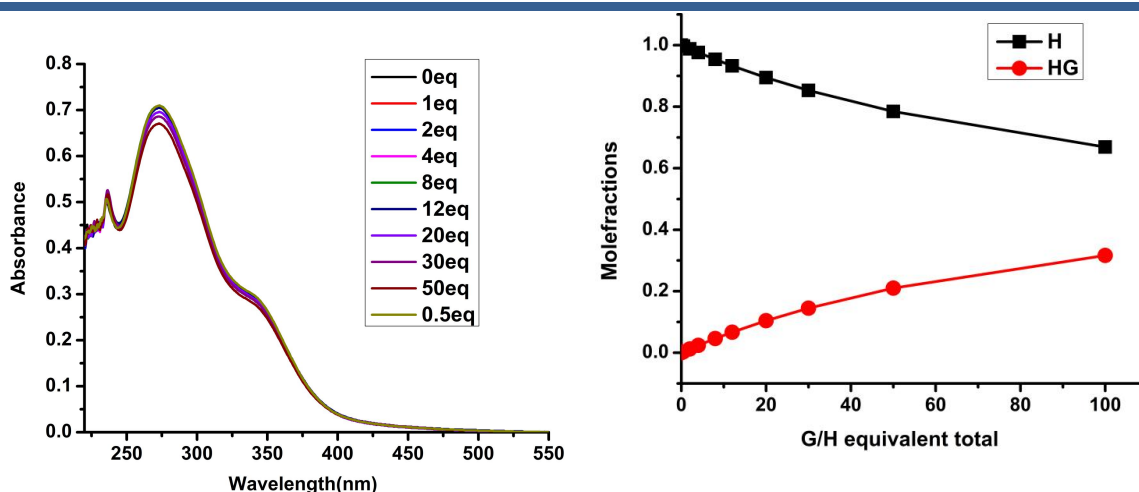


Figure A4.30. (a) UV-Visible titration plots for the host-guest complex of **R-EP** upon addition to the **4.1-R** (left). Bind fit plot for **4.1-R** with **R-EP** (right).

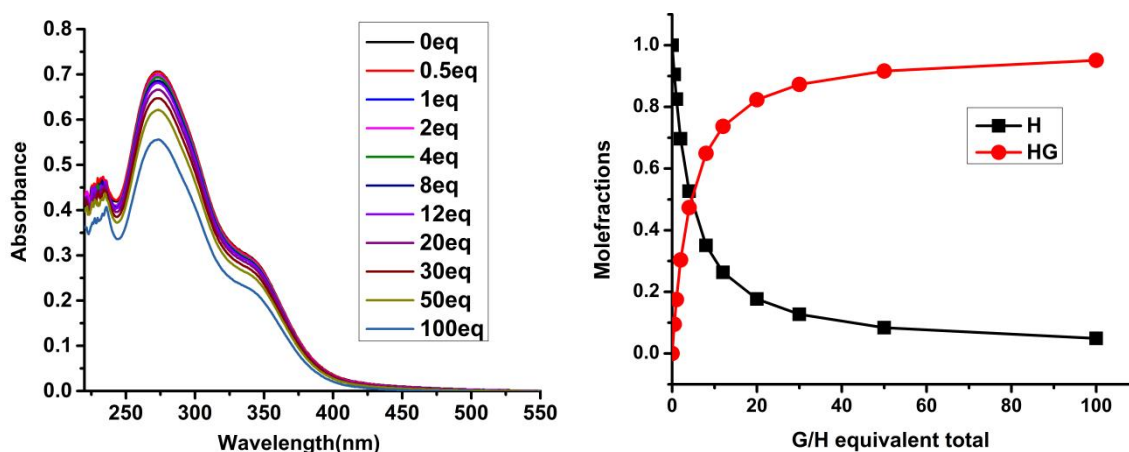


Figure A4.31. (a) UV-Visible titration plots for the host-guest complex of **S-EP** upon addition to the **4.1-R** (left). Bind fit plot for **4.1-R** with **S-EP** (right).

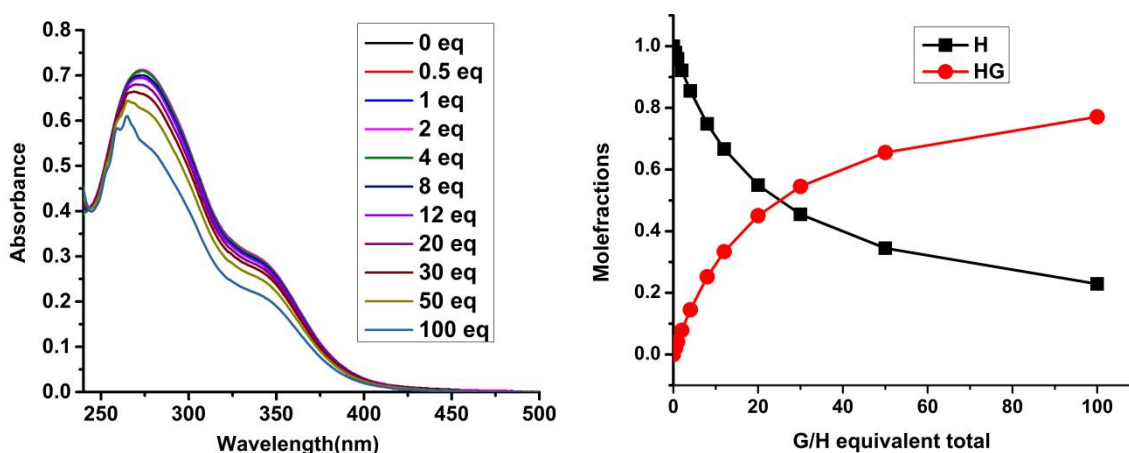


Figure A4.32. (a) UV-Visible titration plots for the host-guest complex of **R-MA** upon addition to the **4.1-R** (left). Bind fit plot for **4.1-R** with **R-MA** (right).

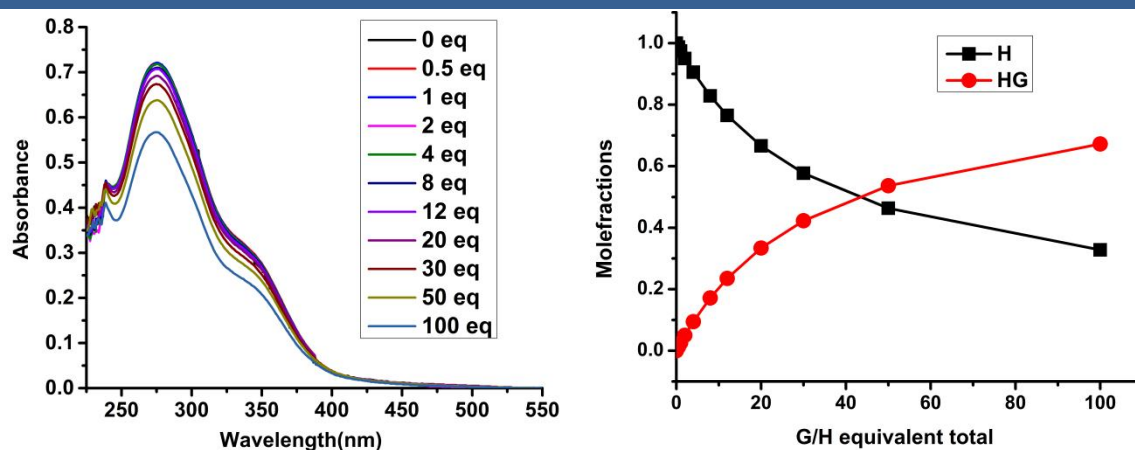


Figure A4.33. (a) UV-Visible titration plots for the host-guest complex of S-MA upon addition to the 4.1-R (left). Bind fit plot for 4.1-R with S-MA (right).

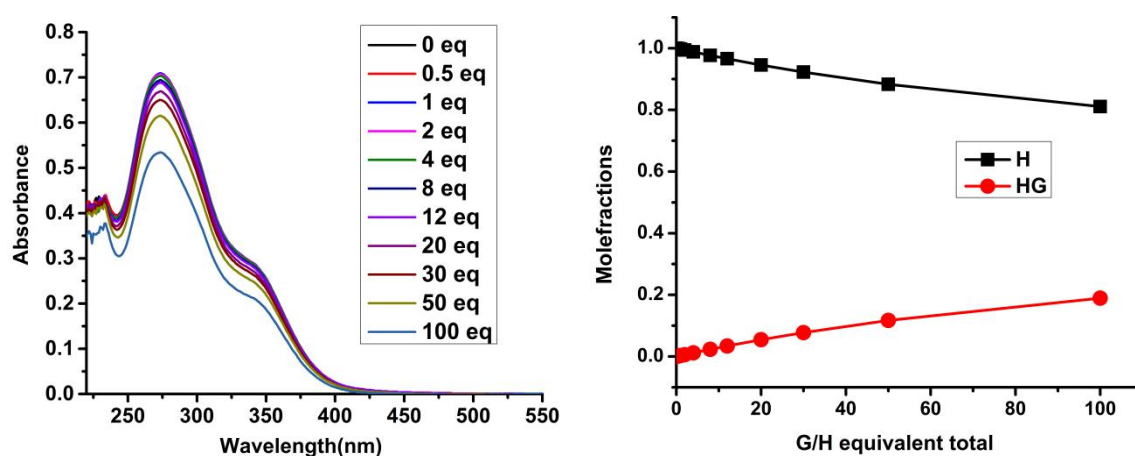


Figure A4.34. (a) UV-Visible titration plots for the host-guest complex of R-PO upon addition to the 4.1-R (left). Bind fit plot for 4.1-R with R-PO (right).

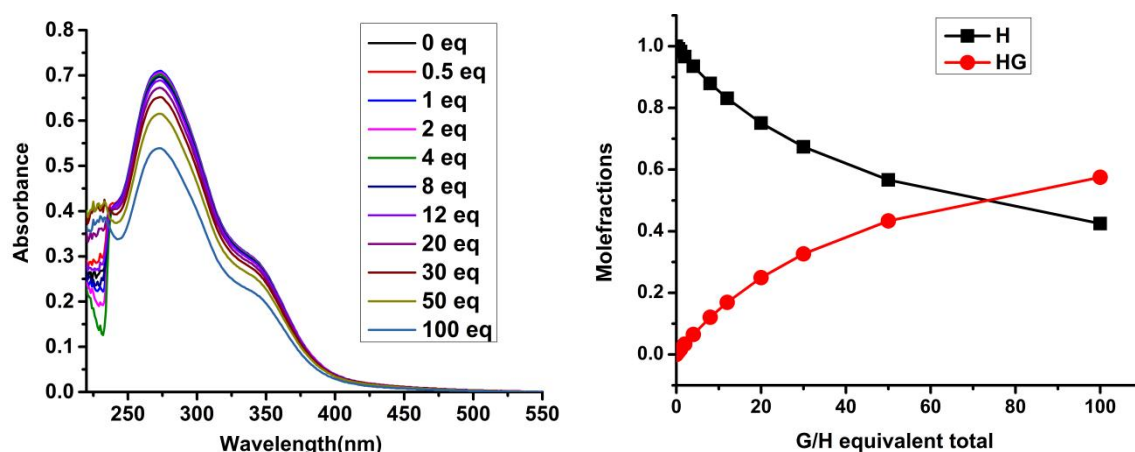


Figure A4.35. (a) UV-Visible titration plots for the host-guest complex of S-PO upon addition to the 4.1-R (left). Bind fit plot for 4.1-R with S-PO (right).

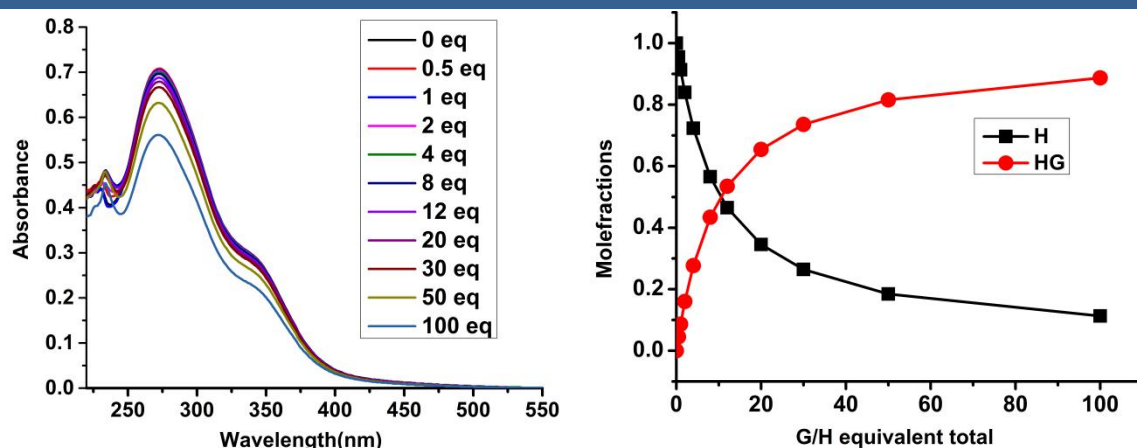


Figure A4.36. (a) UV-Visible titration plots for the host-guest complex of **R-HO** upon addition to the **4.1-R** (left). Bind fit plot for **4.1-R** with **R-HO** (right).

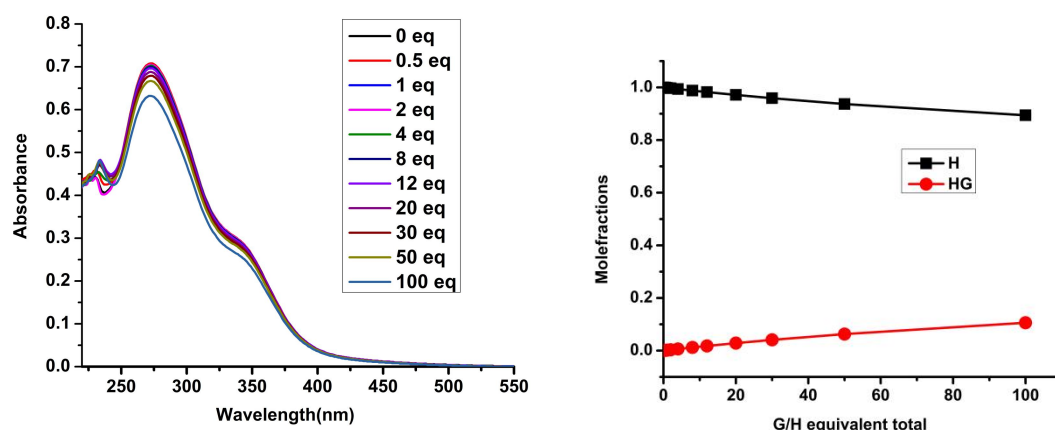


Figure A4.37. (a) UV-Visible titration plots for the host-guest complex of **S-HO** upon addition to the **4.1-R** (left). Bind fit plot for **4.1-R** with **S-HO** (right).

Table S7. Association constants (K_a/M^{-1}) of receptors **4.1-R** with chiral guests **MA**, **PO**, **DO**, **HO** and **EP**.

Chiral guests	4.1-R	Binding selectivity (ξ)
(R)-Mandelic acid (R-MA) (S)-Mandelic acid (S-MA)	$K_{II} = 7164. (13)$ $K_{II} = 4353.4 (16)$	1.7 (R)
(R)-Epichlorohydrin (R-EP) (S)-Epichlorohydrin (S-EP)	$K_{II} = 1010 (18)$ $K_{II} = 41525 (24)$	41.1 (S)
(R)-4-Benzyl-2-oxazolidinone (R-DO) (S)-4-Benzyl-2-oxazolidinone (S-DO)	$K_{II} = 14401.2 (11)$ $K_{II} = 2920.1 (8)$	4.9 (R)
(R)-Propyleneoxide (R-PO) (S)-Propyleneoxide (S-PO)	$K_{II} = 492.7(9)$ $K_{II} = 2871.0 (9)$	5.8 (S)
(R)4-Hydroxydihydrofuran-2(3h)-one (R-HO) (S)4-Hydroxydihydrofuran-2(3h)-one (S-HO)	$K_{II} = 16736.5 (39)$ $K_{II} = 249.7 (56)$	67.0 (R)

1:2 binding constants for all these host-guest pairs except **HO** are very low even with the excess equivalence of the guest molecules. This indicates that under the high dilution

conditions of the titration experiments, the guest molecules are more likely to bind at the interiors of the cage despite the presence of multiple chiral and interacting sites available at their exteriors. In the case of **HO** a low 2:1 binding was observed.

Control experiments with $L^{RRR}H_3$ and **2-R**

Control experiments suggest that both the pure precursor ligand $L^{RRR}H_3$ as well as the precursor hexameric cluster (**2-R**) could not recognize one enantiomer over the other under identical conditions as poor binding constant values were noticed on both these experiments suggesting the role of the supramolecular cage in the chiral recognition studies. (Figure 38-41)

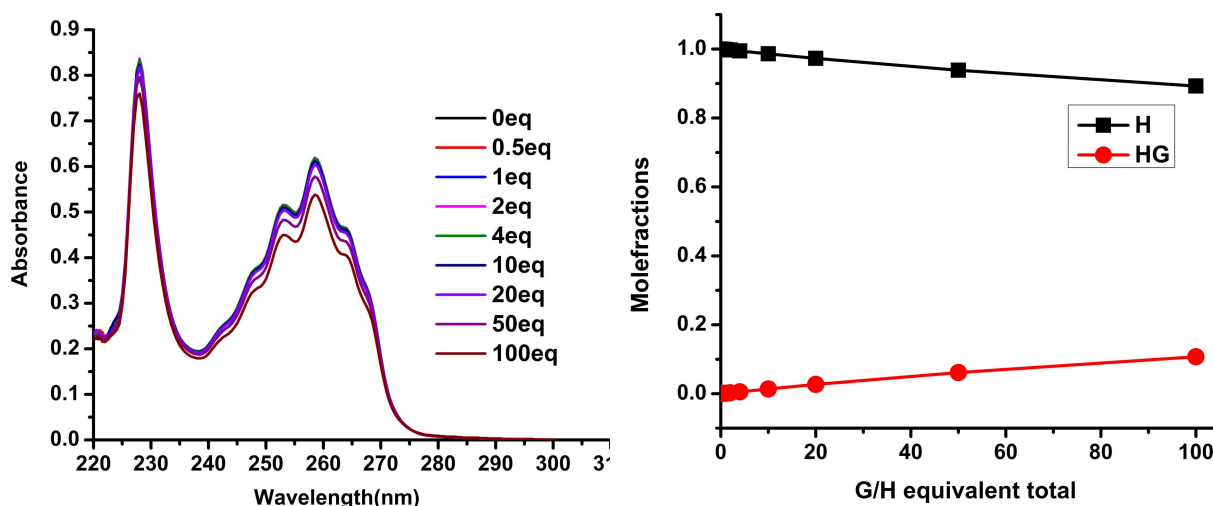


Figure A4.38. (a) UV-Visible titration plots for the host-guest complex of **R-EP** upon addition to the $L^{RRR}H_3$ (left). Bind fit plot for **R-EP** with $L^{RRR}H_3$ (right).

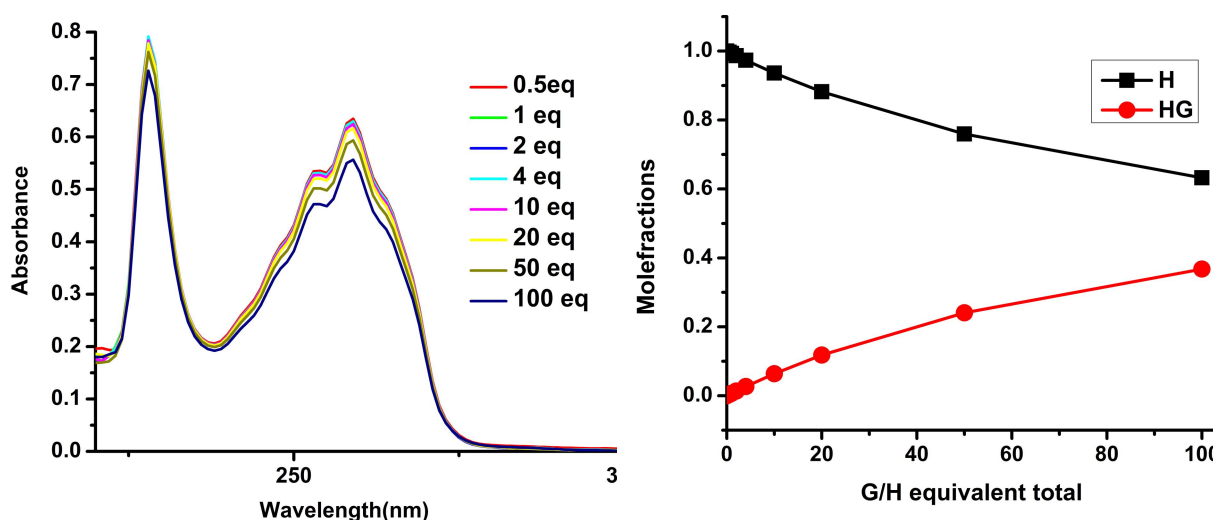


Figure A4.39. (a) UV-Visible titration plots for the host-guest complex of **S-EP** upon addition to the $L^{RRR}H_3$ (left). Bind fit plot for **S-EP** with $L^{RRR}H_3$ (right).

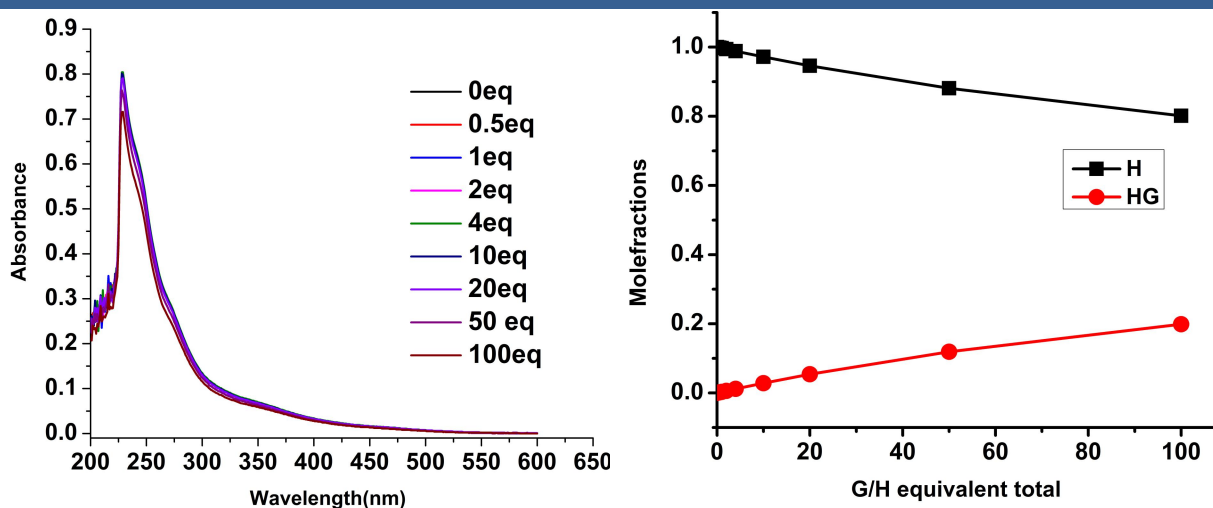


Figure A4.40. (a) UV-Visible titration plots for the host-guest complex of **R-EP** upon addition to the L^{RRR}H₃ (left). Bind fit plot for **2-R** with **R-EP** (right).

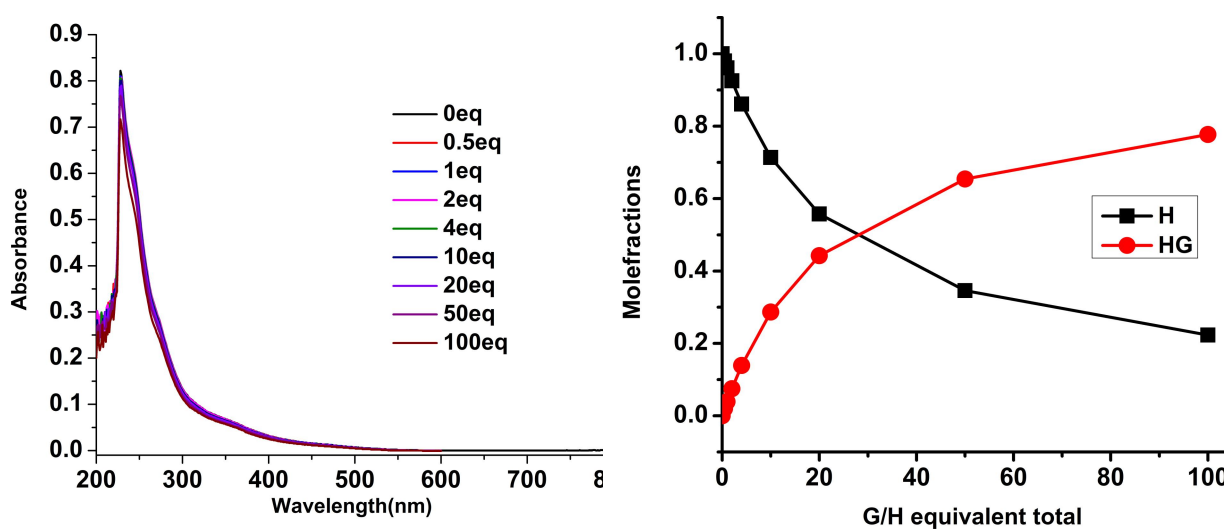


Figure A4.41. (a) UV-Visible titration plots for the host-guest complex of **S-EP** upon addition to the L^{RRR}H₃ (left). Bind fit plot for **2-R** with **S-EP** (right).

Table S8. Association constants (K_a/M^{-1}) of receptors **2-R** and L^{RRR}H₃ with chiral guests **EP**.

Guest	Recognition			
	K_{11} with 2-R	ζ (selective)	K_{11} with L ^{RRR} H ₃	ζ (selective)
R-EP	178	33(S)	47	28(S)
S-EP	5873		1316	

Optimized Structures of Host–Guest Complexes

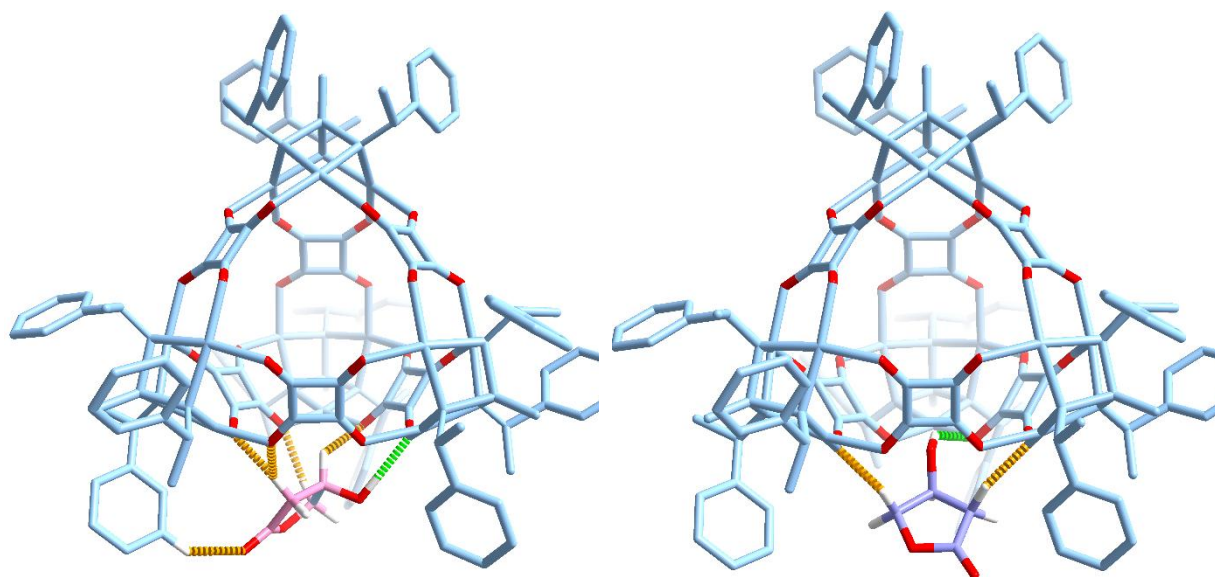


Figure 42. Potential non-covalent interactions responsible for the stabilization of the host–guest assemblies in **R-HO+4.1-R** (right) and **S-HO+4.1-R** (left) complexes. N blue; O red; Cl green; H white. The non-classical interactions (X=N, O) are shown in dotted lines: green O-H $\cdots$ X, yellow C-H $\cdots$ X and blue C-H $\cdots$ π .

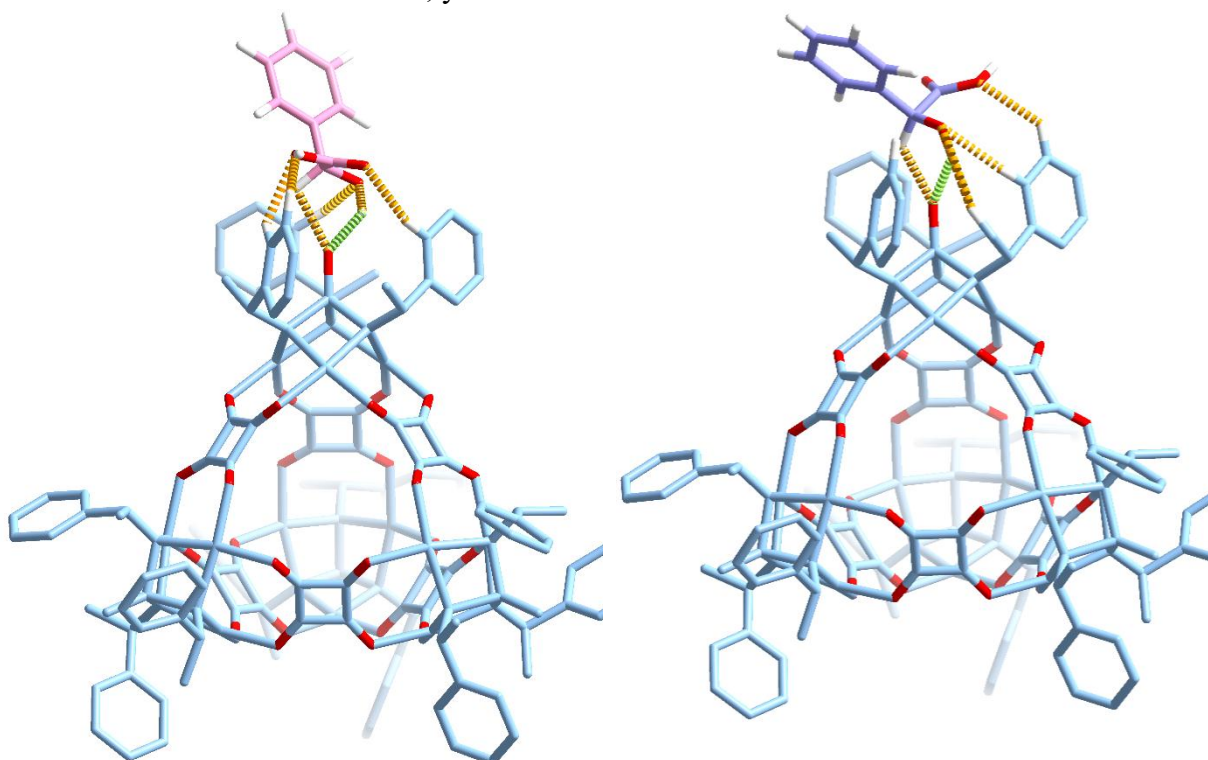


Figure 43. Potential non-covalent interactions responsible for the stabilization of the host–guest assemblies in **R-MA+4.1-R** (right) and **S-MA+4.1-R** (left) complexes. N blue; O red; Cl green; H white. The non-classical interactions (X=N, O) are shown in dotted lines: green O-H $\cdots$ X, yellow C-H $\cdots$ X and blue C-H $\cdots$ π .

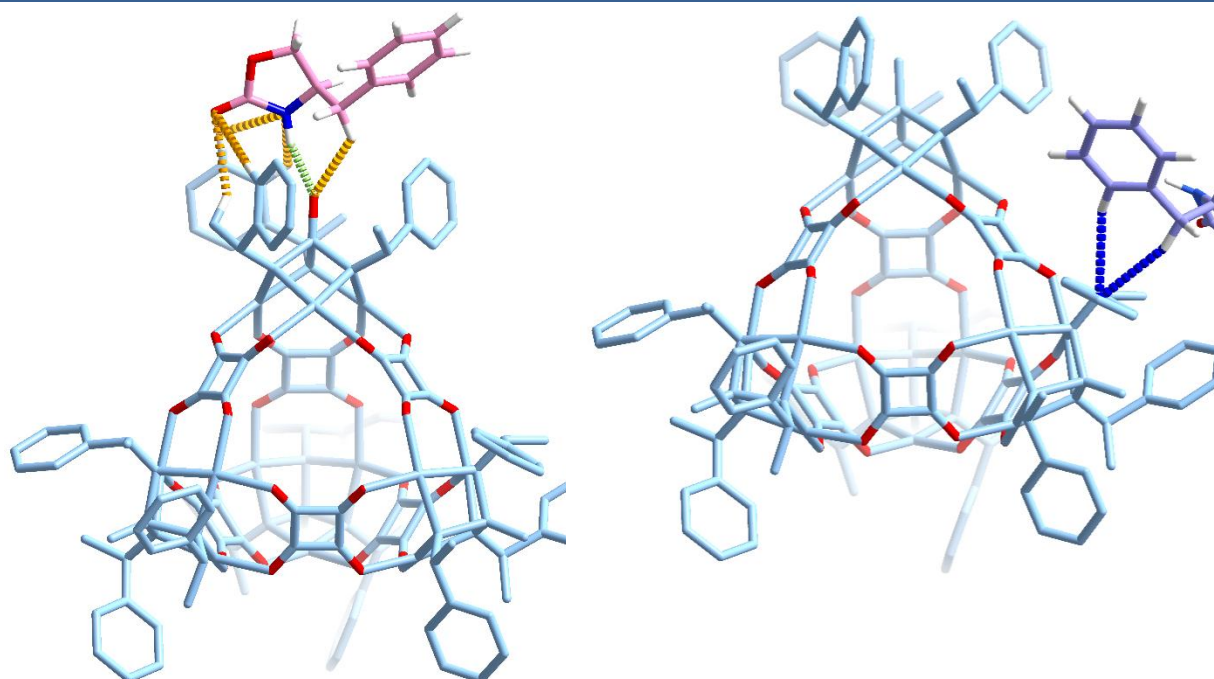


Figure 44. Potential non-covalent interactions responsible for the stabilization of the host-guest assemblies in **R-DO+4.1-R** (right) and **S-DO+4.1-R** (left) complexes. N blue; O red; Cl green; H white. The non-classical interactions ($X=N, O$) are shown in dotted lines: green $O-H\cdots X$, yellow $C-H\cdots X$ and blue $C-H\cdots\pi$.

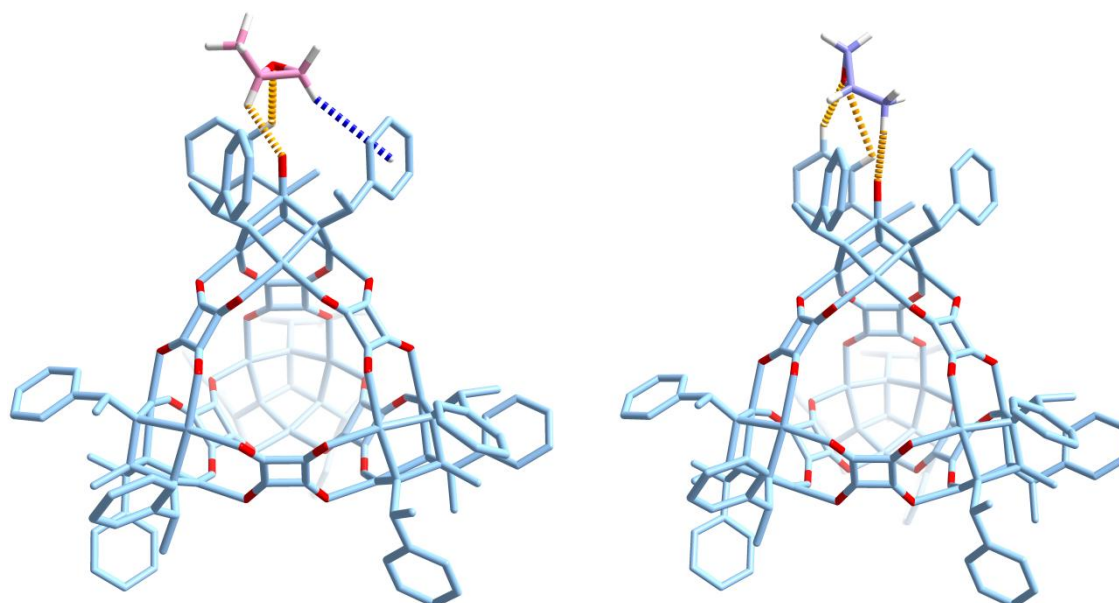


Figure 45. Potential non-covalent interactions responsible for the stabilization of the host-guest assemblies in **R-PO+4.1-R** (right) and **S-PO+4.1-R** (left) complexes. N blue; O red; Cl green; H white. The non-classical interactions ($X=N, O$) are shown in dotted lines: green $O-H\cdots X$, yellow $C-H\cdots X$ and blue $C-H\cdots\pi$.

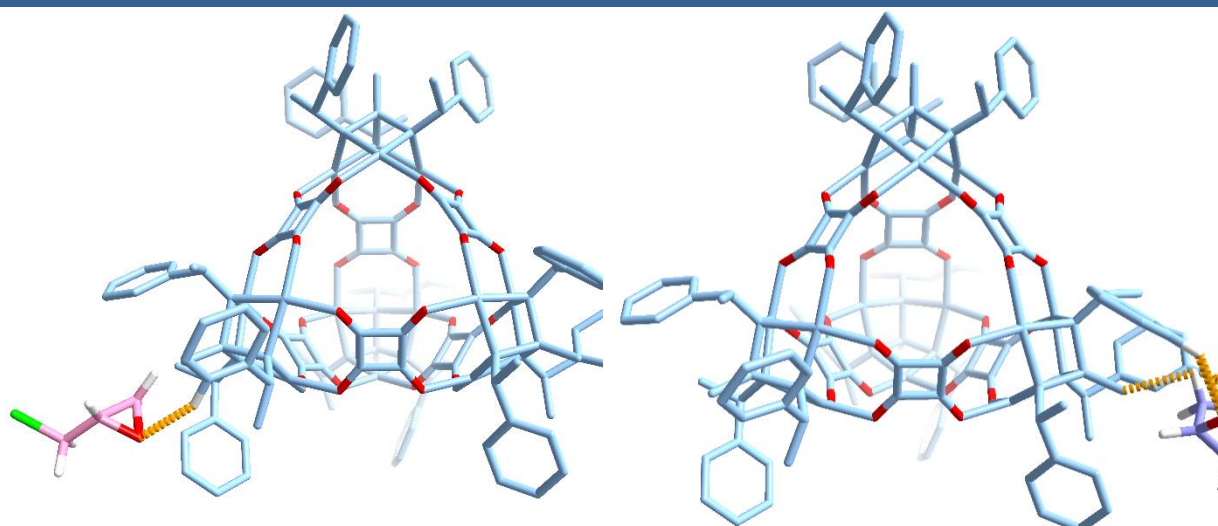


Figure 46. Potential non-covalent interactions responsible for the stabilization of the host–guest assemblies in **R-EP+4.1-R** (right) and **S-EP+4.1-R** (left) complexes. N blue; O red; Cl green; H white. The non-classical interactions (X=N, O) are shown in dotted lines: green O–H···X, yellow C–H···X and blue C–H··· π .

Table S9. Bond length and bond angles for the Host-Guest complexes of the **4.1-R**.

Host+Guest	Interactions (D–H···A)	d(H···A) Å	d(D···A) Å	<DHA °
R-HO+4.1-R	O(296)–H(297)···O(98)	1.8714	2.8731	175.543
	C(288)–H(293)···O(97)	2.2566	2.9867	120.973
	C(285)–H(290)···O(95)	2.2835	3.0455	124.051
	C(161)–H(269)···O(295)	2.2027	3.1533	143.733
	C(287)–H(261)···O(118)	2.3300	3.1835	131.368
	C(287)–H(261).....O(92)	2.1250	3.1134	145.422
S-HO+4.1-R	O(296)–H(297).....O(107)	2.0419	2.8295	134.049
	C(285)–H(290).....O(97)	2.3513	2.9233	119.747
	C(287)–H(291).....O(118)	2.2351	2.9584	119.437
R-MA+4.1-R	O(4)–H(301).....O(300)	1.8154	2.6298	133.824
	C(12)–H(182).....O(300)	2.2518	3.1863	141.829
	C(296)–H(297).....O(4)	2.3178	2.7644	119.060
	C(33)–H(200).....O(302)	2.4389	3.1086	118.162
	C(32)–H(199).....O(302)	2.4472	3.1092	117.755
	C(24)–H(191).....O(299)	2.2570	3.2424	148.350
S-MA+4.1-R	O(300)–H(301).....O(4)	1.8735	2.6896	134.622
	C(296)–H(297).....O(4)	2.1418	2.8459	117.548
	C(13)–H(184).....O(300)	3.1469	4.1748	156.219
	C(11)–H(184).....O(302)	2.3978	3.2563	134.456
	C(12)–H(182).....O(300)	2.3568	3.2803	140.700
R-DO+4.1-R	N(301)–H(302).....O(106)	1.9049	2.90802	160.411
	C(290)–H(292).....O(106)	2.5801	3.3843	127.341
	C(126)–H(241).....O(296)	2.8027	3.8847	170.341
	C(127)–H(244).....O(296)	2.8462	3.7891	143.720
	C(134)–H(249).....O(296)	2.479	3.1650	119.655
	C(135)–H(250).....N(301)	2.8257	3.4794	118.353

	C(134)-H(249).....N(301)	3.1787	3.6507	117.006
S-DO+4.1-R	C(296)-H(297)..... π	3.1717	4.2333	159.48
	C(291)-H(297)..... π	3.1061	4.1313	156.717
R-PO+4.1-R	C(293)-H(294).....O(4)	2.2283	2.9591	121.614
	C(24)-H(191).....O(288)	2.3664	3.1479	126.8
	C(285)-H(287)..... π	3.5028	4.517	155.083
S-PO+4.1-R	C(289)-H(292).....O(4)	2.0534	3.1544	169.285
	C(24)-H(191).....O(288)	3.3090	3.6907	101.808
	C(23)-H(190).....O(288)	2.2101	3.1887	147.689
R-EP+4.1-R	C(12)-H(182).....O(288)	2.1372	3.1222	148.649
S-EP+4.1-R	C(32)-H(199).....Cl(294)	2.9184	3.7640	134.518
	C(23)-H(190).....O(288)	2.2997	3.1644	134.552
	C(289)-H(199).....O(4)	2.467	2.6437	118.373

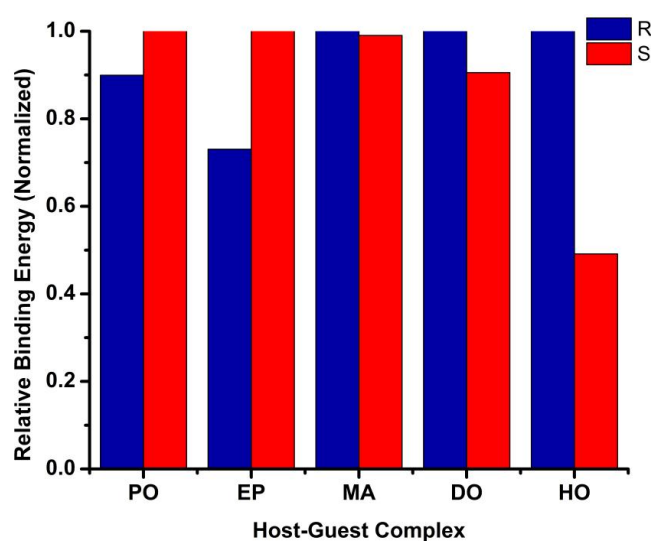


Figure 47. Relative binding energy of the host-guest complex calculated using PM6–modelling by G03 software.

HPLC Methods for the Enantiomeric Separation of the Chiral Guest Molecules

The crystallized host-guest crystallites for **S-EP** were examined with ^{31}P $\{^1\text{H}\}$ NMR spectroscopy and MALDI-TOF spectrometry. From the experiments, it is clear that the cages are in-tact in the host-guest crystallites.

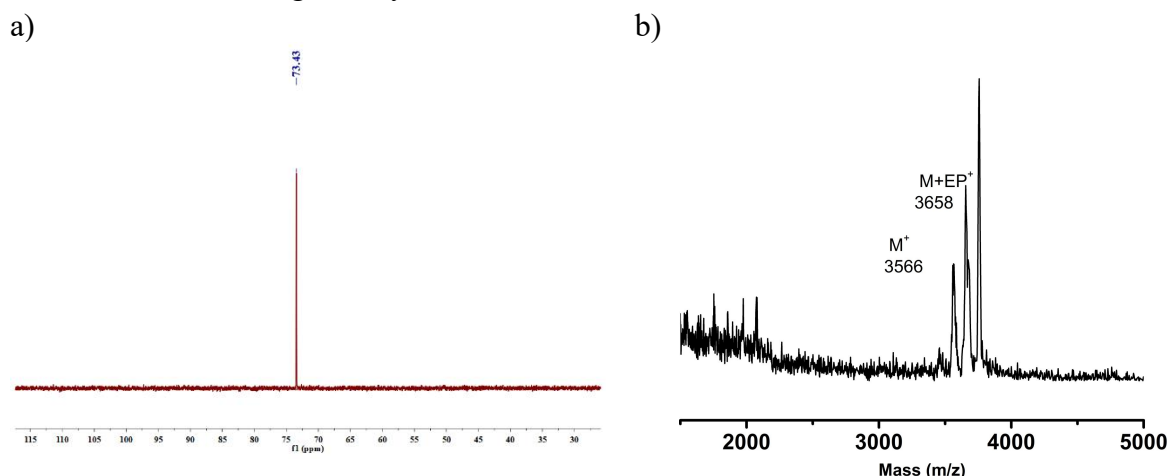


Figure 48. a) ^{31}P $\{^1\text{H}\}$ NMR spectrum and b) MALDI-TOF spectra of crystallized host-guest crystallites of **S-EP**

MA+4.1-R System

Method: Enantiometric purity of **MA** was determined by HPLC with Chiralpak AD-H (20 cm) column with a flow rate of 1 mL/min, 95 /5/0.1 of n-hexane/iso-propanol/trifluoroacetic acid as eluent and the effluent was monitored at a wavelength 254 nm.

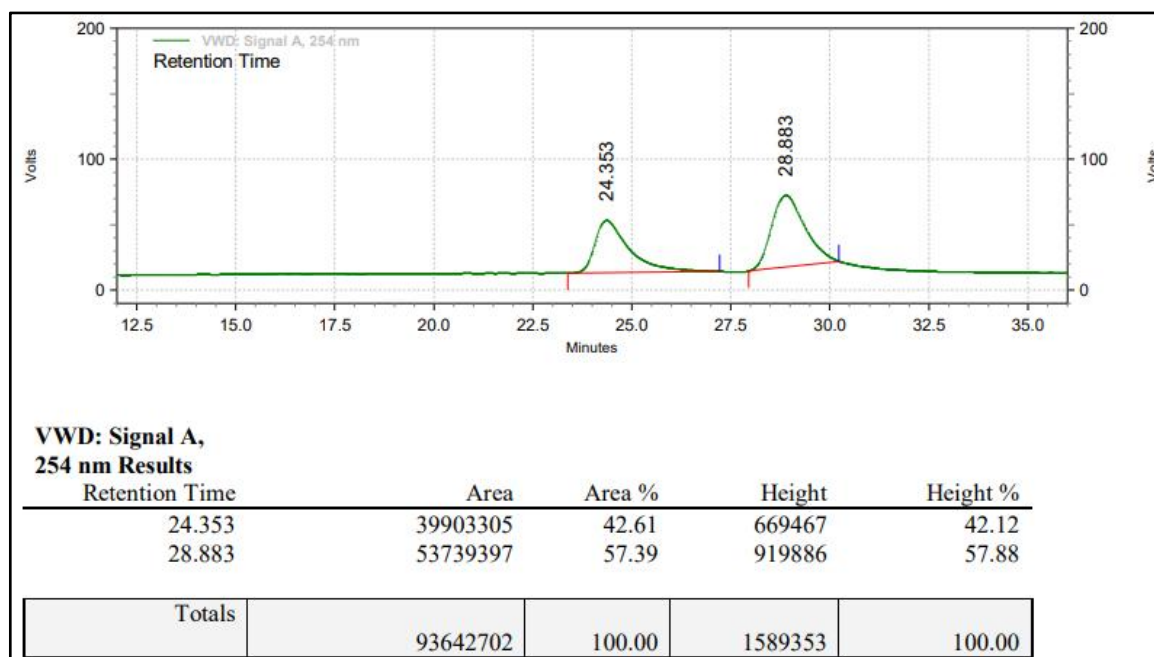


Figure 49. HPLC chromatogram and analysis plot showing the resolved peaks for untreated rac-mandelic acid (**MA**).

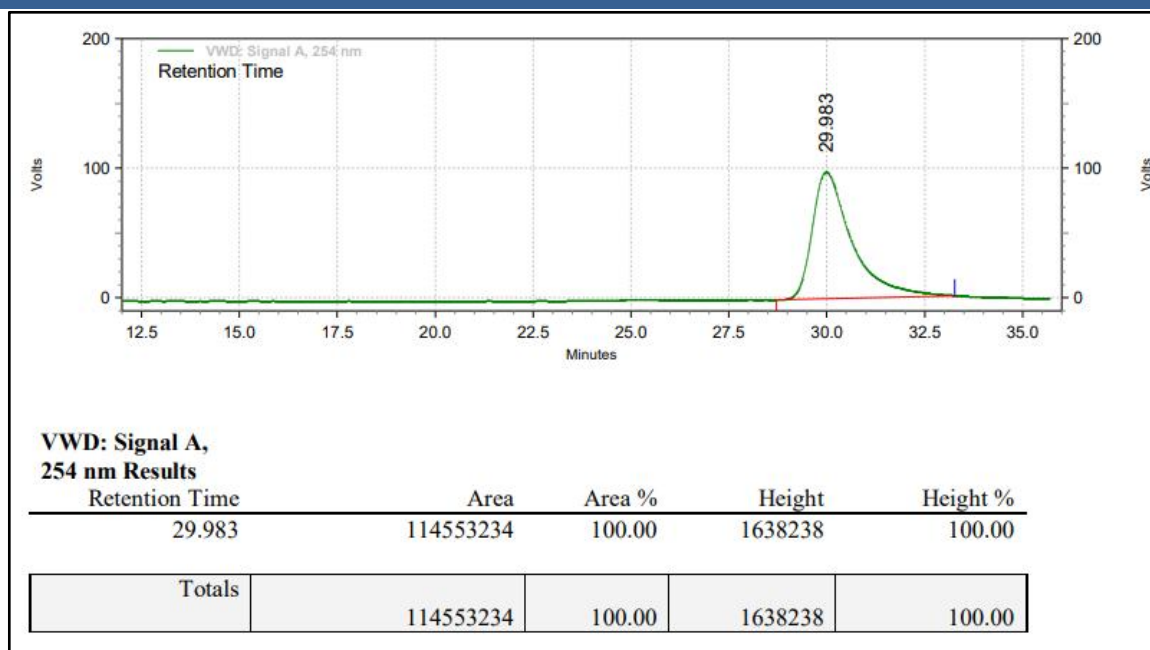


Figure 50. HPLC chromatogram and analysis plot showing the resolved peaks for untreated *R*-mandelic acid (**R-MA**).

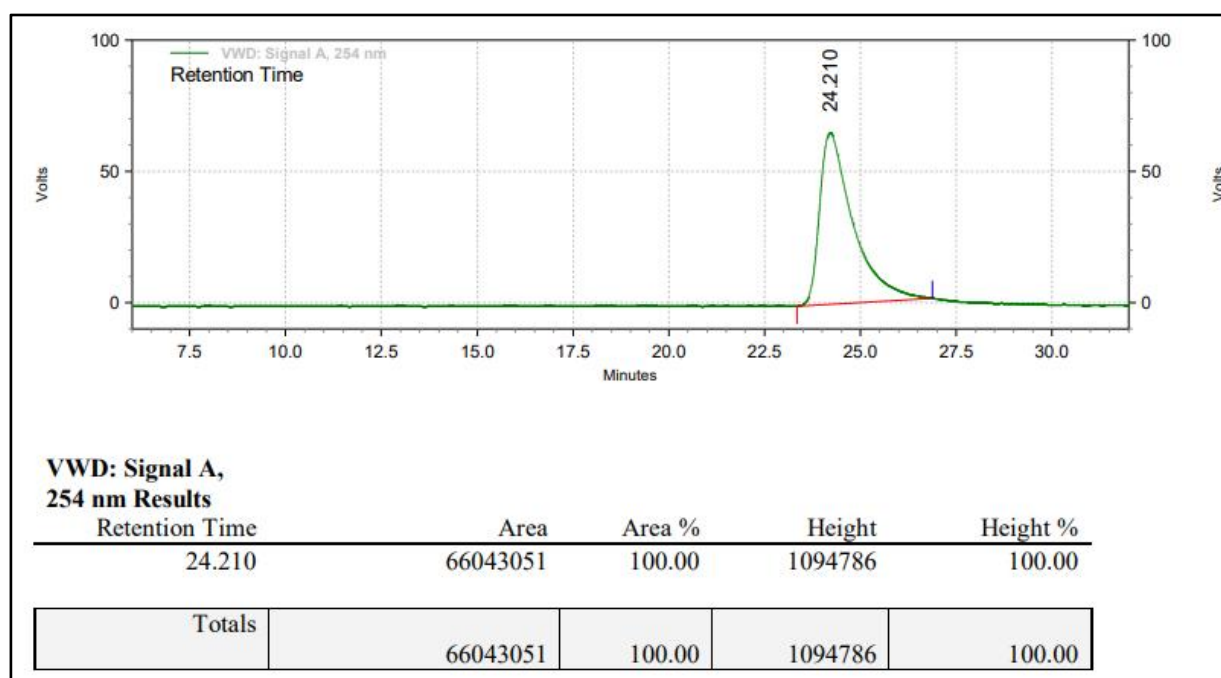


Figure 51. HPLC chromatogram and analysis plot showing the resolved peaks for untreated *S*-mandelic acid (**S-MA**).

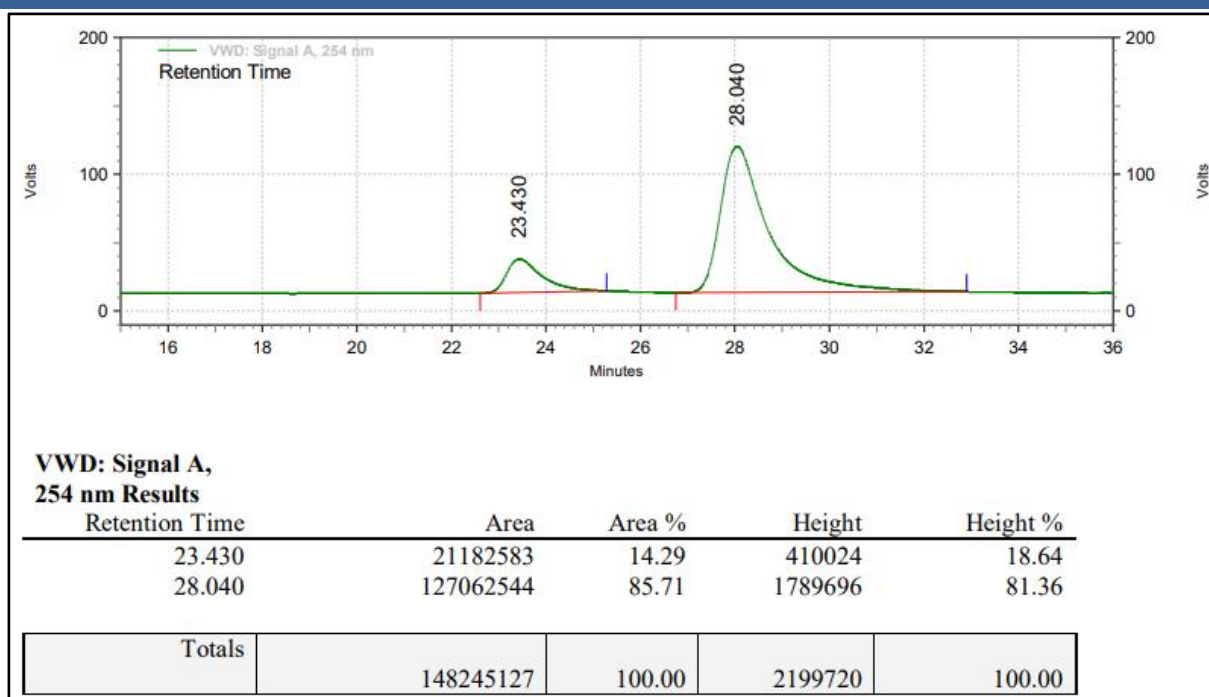


Figure 52. HPLC chromatogram and analysis plot showing the resolved peaks for separation of rac-mandelic acid (MA) by **4.1-R**, %ee = 71.

DO+4.1-R System

Method: Enantiometric purity of **DO** was determined by HPLC with Chiralpak AD-H (20 cm) column with a flow rate of 0.6 mL/min was employed for the chiral HPLC analysis using 45/55 of n-Hexane/Methanol as eluent and the effluent was monitored at a wavelength 254 nm.

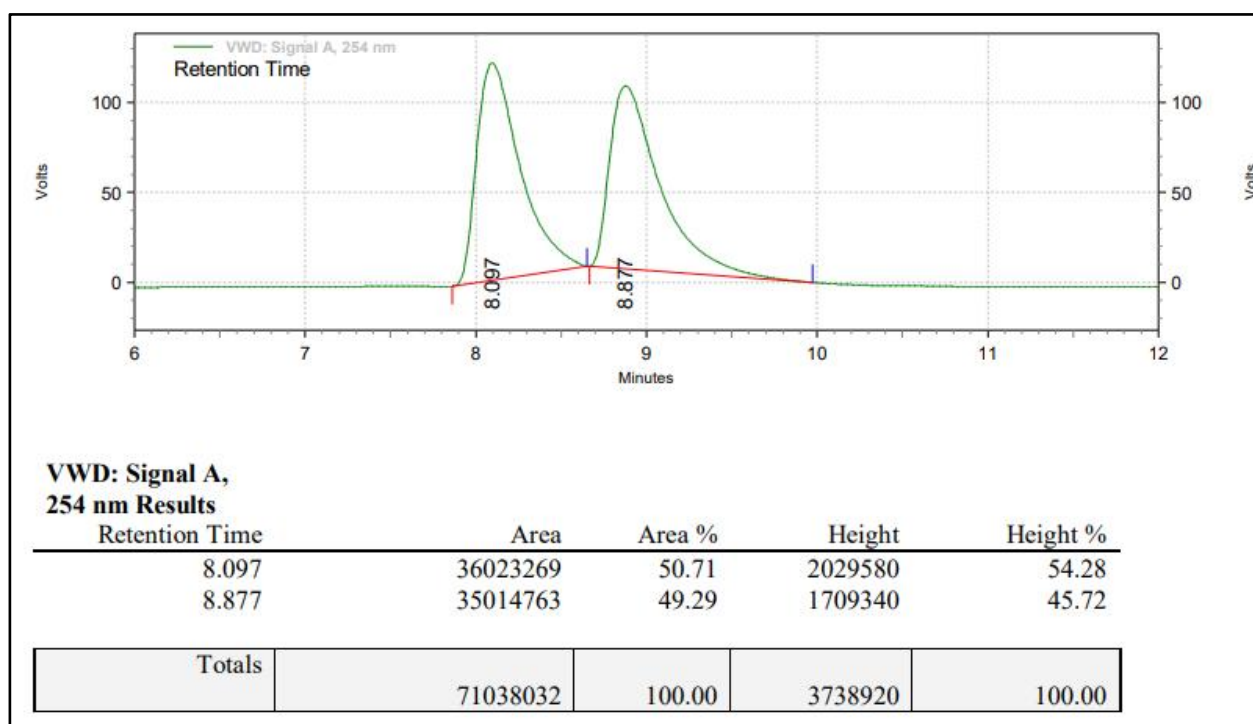


Figure 53. HPLC chromatogram and analysis plot showing the resolved peaks for untreated rac-4-benzyl-2-oxazolidinone (**DO**).

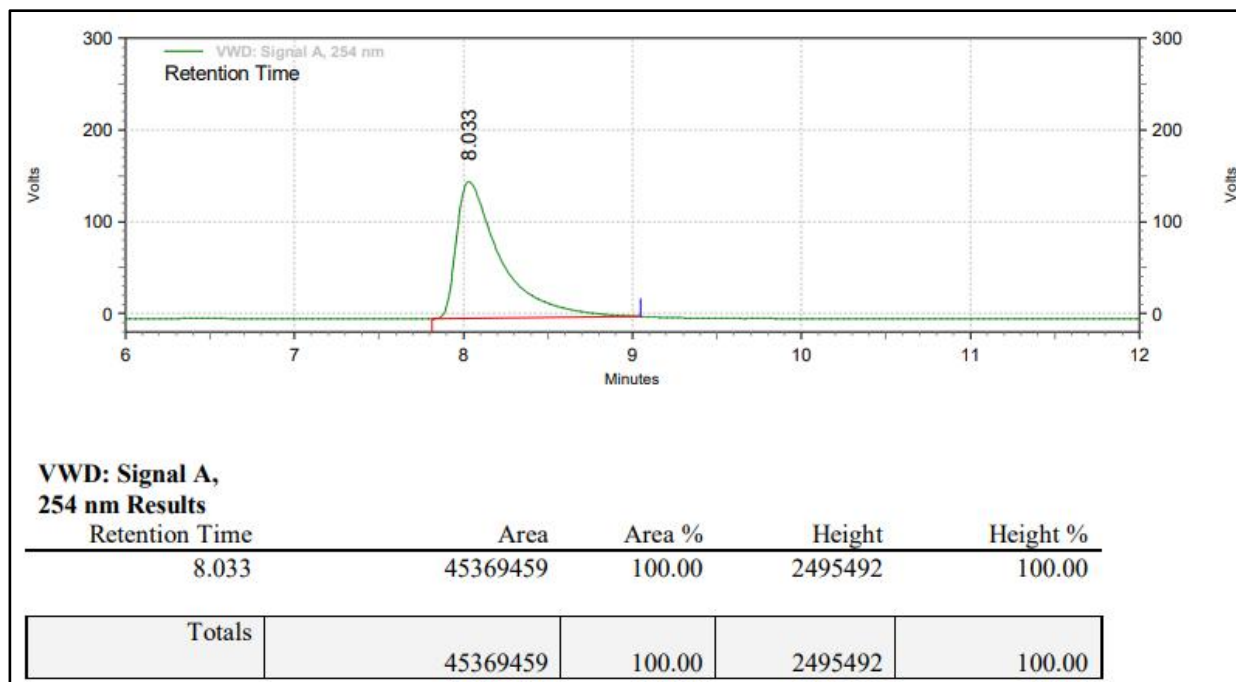


Figure 54. HPLC chromatogram and analysis plot showing the resolved peaks for untreated R-4-benzyl-2-oxazolidinone (**R-DO**).

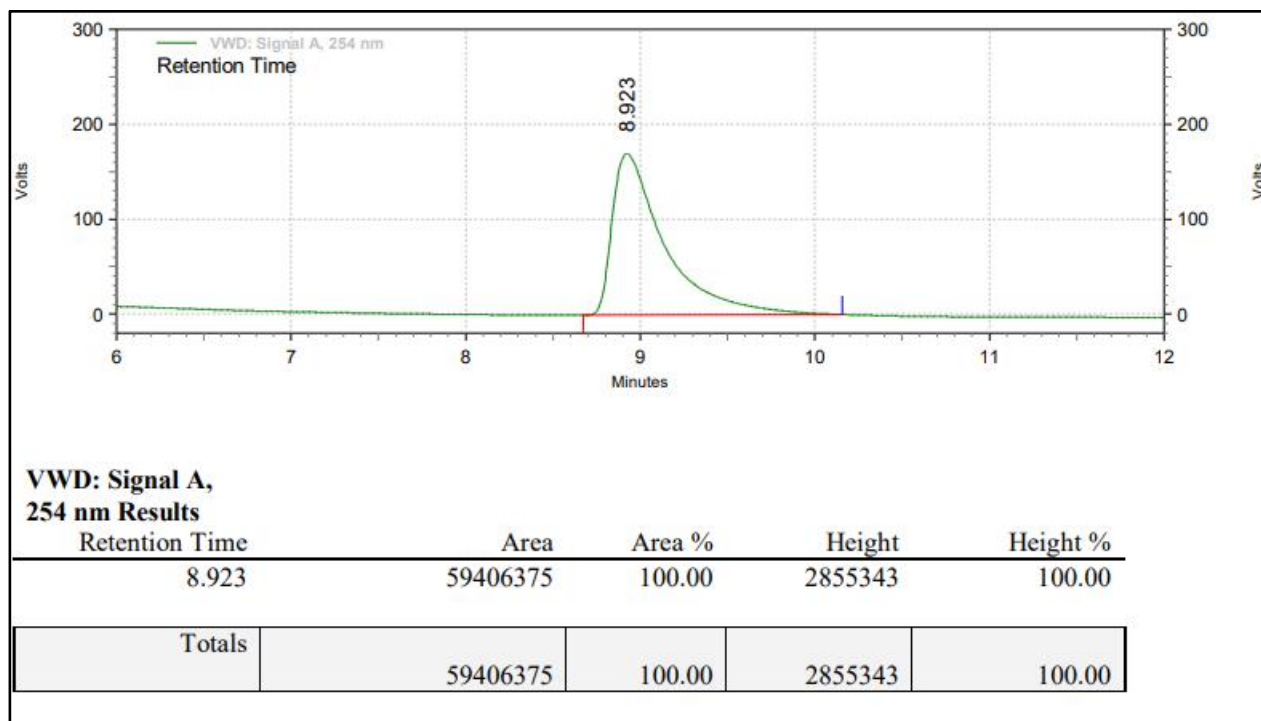


Figure 55. HPLC chromatogram and analysis plot showing the resolved peaks for untreated S-4-benzyl-2-oxazolidinone (**S-DO**).

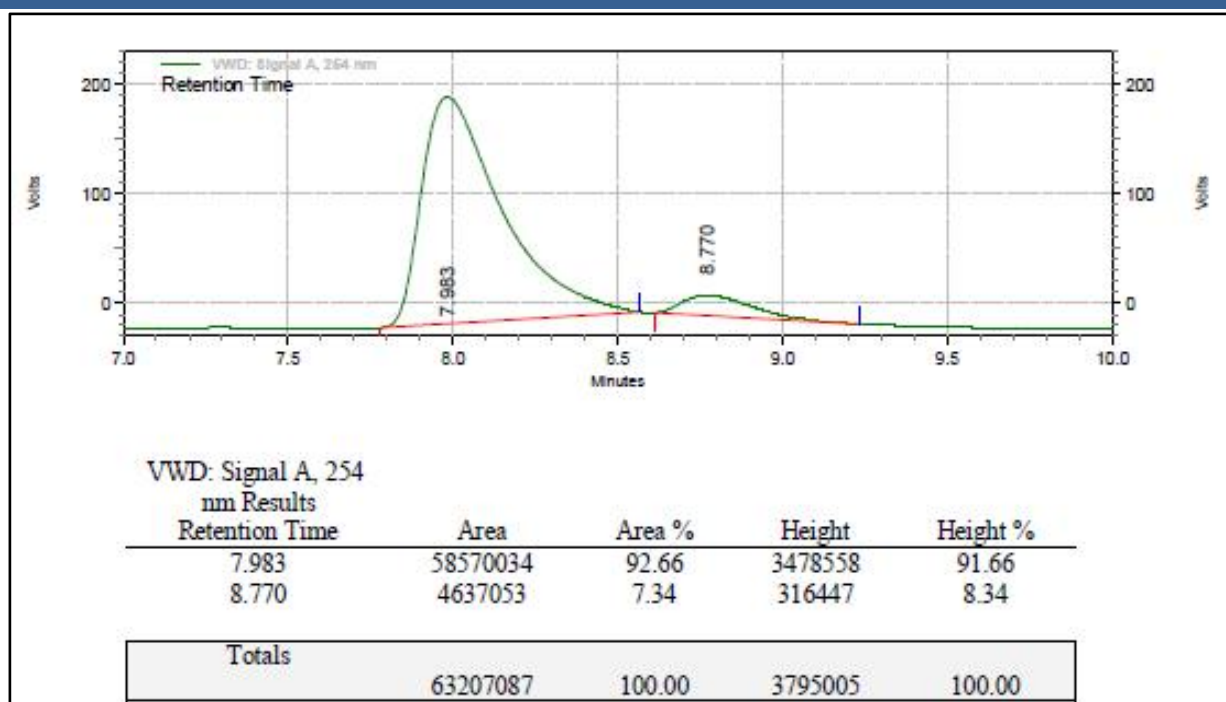


Figure 56. HPLC chromatogram and analysis plot showing the resolved peaks for separation of rac -4-benzyl-2-oxazolidinone (DO) by **4.1-R**, %ee = 85.

EP+4.1-R System

Method: Enantiometric purity of EP was determined by HPLC with Chiralpak IA (20 cm) column with a flow rate of 1 mL/min. was employed for the chiral HPLC analysis using 98/2 of n-hexane/isopropanol as eluent and the effluent was monitored at a wavelength 205 nm.

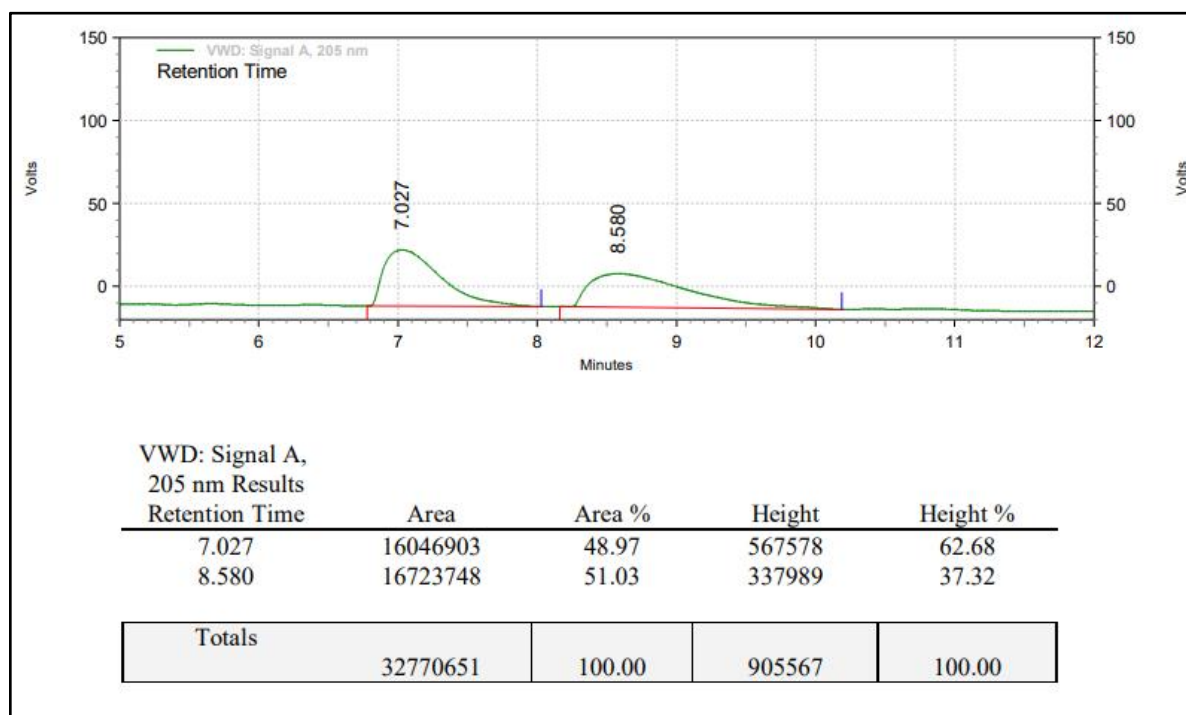


Figure 57. HPLC chromatogram and analysis plot showing the resolved peaks for untreated rac- pichlorohydrin (**EP**).

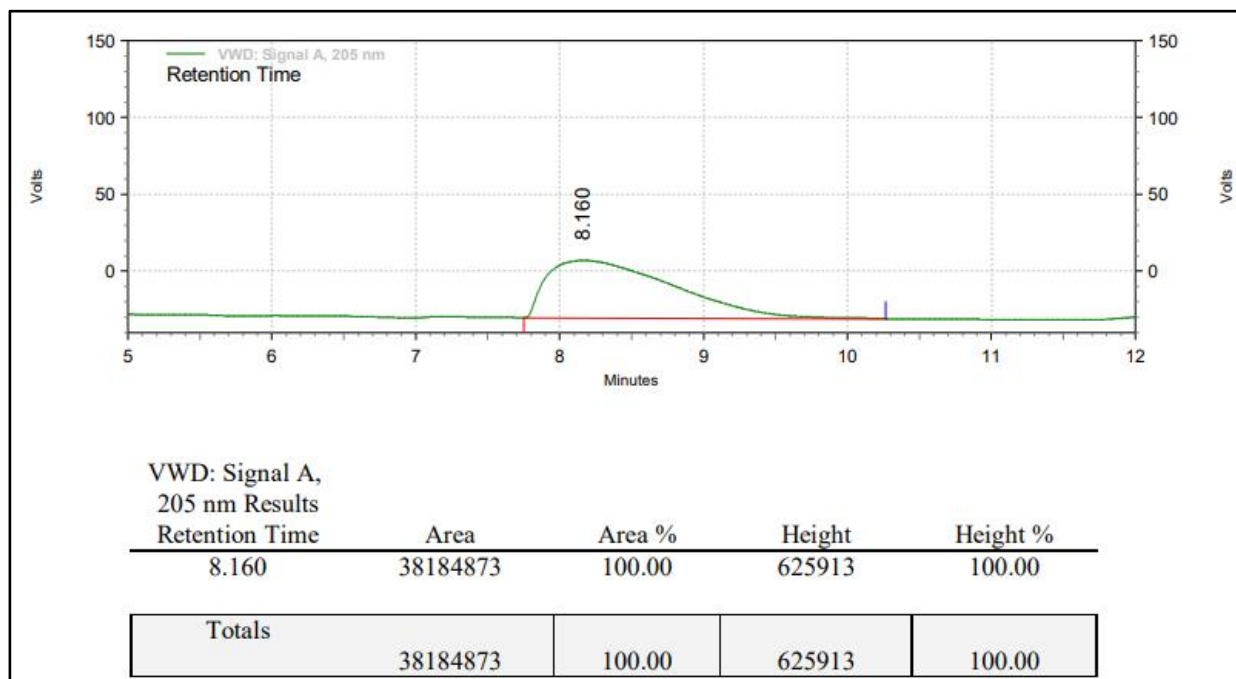


Figure 58. HPLC chromatogram and analysis plot showing the resolved peaks for untreated *R*-epichlorohydrin (**R-EP**).

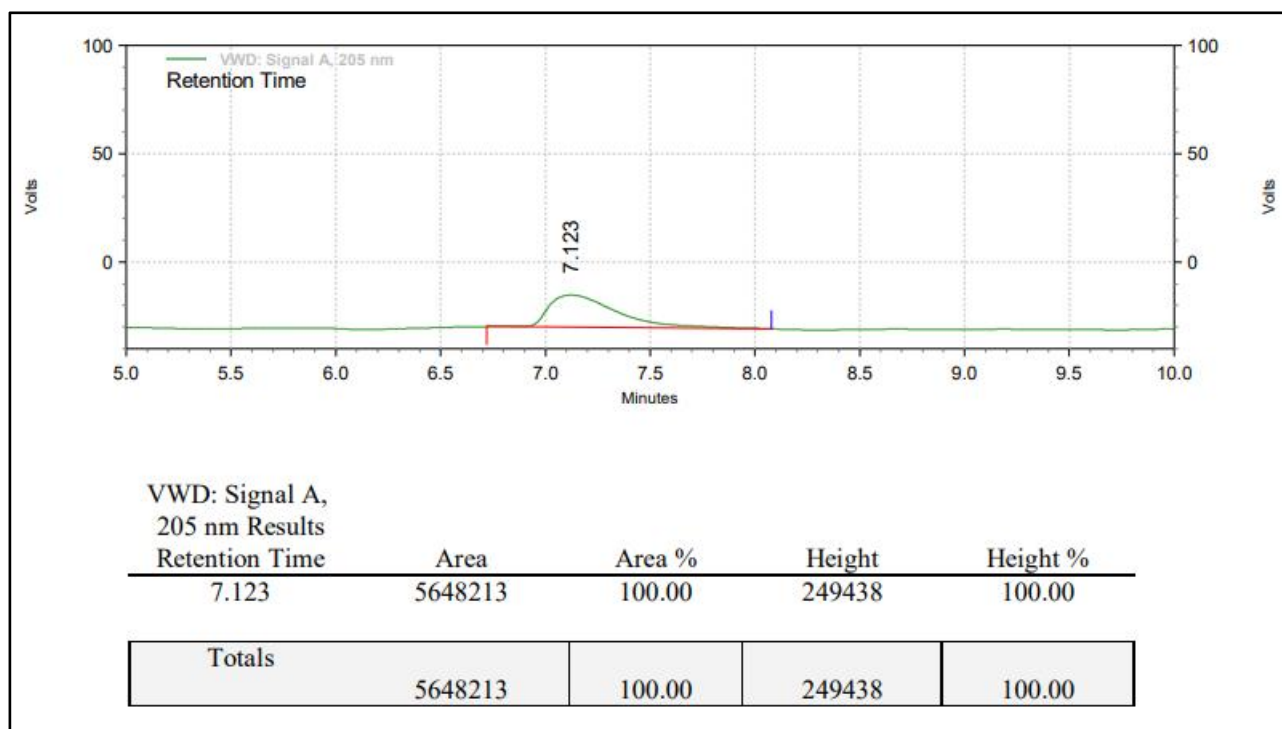


Figure 59. HPLC chromatogram and analysis plot showing the resolved peaks for untreated *S*-epichlorohydrin (**S-EP**).

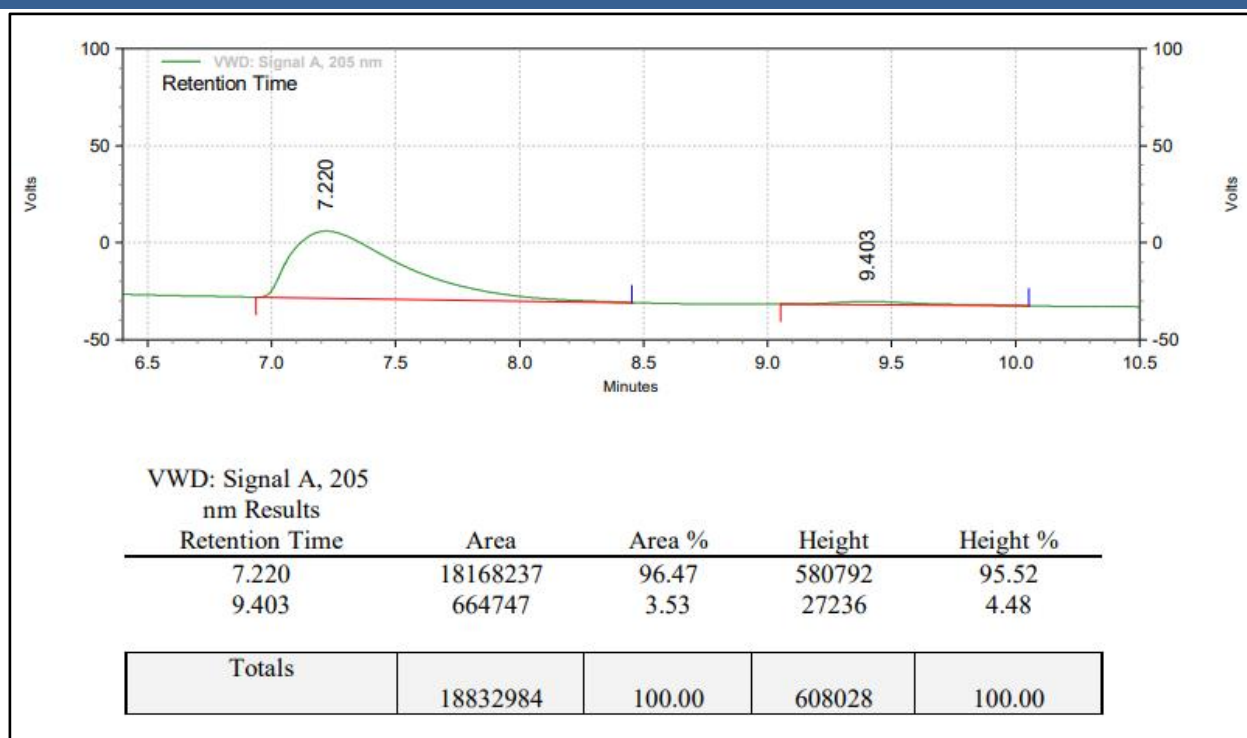


Figure 60. HPLC chromatogram and analysis plot showing the resolved peaks for separation of rac- epichlorohydrin (EP) by **4.1-R**, %ee = 93.

Characterization data for host-guest complexes: mass and ^1H -NMR spectra

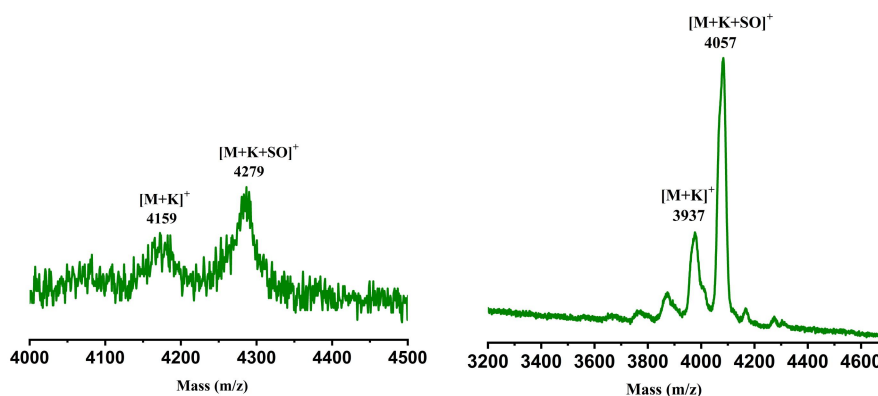


Figure A5.1. MALDI-TOF spectra of $\pm\text{SO}+5.1\text{-R}$ and $\pm\text{SO}+5.2\text{-R}$ in the linear mode.

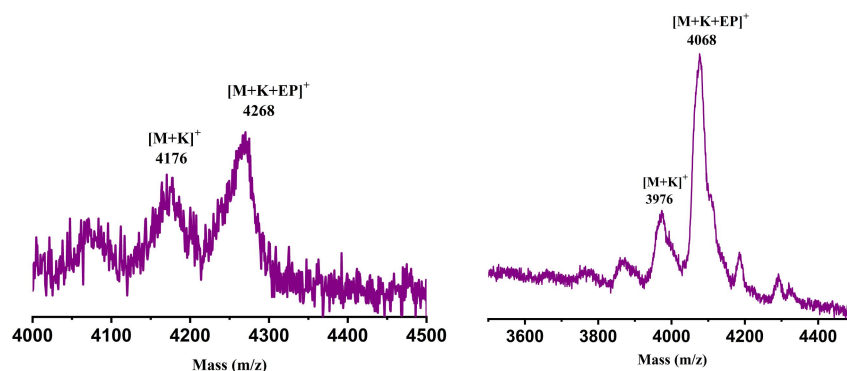


Figure A5.2. MALDI-TOF spectra of $\pm\text{EP}+5.1\text{-R}$ and $\pm\text{EP}+5.2\text{-R}$ in the linear mode.

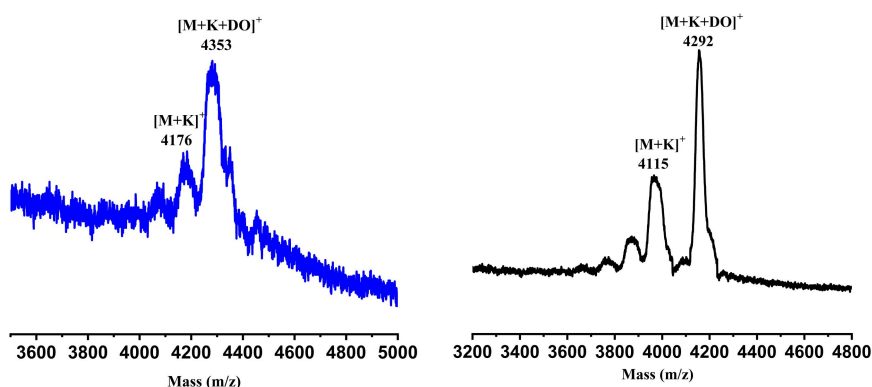


Figure A5.3. MALDI-TOF spectra of $\pm\text{DO}+5.1\text{-R}$ and $\pm\text{DO}+5.2\text{-R}$ in the linear mode

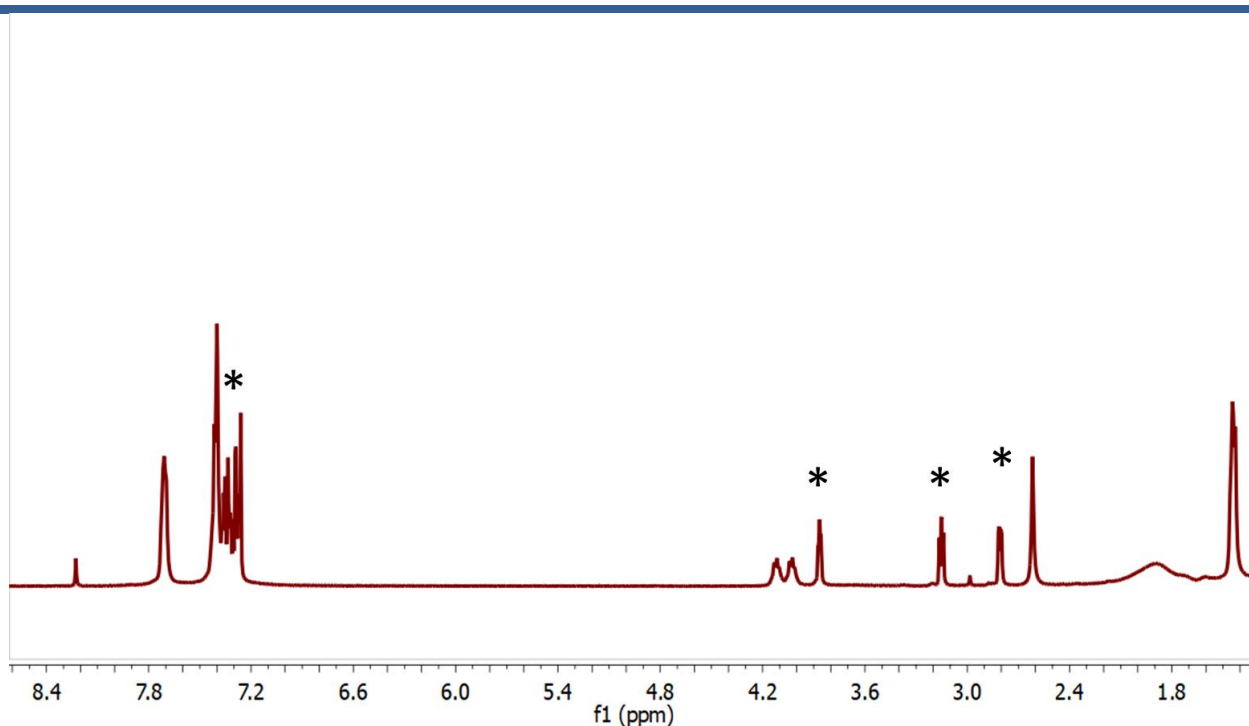


Figure A5.4. ^1H NMR spectrum of $\pm\text{SO}+5.2\text{-R}$. The symbol * indicate the peaks due to the encapsulated $\pm\text{SO}$ guests in the cage.

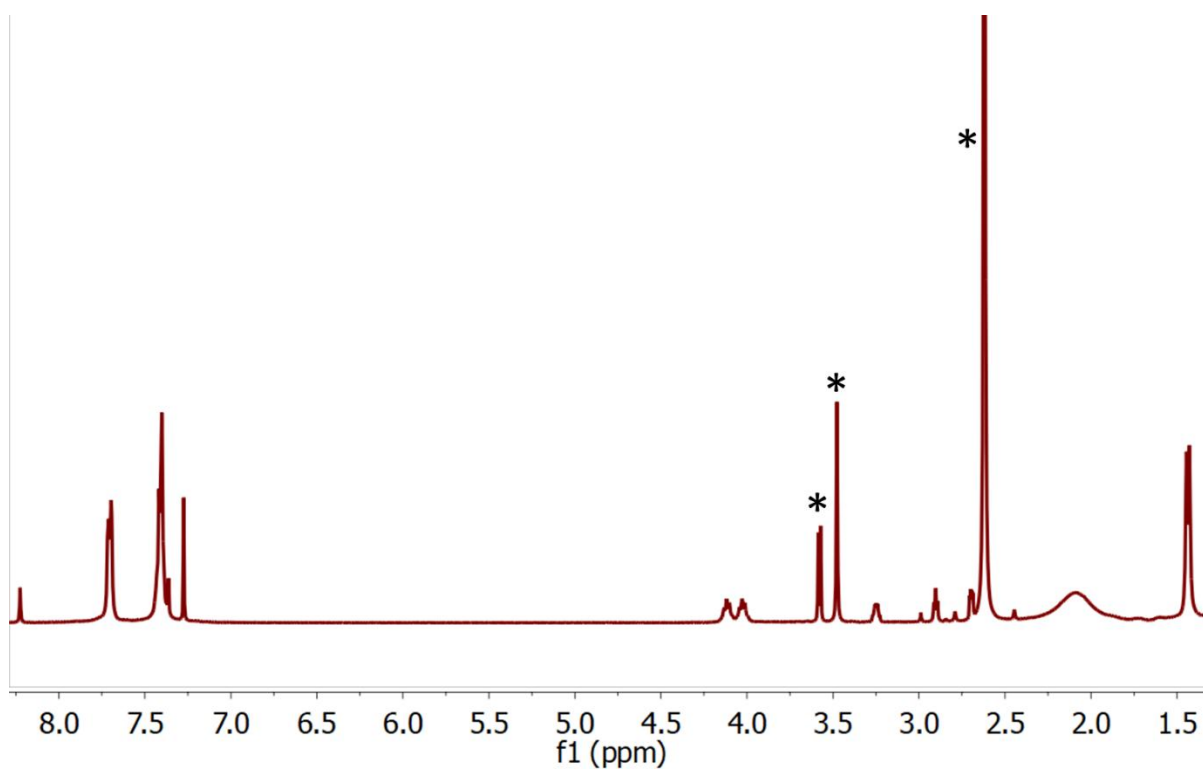


Figure A5.5. ^1H NMR spectrum of $\pm\text{EP}+5.2\text{-R}$. The symbol * indicate the peaks due to the encapsulated $\pm\text{EP}$ guests in the cage.

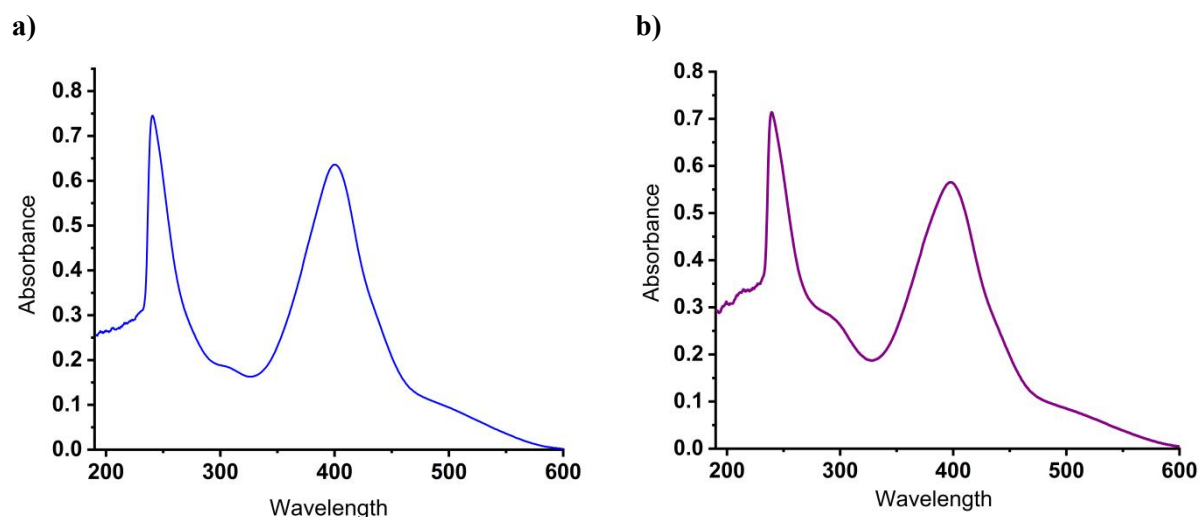


Figure A5.6. UV-Visible spectrum of a) 5.1-R and b) 5.2-R.

Chiral recognition studies using UV-Visible titrations

Table A5.1. Association constants (K/M^{-1}) of receptors 5.1-R and 5.2-R with chiral guests SO, DO, and EP.

Chiral guests	F-Cage	Binding selectivity	Cl-Cage	Binding selectivity
(R)-Styrene oxide (R-SO)	$K_{11} = 116617.9$ (26.1) $K_{12} = 387.6$ (2)	88.51 (R)	$K_{11} = 951.6$ (3) $K_{12} = 1.12\text{E-}06$ (4.7)	1.77 (R)
(S)-Styrene oxide (S-SO)	$K_{11} = 1317.6$ (7.9) $K_{12} = 3.21\text{E-}07$ (61.3)		$K_{11} = 537.6$ (92.5) $K_{12} = 4.2\text{E-}06$ (5.8)	
(R)-Epichlorohydrin (R-EP)	$K_{11} = 5598.3$ (73) $K_{12} = 1.64\text{E-}08$ (6.1)	8.77 (R)	$K_{11} = 519.7$ (8.4) $K_{12} = 665.3$ (55.2)	3 (R)
(S)-Epichlorohydrin (S-EP)	$K_{11} = 638.0$ (23) $K_{12} = 3.66\text{E-}07$ (18)		$K_{11} = 173.14$ (17.8) $K_{12} = 3.40\text{e-}8$ (26.8)	
(R)-4-Benzyl-2-oxazolidinone (R-DO)	$K_{11} = 5220.7$ (21.2) $K_{12} = 907.4$ (8.6)	11.74 (R)	$K_{11} = 6320.2$ (20.1) $K_{12} = 8.03\text{E-}10$ (6.4)	23.83 (R)
(S)-4-Benzyl-2-oxazolidinone (S-DO)	$K_{11} = 444.6$ (7.5) $K_{12} = 863.7$ (28.7)		$K_{11} = 265.2$ (1.2) $K_{12} = 5.16\text{E-}06$ (3.9)	

1:2 binding constants for all these host-guest are very low even with the excess equivalence of the guest molecules. This indicates that under the high dilution conditions of the titration experiments, the guest molecules are more likely to bind at the interiors of the cage despite the presence of multiple chiral and interacting sites available at their exteriors.

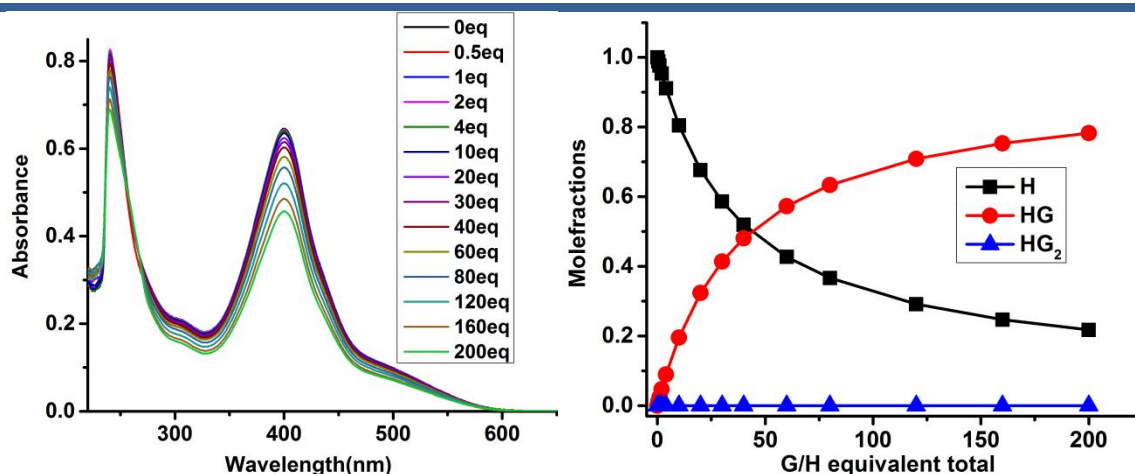


Figure A5.7. (a) UV- Visible titration plots for the host-guest complex of **R-DO** upon addition to the **5.1-R** (left). Bind fit plot for **5.1-R** with **R-DO** (right).

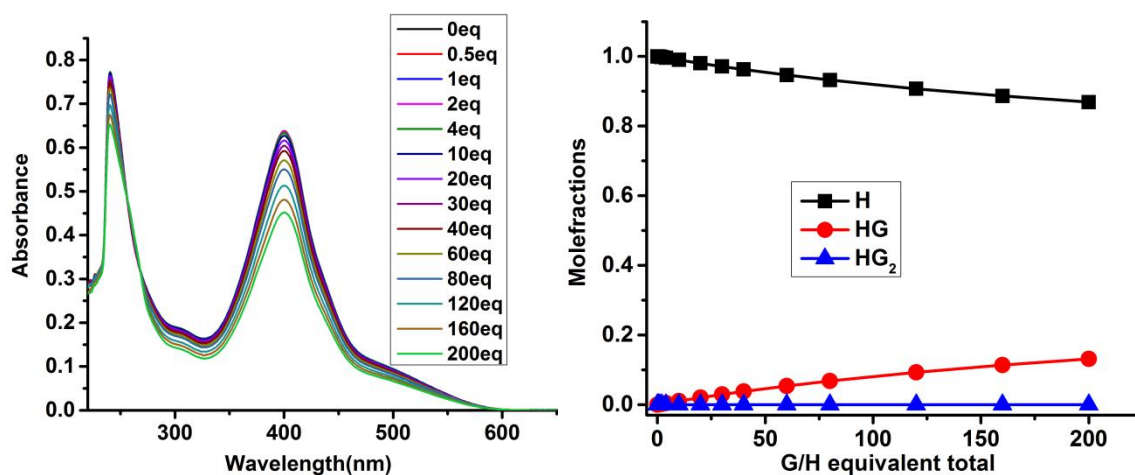


Figure A5.8. (a) UV- Visible titration plots for the host-guest complex of **S-DO** upon addition to the **5.1-R** (left). Bind fit plot for **5.1-R** with **S-DO** (right).

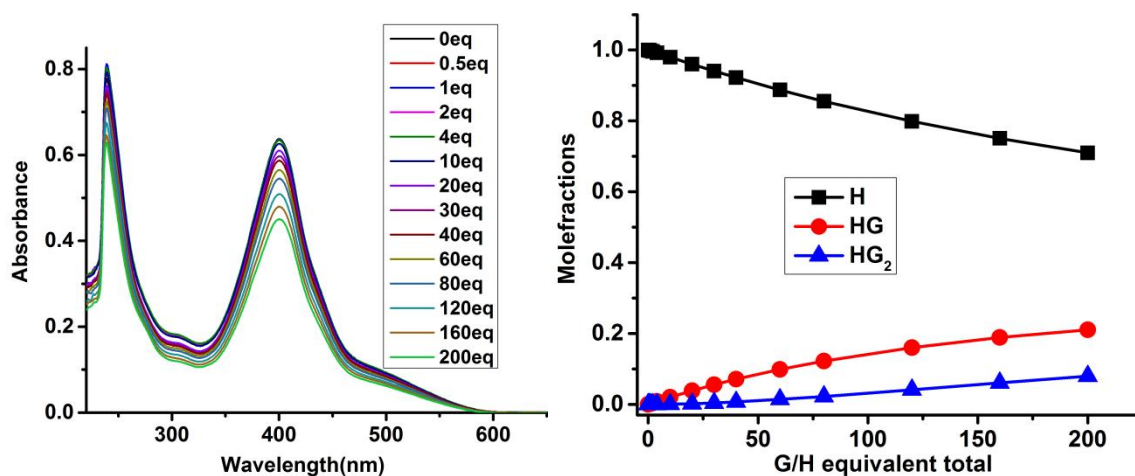


Figure A5.9. (a) UV- Visible titration plots for the host-guest complex of **R-EP** upon addition to the **5.1-R** (left). Bind fit plot for **5.1-R** with **R-EP** (right).

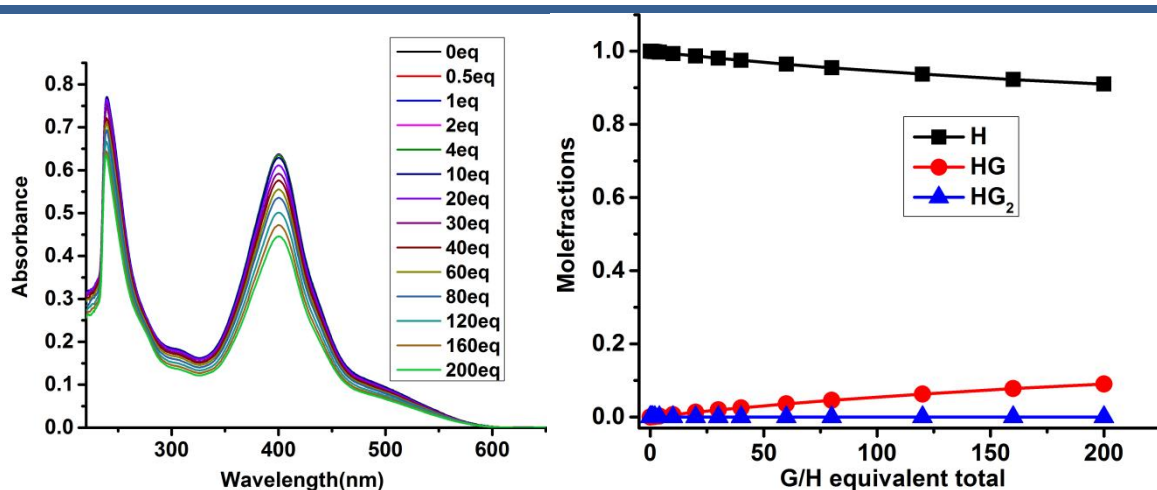


Figure A5.10. (a) UV- Visible titration plots for the host-guest complex of S-EP upon addition to the 5.1-R (left). Bind fit plot for 5.1-R with S-EP (right).

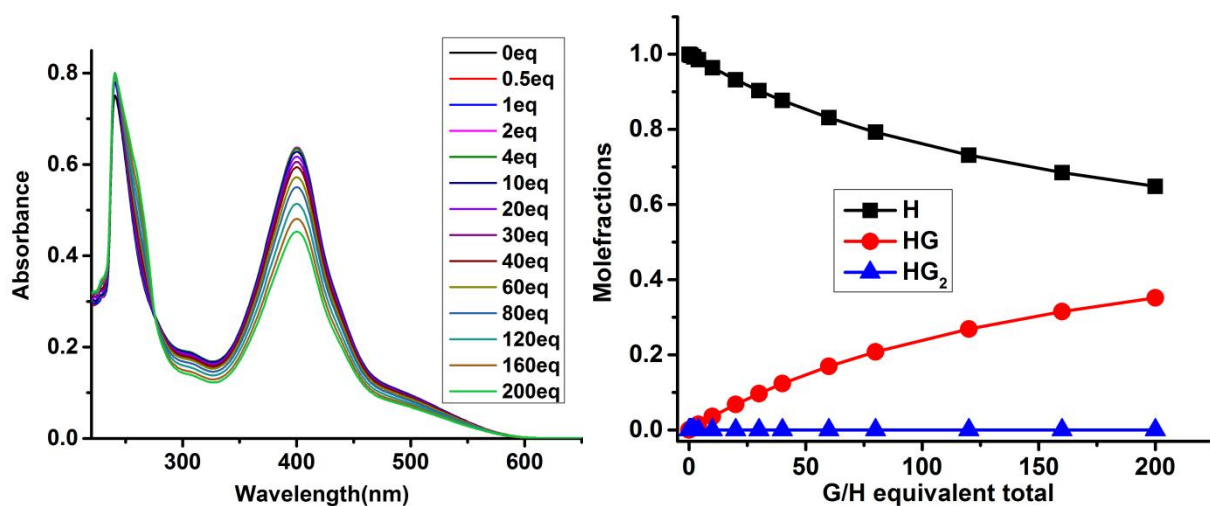


Figure A5.11. (a) UV- Visible titration plots for the host-guest complex of R-SO upon addition to the 5.1-R (left). Bind fit plot for 5.1-R with R-SO (right).

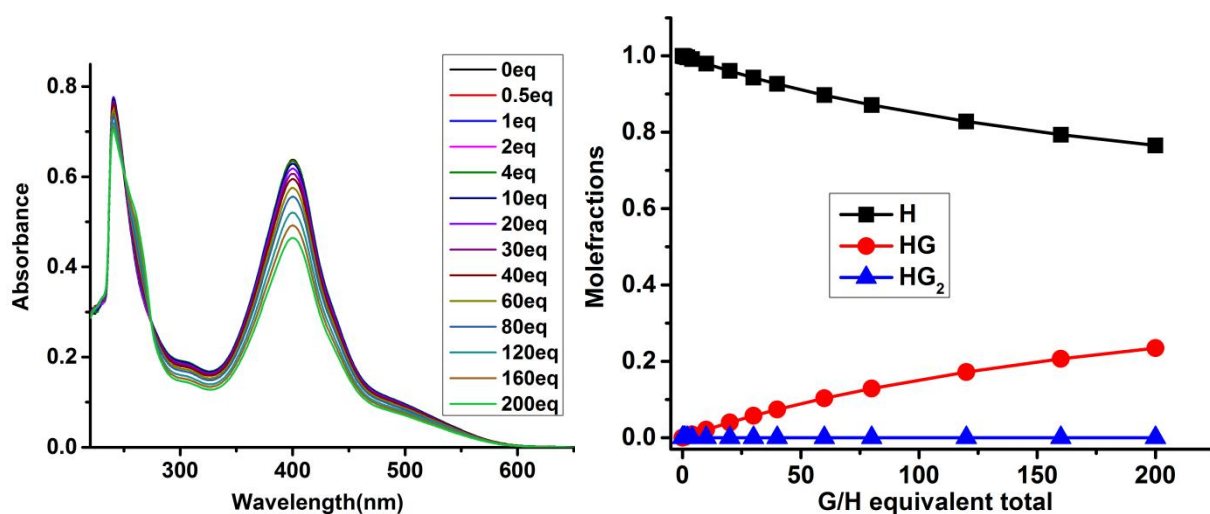


Figure A5.12. (a) UV- Visible titration plots for the host-guest complex of S-SO upon addition to the 5.1-R (left). Bind fit plot for 5.1-R with S-SO (right).

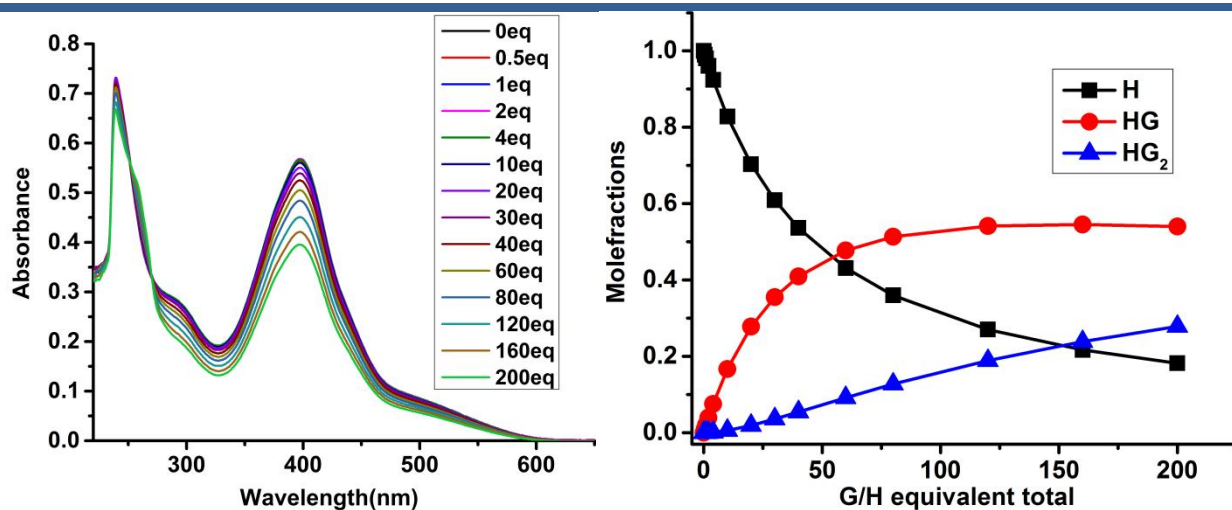


Figure A5.13. (a) UV- Visible titration plots for the host-guest complex of **R-DO** upon addition to the **5.2-R** (left). Bind fit plot for **5.2-R** with **R-DO** (right).

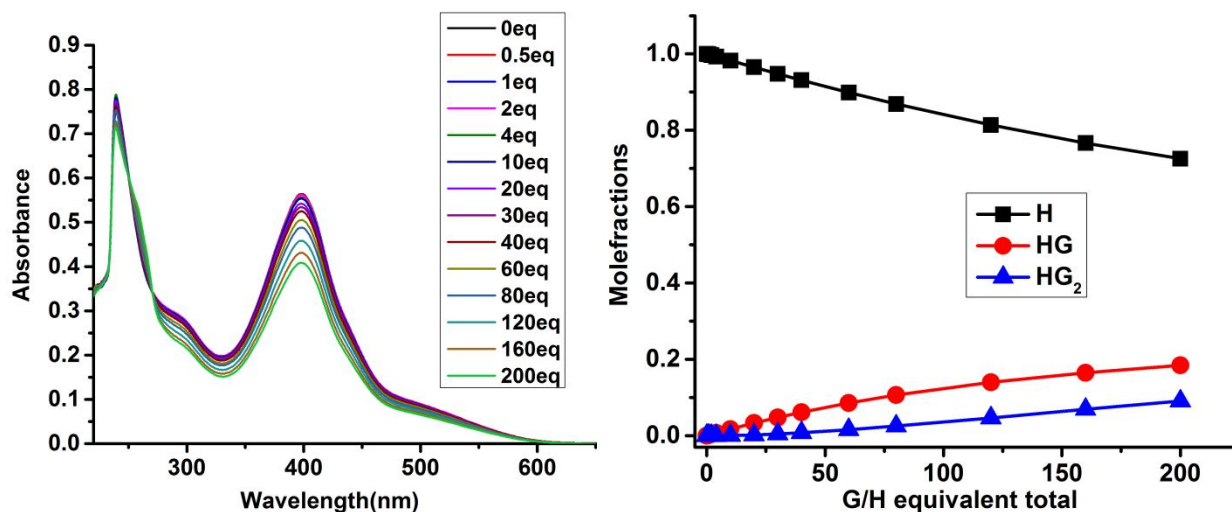


Figure A5.14. (a) UV- Visible titration plots for the host-guest complex of **S-DO** upon addition to the **5.2-R** (left). Bind fit plot for **5.2-R** with **S-DO** (right).

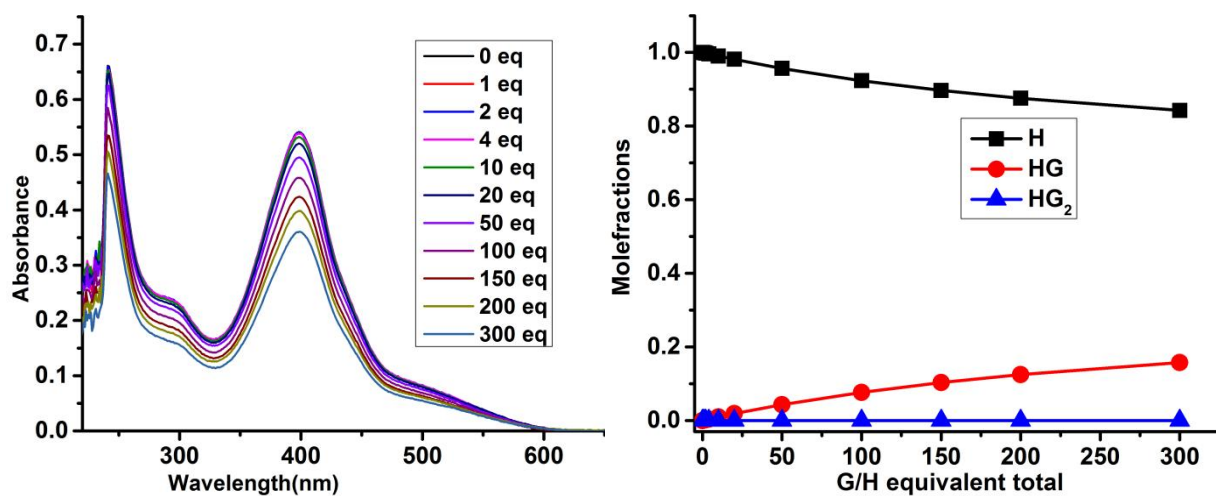


Figure A5.15. (a) UV- Visible titration plots for the host-guest complex of **R-EP** upon addition to the **5.2-R** (left). Bind fit plot for **5.2-R** with **R-EP** (right).

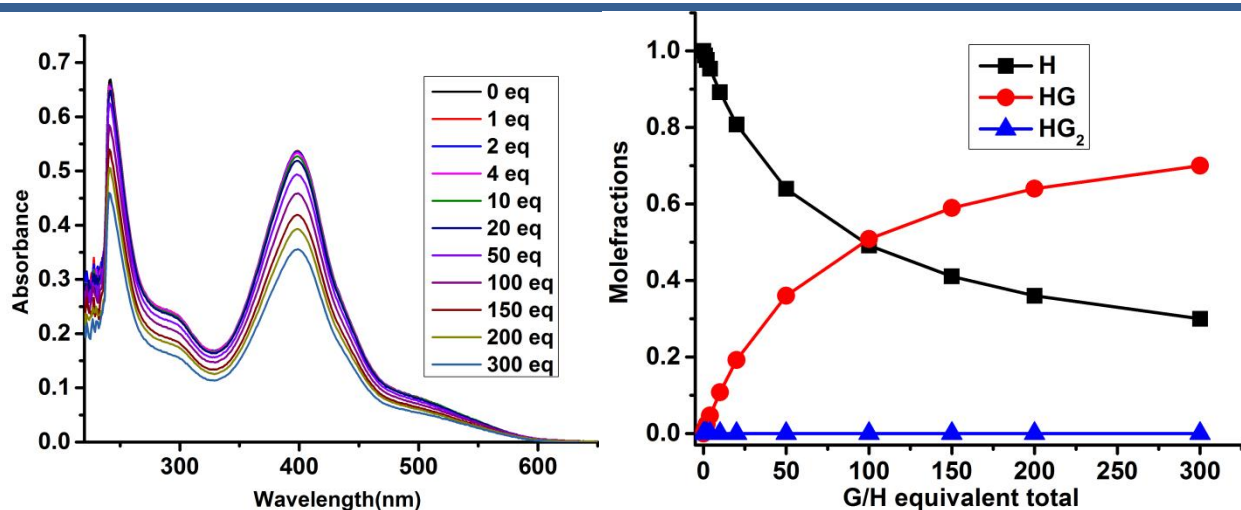


Figure A5.16. (a) UV- Visible titration plots for the host-guest complex of S-EP upon addition to the 5.2-R (left). Bind fit plot for 5.2-R with S-EP (right)

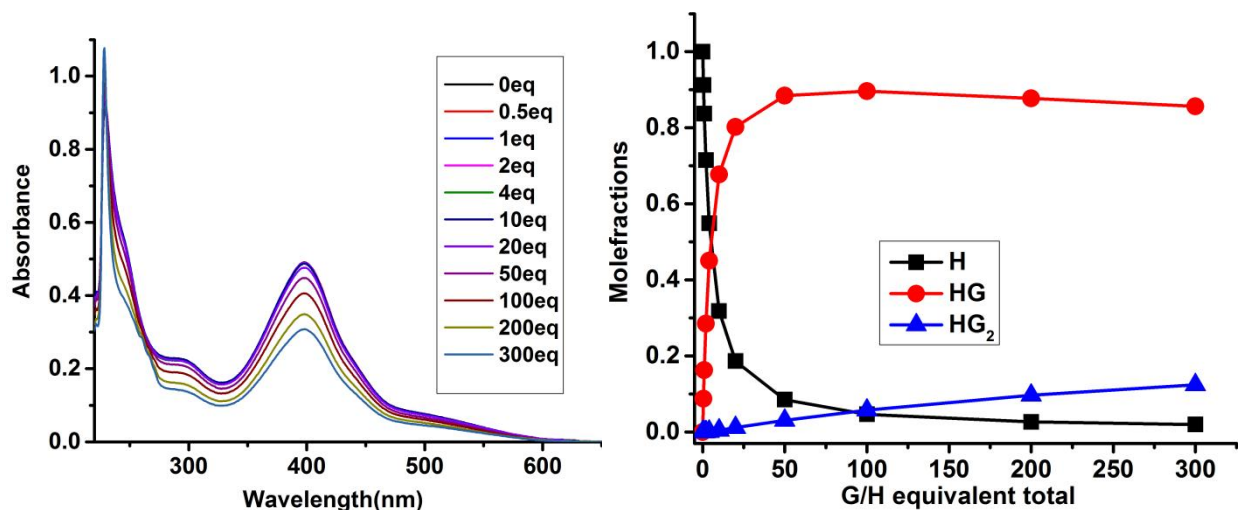


Figure A5.17. (a) UV- Visible titration plots for the host-guest complex of R-SO upon addition to the 5.2-R (left). Bind fit plot for 5.2-R with R-SO (right).

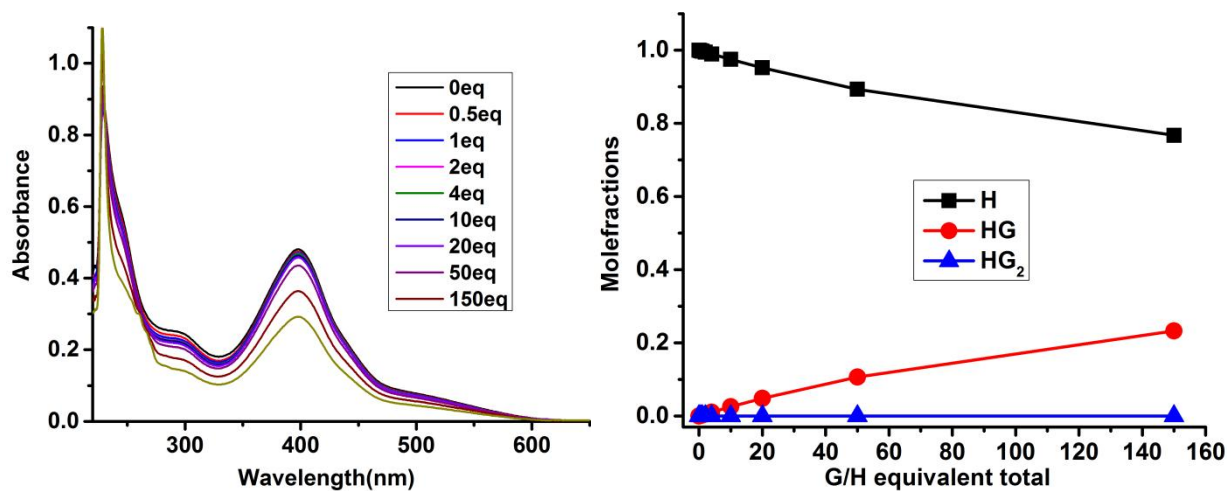


Figure A5.18. (a) UV- Visible titration plots for the host-guest complex of S-SO upon addition to the 5.2-R (left). Bind fit plot for 5.2-R with S-SO (right).

Characterisation data for host-guest complexes: DOSY NMR data

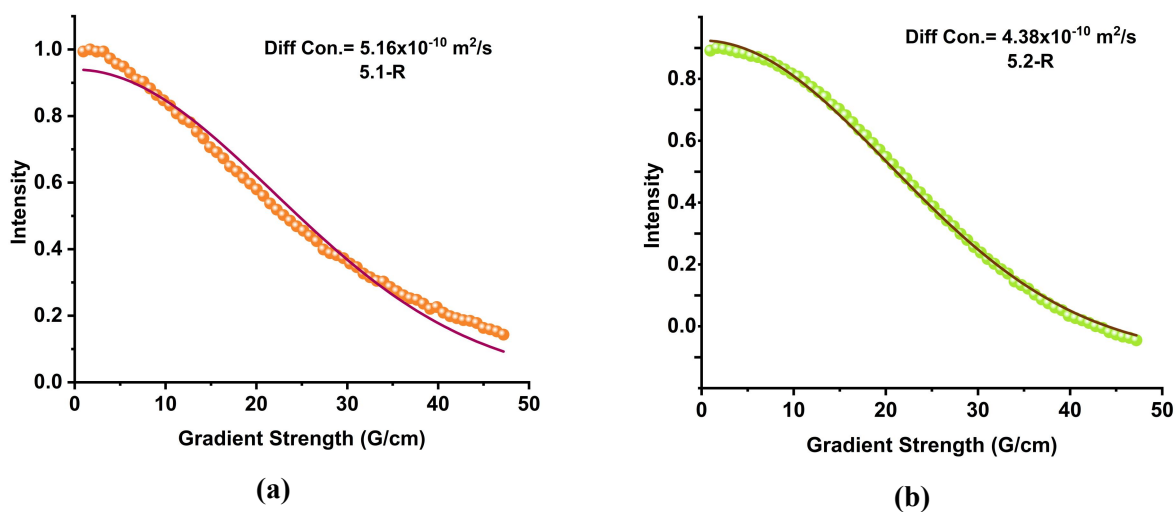
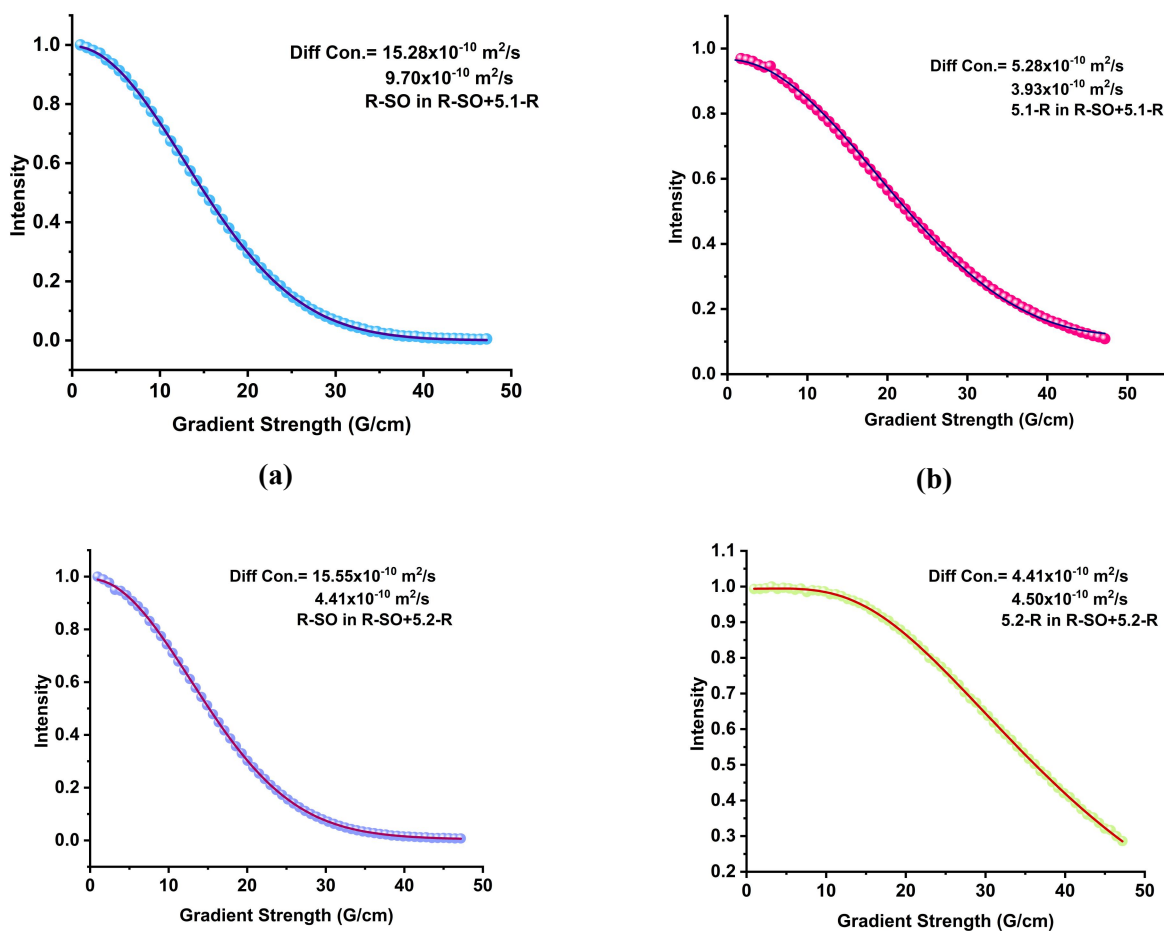


Figure A5.19. Integral decay profile of host proton of cages (a) **5.1-R** and (b) **5.2-R** (DOSY NMR performed in CDCl_3 at 298K) without any guest showing mono-exponential decay curve with only one diffusion coefficient.



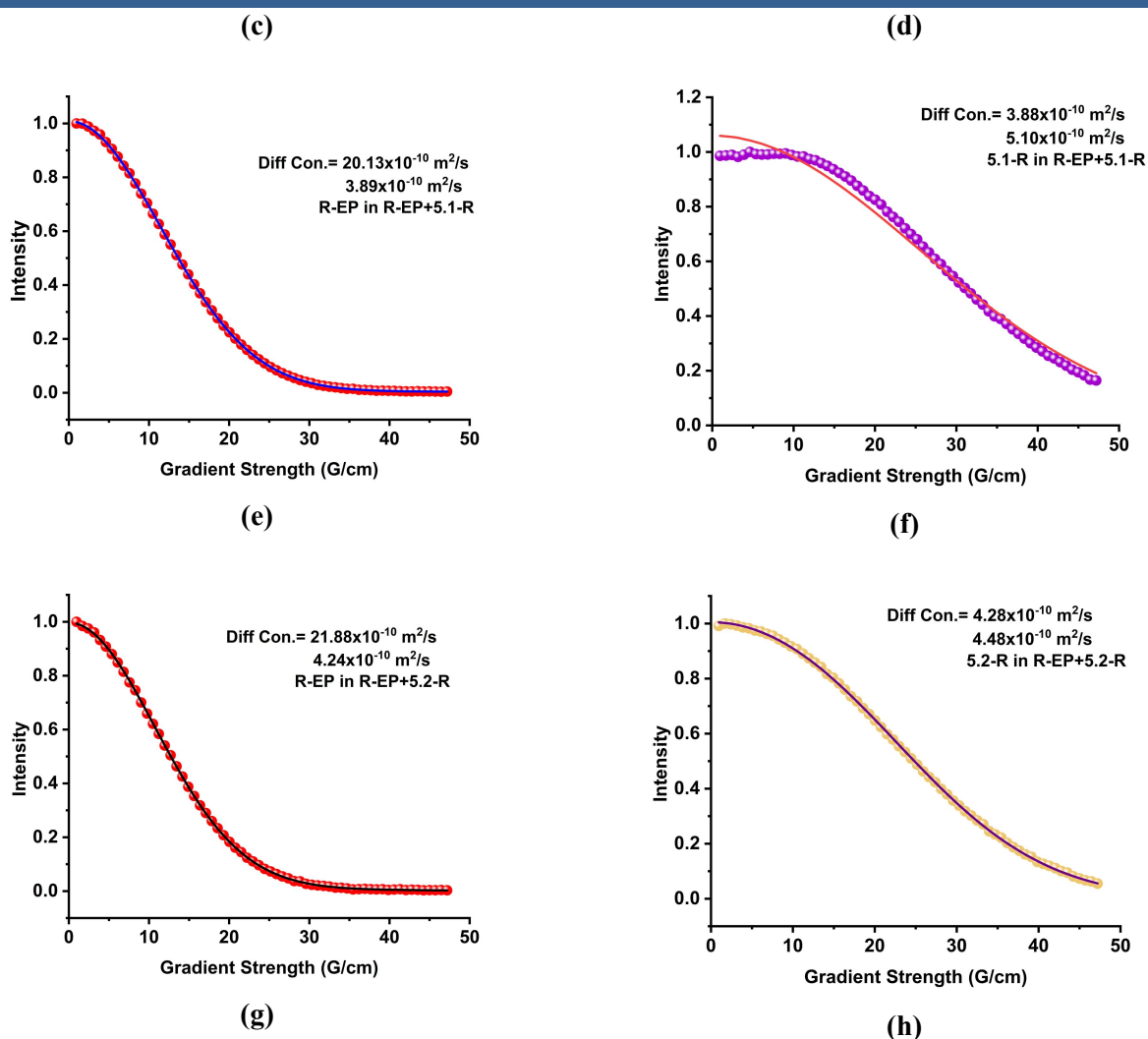


Figure A5.20. DOSY NMR data (CDCl_3 , 298K) for the successful host-guest events. Integral decay profile of guest protons (left), and host protons (right) in the host-guest system plotted as a function of gradient strength. All the DOSY NMR data were fit to biexponential decay curves wherein the dots represent experimental data and the solid-lines show the best fit using the equation 1. Diffusion coefficients obtained for free and bound guest molecules, a) $\pm\text{SO}+5.1\text{-R}$, c) $\pm\text{SO}+5.2\text{-R}$, e) $\pm\text{EP}+5.1\text{-R}$, and g) $\pm\text{EP}+5.2\text{-R}$, and diffusion coefficients obtained for free and bound **5.1-R** and **5.2-R**, b) $\pm\text{SO}+5.1\text{-R}$, d) $\pm\text{SO}+5.2\text{-R}$, f) $\pm\text{EP}+5.1\text{-R}$, and h) $\pm\text{EP}+5.2\text{-R}$ are shown in the figures.

Table A5.2. Diffusion coefficients as obtained from the DOSY experiment for host and different guests in the studied host-guest systems.

Host+Guest	Diffusion Coefficient ($\text{E}^{-10} \text{ m}^2/\text{s}$)			
	Free		Bound	
	Host	Guest	Host	Guest
5.1-R+R-SO	5.28	15.28	3.93	9.70
5.2-R+R-SO	4.50	15.55	4.41	4.41
5.1-R+R-EP	5.10	20.13	3.88	3.89
5.2-R+R-EP	4.48	21.10	4.28	4.24
5.1-R+R-DO	5.19	15.61	3.84	8.98

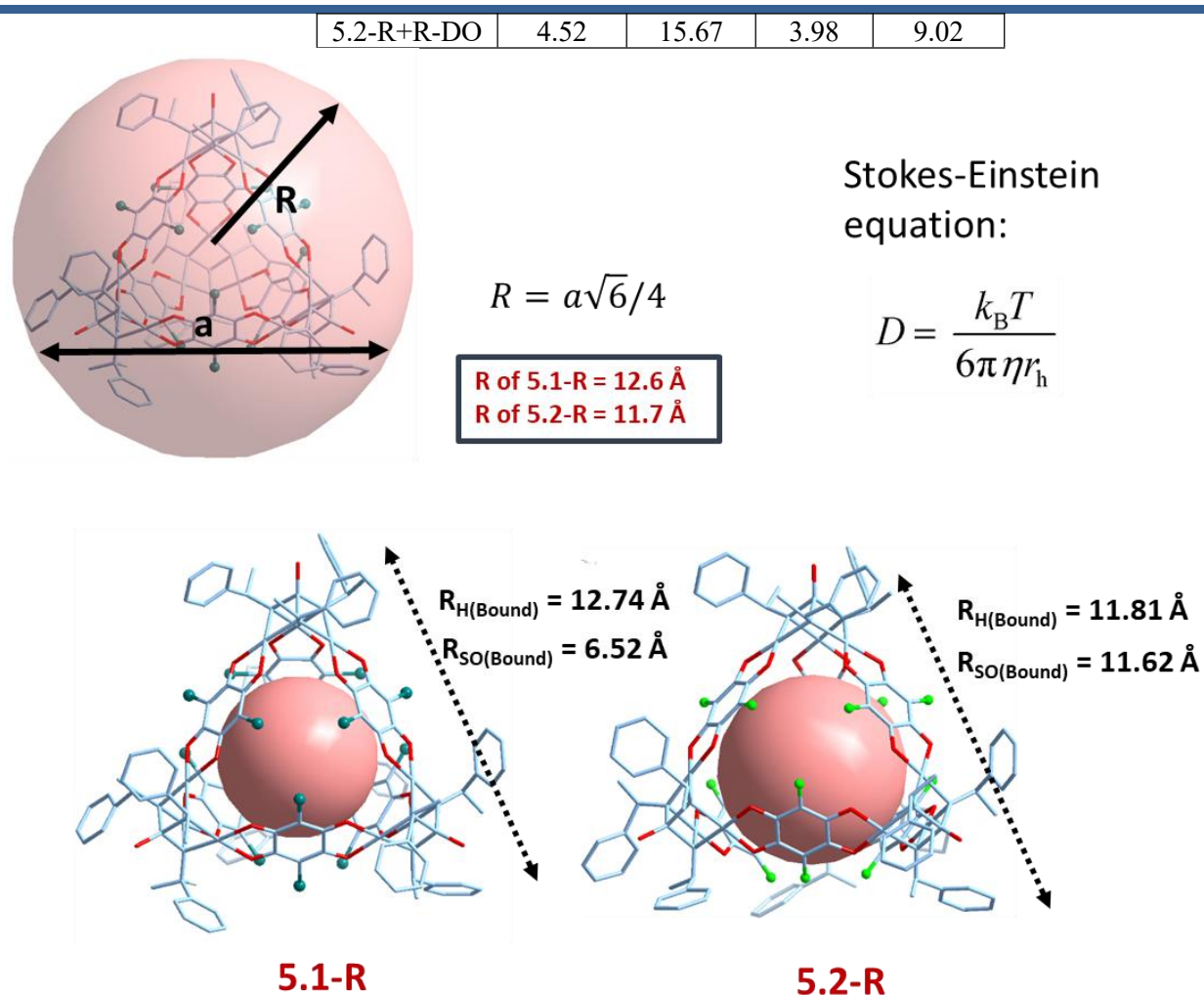


Figure A5.21. (a) Schematic representation of hydrodynamic radii and molecular models of systems (b) **5.1-R+R-SO** and (c) **5.2-R+R-SO** systems.

Table A5.3. Comparison of the hydrodynamic radii as obtained from DOSY experiment and radii of the circumscribed sphere calculated from the respective energy-minimized models of the guest-bound cage systems.

Host+Guest	Hydrodynamic Radius (Å)			
	Free		Bound	
	Host	Guest	Host	Guest
5.1-R+R-SO	10.11	4.83	12.74	6.52
5.2-R+R-SO	11.44	4.78	11.62	11.63
5.1-R+R-EP	10.38	4.07	12.87	12.84
5.2-R+R-EP	11.48	3.96	11.90	11.99
5.1-R+R-DO	10.25	4.77	12.98	6.88
5.2-R+R-DO	11.40	4.76	12.61	6.86

Control experiments

The crystallised host-guest crystallites for R-SO were examined with ^{31}P -NMR spectroscopy and MALDI-TOF spectrometry. From the experiments, it is clear that the cages are in-tact in the host-guest crystallites.

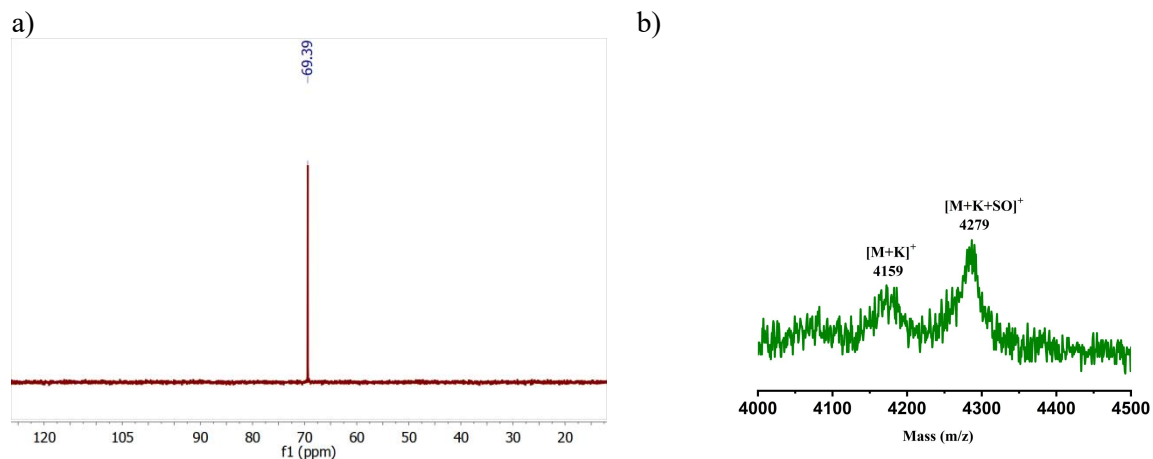


Figure A5.22. a) ^{31}P -NMR spectra and b) MALDI-TOF spectra of crystallised host-guest crystallites of **5.1-R+R-SO**

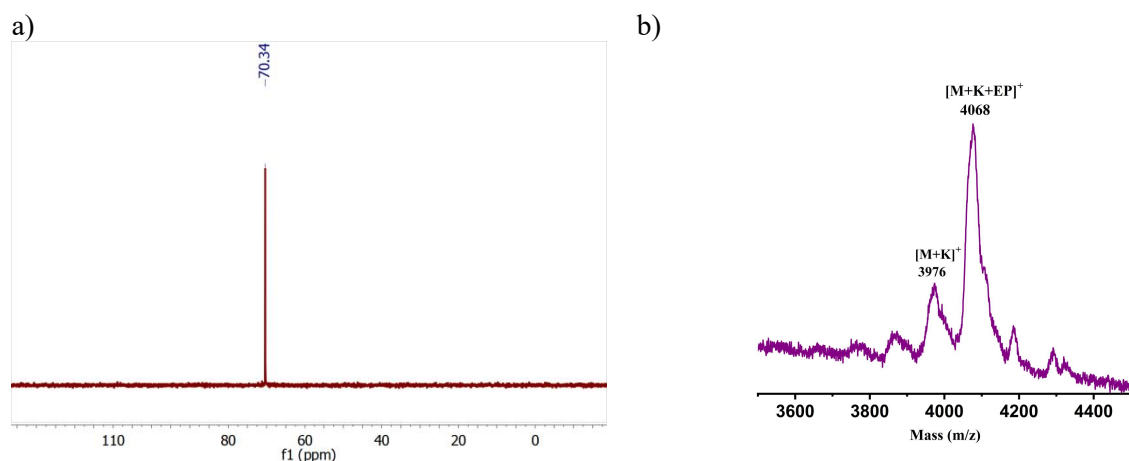


Figure A5.23. a) ^{31}P -NMR spectra and b) MALDI-TOF spectra of crystallised host-guest crystallites of **5.2-R+R-SO**

Optimized Structures of Host–Guest Complexes

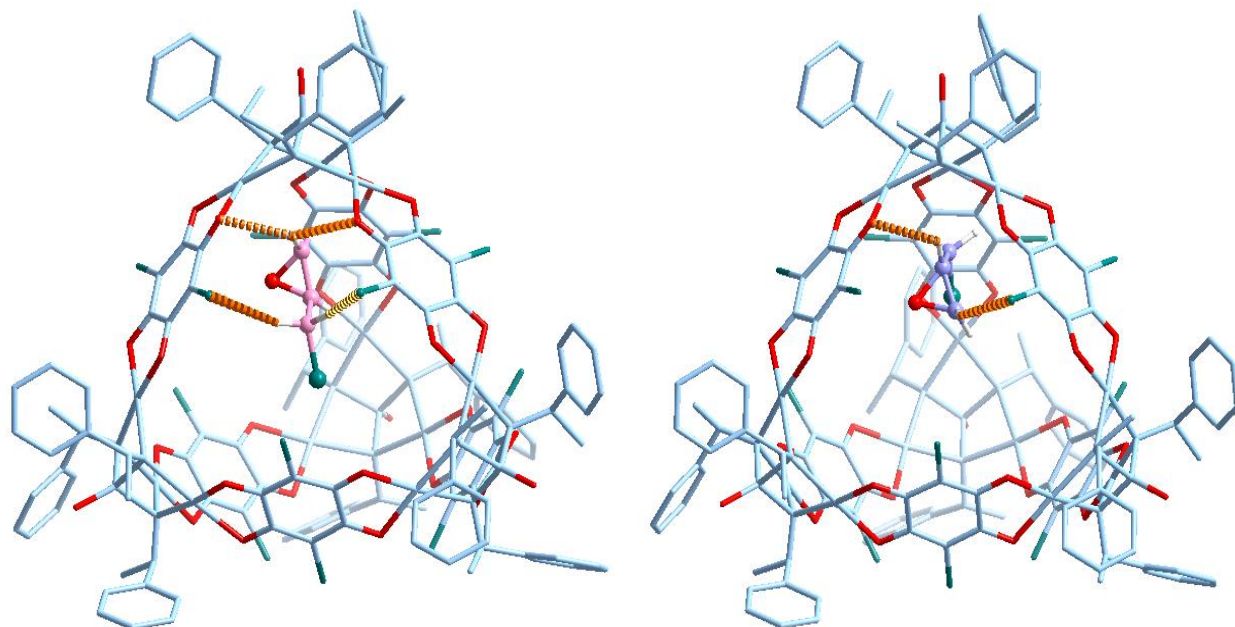


Figure A5.24. Potential non-covalent interactions responsible for the stabilization of the host–guest assemblies in **5.1-R+ R-EP** (right) and **5.1-R+ S-EP** (left) complexes. N blue; O red; Cl dark green; H white. The non-classical interactions (X=N, O) are shown in dotted lines: blue O-H $\cdots$ X, orange C-H $\cdots$ X and red C-H $\cdots$ π .

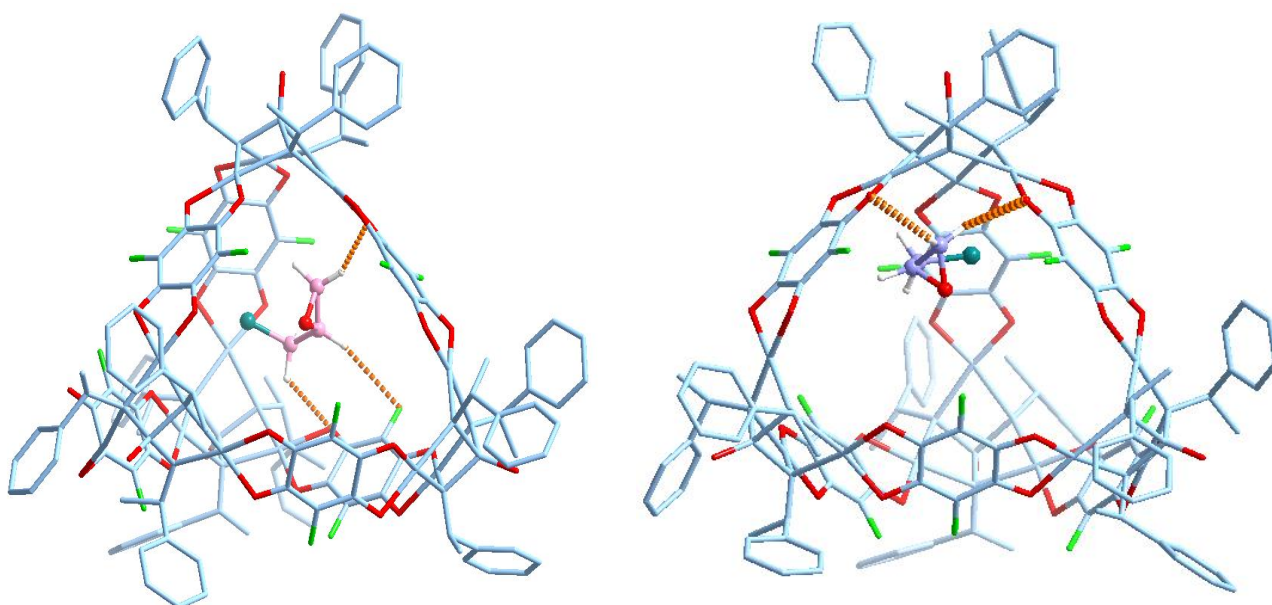


Figure A5.25. Potential non-covalent interactions responsible for the stabilization of the host–guest assemblies in **5.2-R+ R-EP** (right) and **5.2-R+ S-EP** (left) complexes. N blue; O red; Cl dark green; H white. The non-classical interactions (X=N, O) are shown in dotted lines: blue O-H $\cdots$ X, orange C-H $\cdots$ X and green C-H $\cdots$ π .

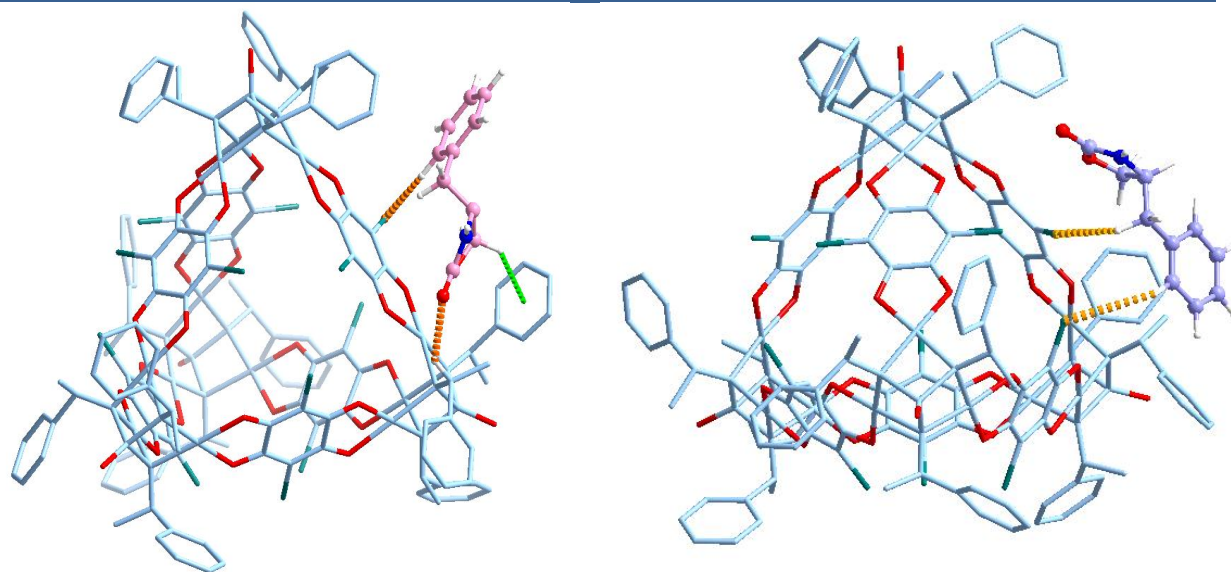


Figure A5.26. Potential non-covalent interactions responsible for the stabilization of the host–guest assemblies in **5.1-R+ R-DO** (right) and **5.1-R+ S-DO** (left) complexes. N blue; O red; Cl dark green; H white. The non-classical interactions (X=N, O) are shown in dotted lines: blue O-H···X, orange C-H···X and green C-H··· π .

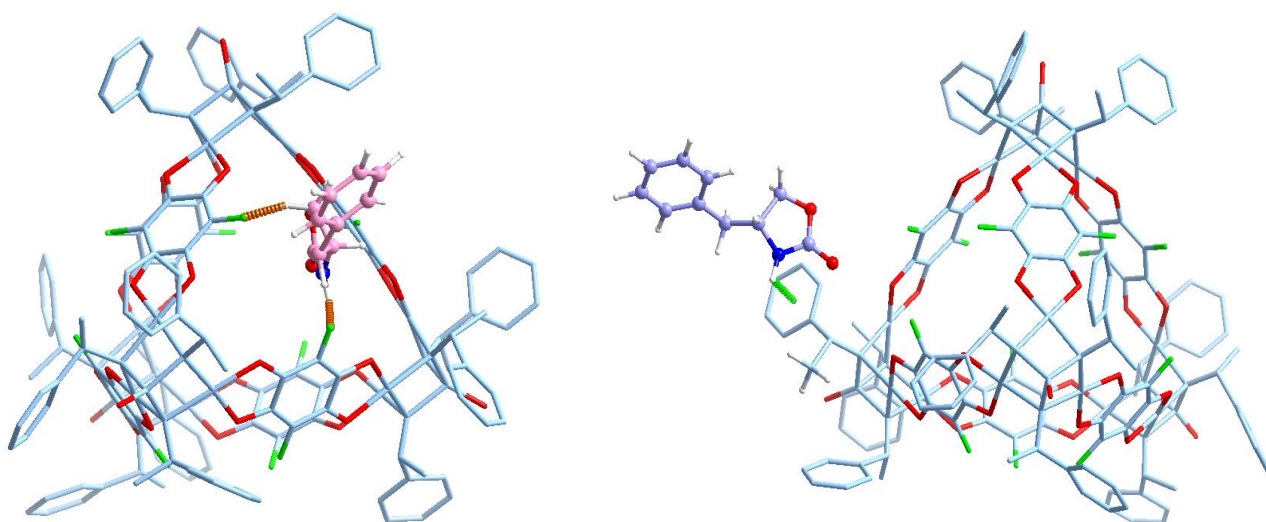


Figure A5.27. Potential non-covalent interactions responsible for the stabilization of the host–guest assemblies in **5.2-R+ R-DO** (right) and **5.2-R+ S-DO** (left) complexes. N blue; O red; Cl dark green; H white. The non-classical interactions (X=N, O) are shown in dotted lines: blue O-H···X, orange C-H···X and green C-H··· π .

Table A5.4. Bond length and bond angles for the Host-Guest complexes of the **5.1-R** and **5.2-R**.

Host + Guest	Interactions (D-H···A)	d(H···A)	d(D···A)	<DHA	Type of Interaction
5.1-R+R-DO	C317-H318···Cl28	2.8593	3.8314	151.0(6)	Weak H-Bond
	C57-H58···O313	2.3678	3.1938	132.3(2)	Weak H-Bond

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	C311-H320 $\cdots\pi$	3.0043	3.7537	127.2(5)	CH- π
5.1-R+S-DO	C321-H328 $\cdots$ Cl160	3.3002	4.1287	133.9(3)	Weak H-Bond
	C318-H330 $\cdots$ Cl2	2.9424	3.7920	132.9(4)	Weak H-Bond
5.2-R+R-DO	N323-H327 $\cdots$ F93	1.4744	2.2333	125.1(1)	H-Bond
	C307-H305 $\cdots$ F179	1.6311	2.7048	159.3(9)	Weak H-Bond
5.2-R+S-DO	N323-H327 $\cdots\pi$	3.6401	3.5491	76.7(7)	Polar- π
5.1-R+R-EP	C309-H317 $\cdots$ Cl243	2.8933	3.9619	160.6(2)	Weak H-Bond
	C309-H318 $\cdots$ Cl224	2.8175	3.8805	160.2(5)	Weak H-Bond
	C311-H314 $\cdots$ O245	2.5425	3.2800	123.3(3)	Weak H-Bond
	C311-H314 $\cdots$ O235	2.7232	3.2939	111.6(9)	Weak H-Bond
5.1-R+S-EP	C311-H315 $\cdots$ Cl2	2.9344	3.8991	147.4(3)	Weak H-Bond
	C310-H313 $\cdots$ O33	2.6504	3.2042	109.7(8)	Weak H-Bond
	C310-H313 $\cdots$ O143	2.6155	3.3395	121.7(5)	Weak H-Bond
5.2-R+R-EP	C310-H312 $\cdots$ O34	2.1653	3.1698	150.7(7)	Weak H-Bond
	C308-H311 $\cdots$ F32	3.1384	4.1658	155.7(8)	Weak H-Bond
	C309-H307 $\cdots$ O26	2.5189	3.2628	122.6(5)	Weak H-Bond
5.2-R+S-EP	C306-H308 $\cdots$ O26	2.7968	3.4793	119.7(9)	Weak H-Bond
	C306-H309 $\cdots$ O206	2.3778	3.0928	121.5(4)	Weak H-Bond
5.1-R+R-SO	C209-H212 $\cdots$ Cl148	2.8830	3.9448	166.6(3)	Weak H-Bond
	C209-H212 $\cdots$ O155	3.6252	4.4788	137.0(1)	Weak H-Bond

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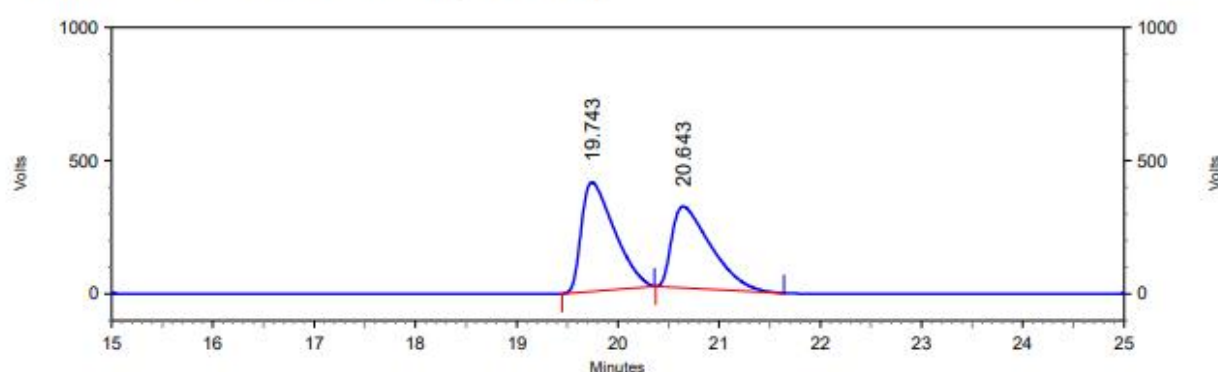
5.1-R+R-SO-1	C316-H322 $\cdots\pi$	2.8481	3.5046	122.5(2)	CH- π
2-F+R-SO	C309-H310 $\cdots$ F28	2.9622	3.9864	157.2(4)	Weak H-Bond
	C311-H312 $\cdots$ O152	3.9820	4.8656	140.742	Weak H-Bond
	C306-H305 $\cdots$ O145	3.3720	4.2810	142.0(9)	Weak H-Bond
	C314-H321 $\cdots$ F93	3.5291	4.4762	150.1(3)	Weak H-Bond
	C318-H320 $\cdots$ O68	2.5285	3.6129	163.1(1)	Weak H-Bond
	C318-H319 $\cdots$ O35	3.3320	4.2156	138.9(3)	Weak H-Bond
2-F+S-SO	C309-H310 $\cdots$ O206	3.2889	4.3027	157.0(6)	Weak H-Bond
	C307-H308 $\cdots$ F28	3.1417	4.2003	166.7(4)	Weak H-Bond
	C306-H305 $\cdots$ O152	3.2638	4.2164	147.4(6)	Weak H-Bond

HPLC Methods for the Enantiomeric Separation of the Chiral Guest Molecules

SO System

Method: Enantiometric purity of **SO** was determined by HPLC with Chiralpak IA (20 cm) column with a flow rate of 0.5 mL/min, 95 /5/0.1 of n-hexane/iso-propanol/trifluoroacetic acid as eluent and the effluent was monitored at a wavelength 220 nm.

Data File: D:\KISHOR\Cavya\241123\SO Racemic rep2.rslt\SO Racemic rep2cavya1.met2023-11-24 20-59-47 (GMT +05-30).dat
 Method: D:\KISHOR\Sandeep K\11082022\SHK-97.rslt\3%ipa.met
 Acquired: 11/24/2023 9:00:17 PM (GMT +05:30)
 Printed: 11/25/2023 5:33:48 PM (GMT +05:30)



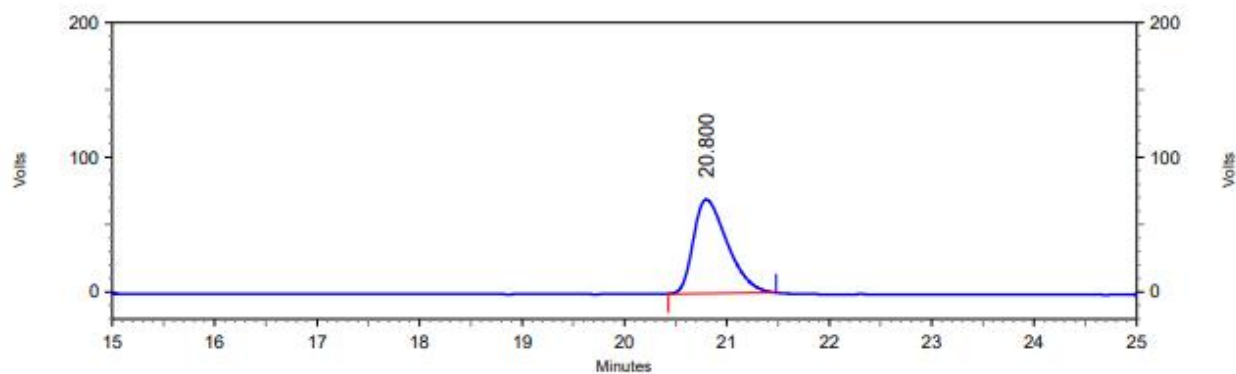
VWD: Signal A,
220 nm Results

Retention Time	Area	Area %	Height	Height %
19.743	155821604	52.95	6869785	57.23
20.643	138476344	47.05	5134102	42.77
Totals	294297948	100.00	12003887	100.00

Figure A5.28. HPLC chromatogram and analysis plot showing the resolved peaks for untreated rac-SO

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Data File: D:\KISHOR\Cavya\241123\R-SO rep2.rslt\R-SO rep2cavya1.met2023-11-25 17-14-11 (GMT +05-30).dat
Method: D:\KISHOR\Sandeep K\11082022\SHK-97.rslt\3%ipa.met
Acquired: 11/25/2023 5:14:53 PM (GMT +05:30)
Printed: 11/25/2023 5:45:41 PM (GMT +05:30)



VWD: Signal A,
220 nm Results

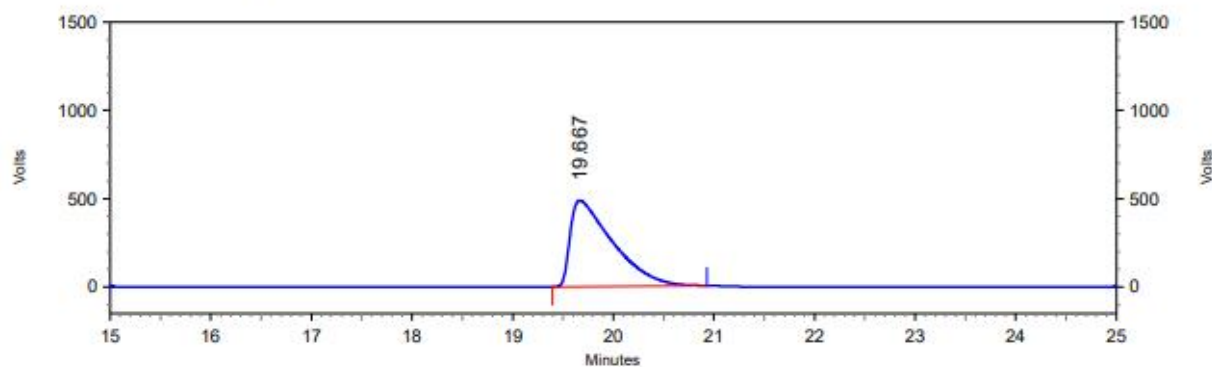
Retention Time	Area	Area %	Height	Height %
20.800	26815373	100.00	1168032	100.00
Totals	26815373	100.00	1168032	100.00

Figure A5.29. HPLC chromatogram and analysis plot showing the resolved peaks for untreated **R-SO**

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Area % Report

Data File: D:\KISHOR\Cavya\241123\S-SO rep2.rslt\S-SO rep2cavya1.met2023-11-25 17-40-57 (GMT +05-30).dat
Method: D:\KISHOR\Sandeep K\11082022\SHK-97.rslt\3%ipa.met
Acquired: 11/25/2023 5:41:56 PM (GMT +05:30)
Printed: 11/25/2023 6:16:28 PM (GMT +05:30)



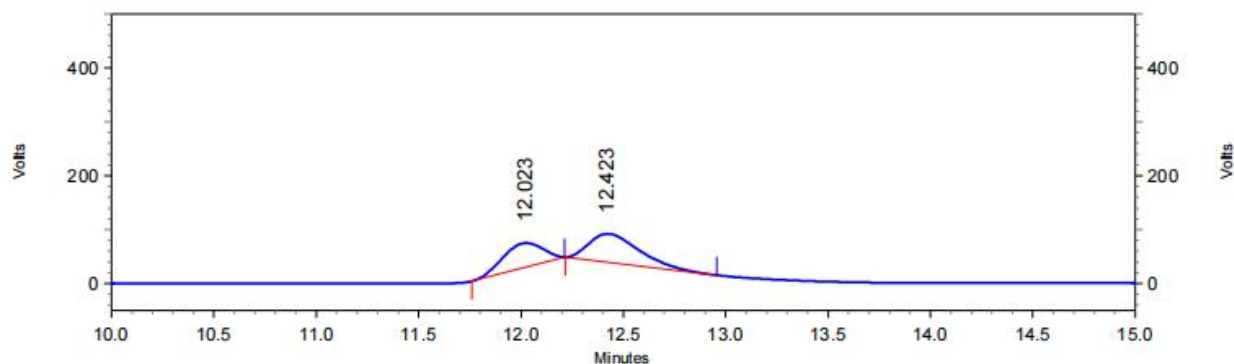
VWD: Signal A,
220 nm Results

Retention Time	Area	Area %	Height	Height %
19.667	239359427	100.00	8190958	100.00
Totals	239359427	100.00	8190958	100.00

Figure A5.30. HPLC chromatogram and analysis plot showing the resolved peaks for untreated S-SO

Area % Report

Data File: D:\KISHOR\Cavya\11112024\SO23rep.rslt\SO23rep.dat
 Method: D:\KISHOR\Cavya\30102024\EP-11R.rslt\EP10.met
 Acquired: 11/11/2024 4:02:33 PM (GMT +05:30)
 Printed: 11/12/2024 9:02:52 AM (GMT +05:30)



VWD: Signal A, 220 nm Results

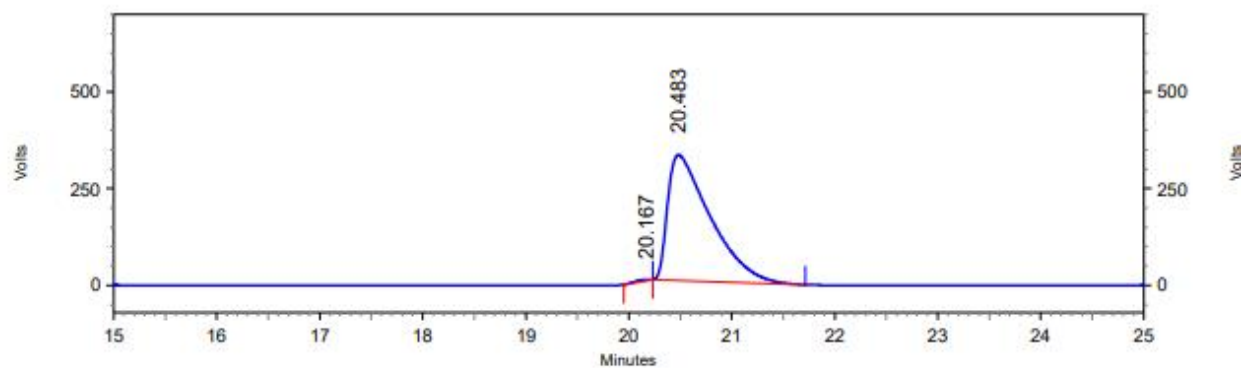
Retention Time	Area	Area %	Height	Height %
12.023	10394707	40.51	752284	45.98
12.423	15266614	59.49	884002	54.02
Totals	25661321	100.00	1636286	100.00

Figure A5.31. HPLC chromatogram and analysis plot showing the resolved peaks for separation of rac-SO by 5.1-R, ee = 9%.

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Area % Report

Data File: D:\KISHOR\Cavya\241123\CA-1rep.rslt\CA-1repCavya1.met2023-11-25 18-07-48 (GMT +05-30).dat
 Method: D:\KISHOR\Sandeep K\11082022\SHK-97.rslt\3%ipa.met
 Acquired: 11/25/2023 6:08:24 PM (GMT +05:30)
 Printed: 11/25/2023 6:35:55 PM (GMT +05:30)



VWD: Signal A,
220 nm Results

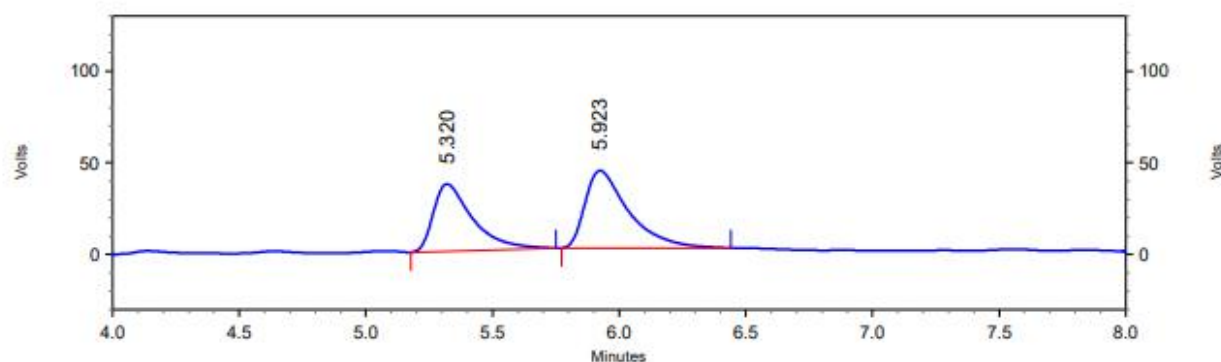
Retention Time	Area	Area %	Height	Height %
20.167	602985	0.38	52522	0.96
20.483	156615332	99.62	5444476	99.04
Totals	157218317	100.00	5496998	100.00

Figure A5.32. HPLC chromatogram and analysis plot showing the resolved peaks for separation of rac-SO by 5.2-R, ee = 98.2%.

DO System

Method: Enantiometric purity of DO was determined by HPLC with Chiralpak AD-H (20 cm) column with a flow rate of 0.6 mL/min was employed for the chiral HPLC analysis using 45/55 of n-Hexane/Methanol as eluent and the effluent was monitored at a wavelength 254 nm.

Data File: D:\KISHOR\Cavya\14072024\ethanol met\DO-R and SREP1.rslt\DO-R and SREP1ETMEHEX.met2024-07-15 16-20-21 (GMT +05-30).dat
 Method: D:\PROJECTS\02MAR15\Method\Amol\3% IPA and 97% Hexane_230 nm_1 ml_60 min.met
 Acquired: 7/15/2024 4:20:53 PM (GMT +05:30)
 Printed: 7/15/2024 5:07:54 PM (GMT +05:30)



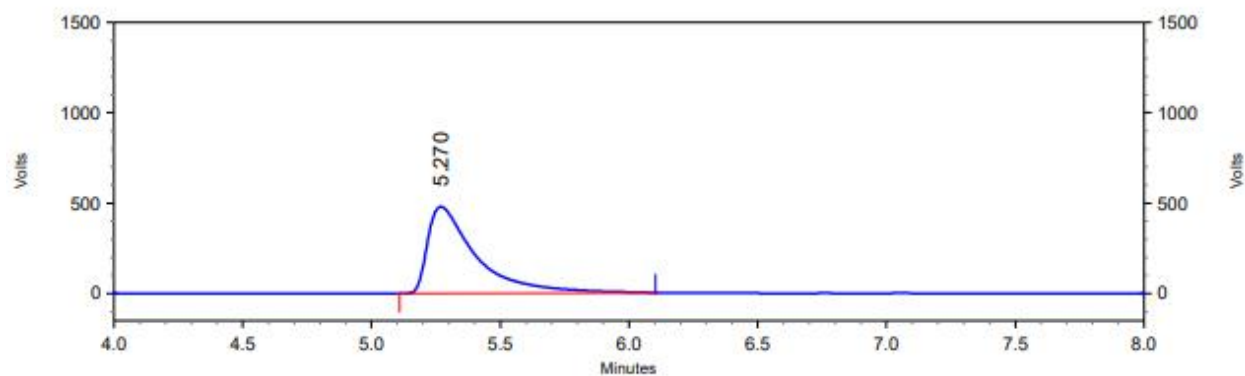
**VWD: Signal A,
254 nm Results**

Retention Time	Area	Area %	Height	Height %
5.320	6628972	43.78	614888	46.42
5.923	8514207	56.22	709731	53.58
Totals	15143179	100.00	1324619	100.00

Figure A5.34. HPLC chromatogram and analysis plot showing the resolved peaks for untreated rac -4-benzyl-2-oxazolidinone (DO)

Area % Report

Data File: D:\KISHOR\Cavya\14072024\ethanol met\DO-R.rsl\DO-RETMEHEX.met2024-07-15 16-30-18 (GMT +05-30).dat
 Method: D:\PROJECTS\02MAR15\Method\Amol\3% IPA and 97% Hexane_230 nm_1 ml_60 min.met
 Acquired: 7/15/2024 4:30:52 PM (GMT +05:30)
 Printed: 7/15/2024 5:10:00 PM (GMT +05:30)



VWD: Signal A,
 254 nm Results

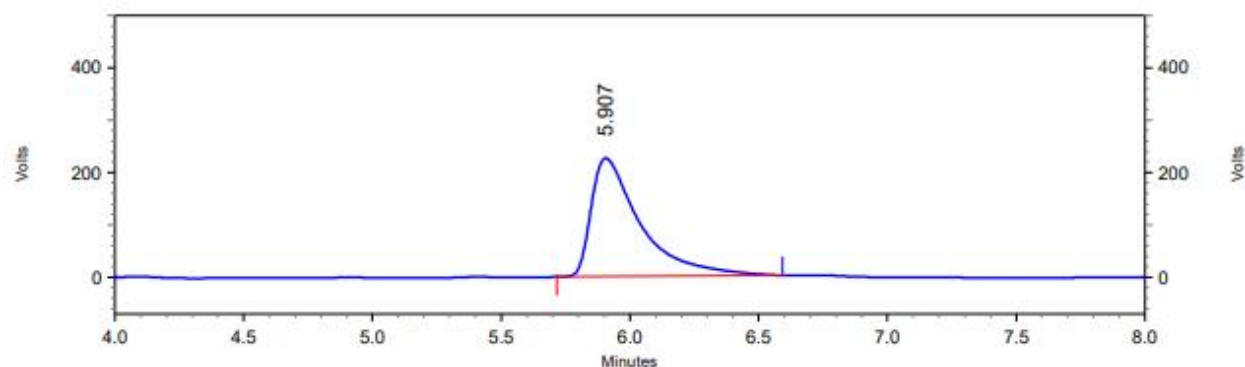
Retention Time	Area	Area %	Height	Height %
5.270	104576936	100.00	8025797	100.00
Totals	104576936	100.00	8025797	100.00

Figure A5.35. HPLC chromatogram and analysis plot showing the resolved peaks for untreated R -4-benzyl-2-oxazolidinone (**R-DO**)

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Area % Report

Data File: D:\KISHOR\Cavya\14072024\ethanol met\DO-S.rslt\DO-SETMEHEX.met2024-07-15 16-39-32 (GMT +05-30).dat
Method: D:\PROJECTS\02MAR15\Method\Amol\3% IPA and 97% Hexane_230 nm_1 ml_60 min.met
Acquired: 7/15/2024 4:39:59 PM (GMT +05:30)
Printed: 7/15/2024 5:11:10 PM (GMT +05:30)



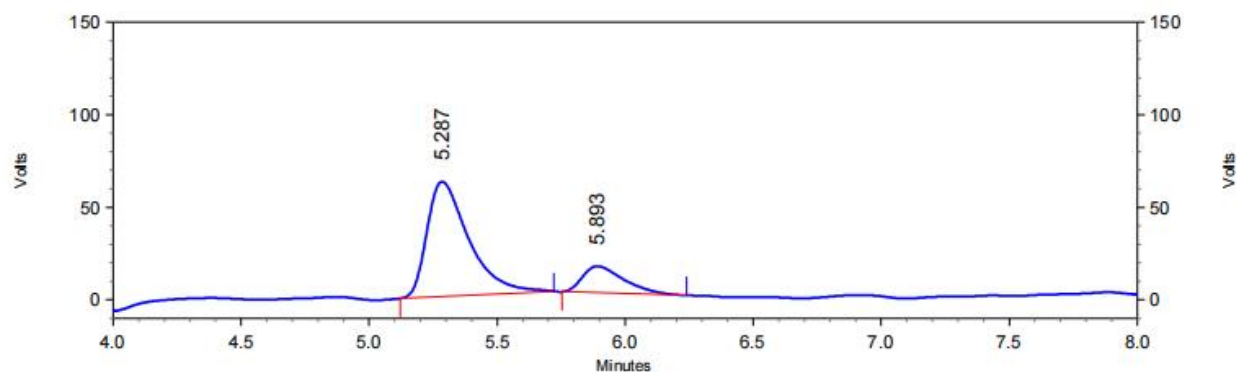
VWD: Signal A, 254 nm Results

Retention Time	Area	Area %	Height	Height %
5.907	50273135	100.00	3790592	100.00
Totals	50273135	100.00	3790592	100.00

Figure A5.36. HPLC chromatogram and analysis plot showing the resolved peaks for untreated S-4-benzyl-2-oxazolidinone (S-DO)

Area % Report

Data File: D:\KISHOR\Cavya\23072024\DO-1rep111.rslt\DO-1rep1110.6ETMEHEX.me.met2024-07-23
12-20-16 (GMT +05-30).dat
Method: D:\KISHOR\Cavya\23072024\DO-1rep111.rslt\0.6ETMEHEX.me.met
Acquired: 7/23/2024 12:20:50 PM (GMT +05:30)
Printed: 7/23/2024 12:32:55 PM (GMT +05:30)



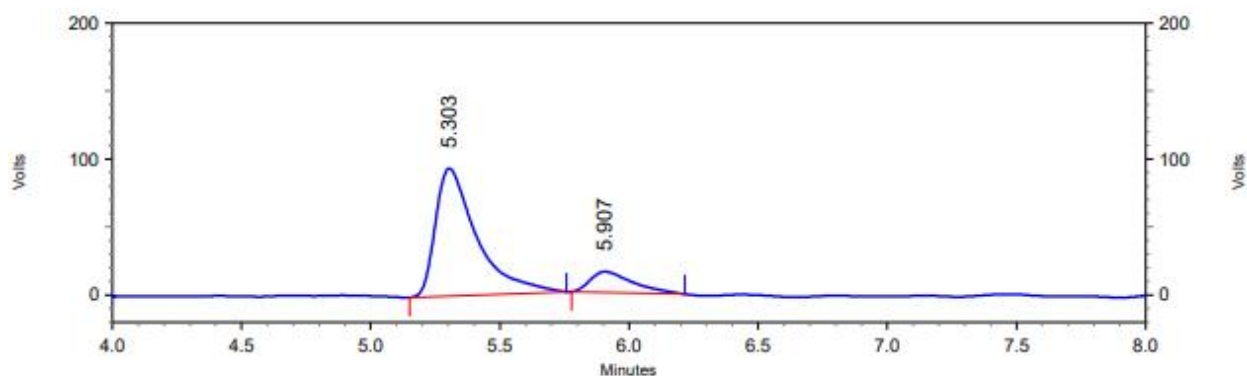
VWD: Signal A, 254 nm Results

Retention Time	Area	Area %	Height	Height %
5.287	11807018	81.33	1041278	81.20
5.893	2709657	18.67	241078	18.80
Totals	14516675	100.00	1282356	100.00

Figure A5.37. HPLC chromatogram and analysis plot showing the resolved peaks for separation of rac -4-benzyl-2-oxazolidinone (DO) by **5.1-R**, ee = 63%.

Area % Report

Data File: D:\KISHOR\Cavya\14072024\ethanol met\DO-1.rslt\DO-1ETMEHEX.met2024-07-15 16-48-44 (GMT +05-30).dat
 Method: D:\PROJECTS\02MAR15\Method\Amol\3% IPA and 97% Hexane_230 nm_1 ml_60 min.met
 Acquired: 7/15/2024 4:49:19 PM (GMT +05:30)
 Printed: 7/15/2024 5:12:43 PM (GMT +05:30)



VWD: Signal A, 254 nm Results

Retention Time	Area	Area %	Height	Height %
5.303	17429846	85.53	1573061	85.96
5.907	2947935	14.47	256949	14.04
Totals	20377781	100.00	1830010	100.00

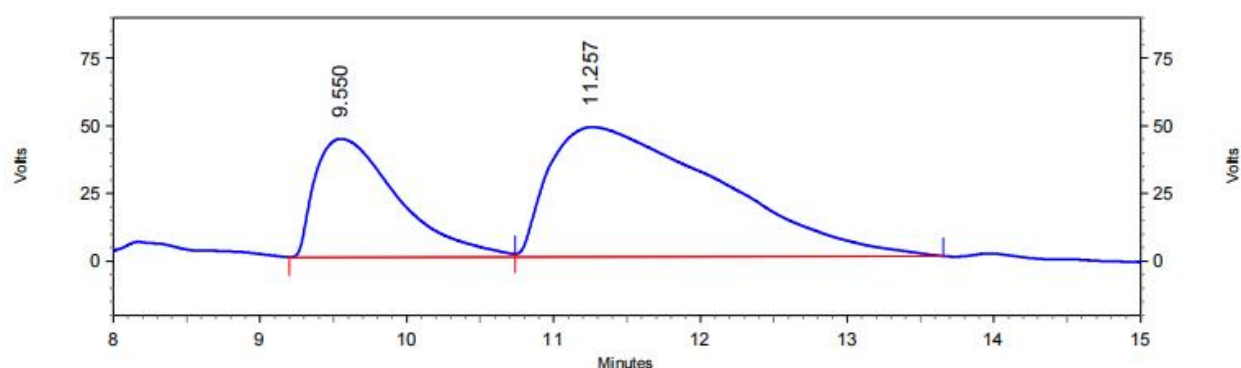
Figure A5.38. HPLC chromatogram and analysis plot showing the resolved peaks for separation of rac -4-benzyl-2-oxazolidinone (DO) by **5.2-R**, ee = 72%.

EP System

Method: Enantiometric purity of EP was determined by HPLC with Chiralpak IA (20 cm) column with a flow rate of 1 mL/min. was employed for the chiral HPLC analysis using 98/2 of n-hexane/isopropanol as eluent and the effluent was monitored at a wavelength 205 nm.⁷

Area % Report

Data File: D:\KISHOR\Cavya\17072024\EP 1.rsl\EP 1EP10.met2024-07-17 16-35-54 (GMT +05-30).dat
 Method: D:\PROJECTS\02MAR15\Method\Amol\3% IPA and 97% Hexane_230 nm_1 ml_60 min.met
 Acquired: 7/17/2024 4:36:36 PM (GMT +05:30)
 Printed: 7/17/2024 5:37:02 PM (GMT +05:30)



VWD: Signal A, 205 nm Results

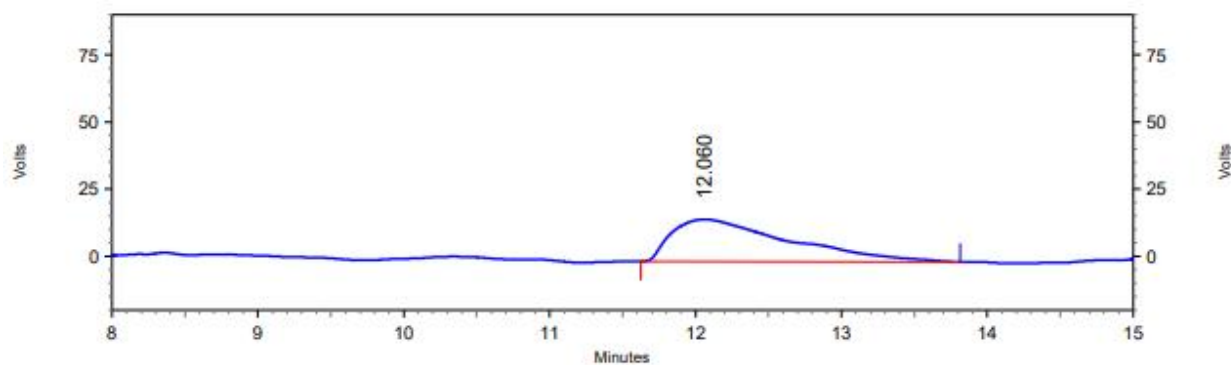
Retention Time	Area	Area %	Height	Height %
9.550	28753150	30.58	732913	47.66
11.257	65268422	69.42	804829	52.34
Totals	94021572	100.00	1537742	100.00

Figure A5.39. HPLC chromatogram and analysis plot showing the resolved peaks for untreated rac-pichlorohydrin (EP)

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Area % Report

Data File: D:\KISHOR\Cavya\17072024\EP R REP.rsl\EP R REPEP10.met2024-07-17 17-30-40 (GMT +05-30).dat
Method: D:\PROJECTS\02MAR15\Method\Amol\3% IPA and 97% Hexane_230 nm_1 ml_60 min.met
Acquired: 7/17/2024 5:31:11 PM (GMT +05:30)
Printed: 7/17/2024 5:50:03 PM (GMT +05:30)



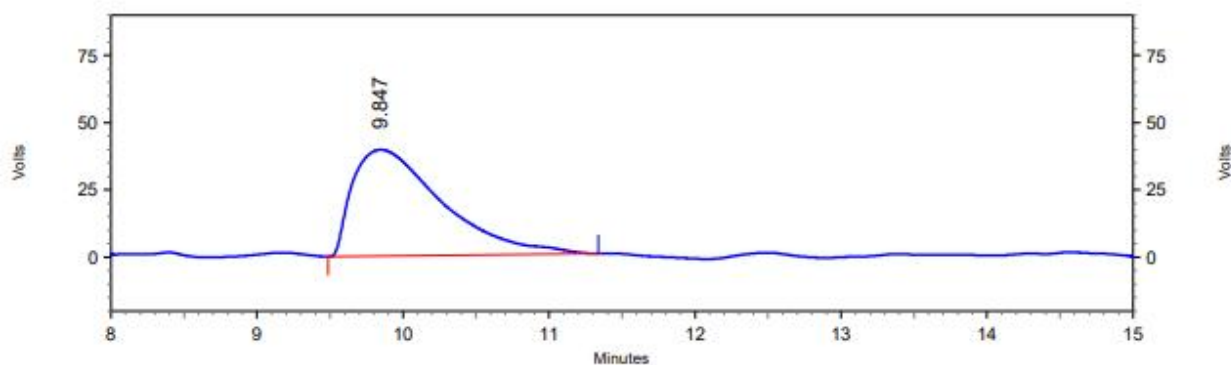
VWD: Signal A, 205 nm Results

Retention Time	Area	Area %	Height	Height %
12.060	14572654	100.00	262783	100.00
Totals	14572654	100.00	262783	100.00

Figure A5.40. HPLC chromatogram and analysis plot showing the resolved peaks for untreated R-epichlorohydrin (**R-EP**)

Area % Report

Data File: D:\KISHOR\Cavya\17072024\EP S.rsl\EP SEP10.met2024-07-17 16-17-05 (GMT +05-30).dat
 Method: D:\PROJECTS\02MAR15\Method\Amol\3% IPA and 97% Hexane_230 nm_1 ml_60 min.met
 Acquired: 7/17/2024 4:17:46 PM (GMT +05:30)
 Printed: 7/17/2024 5:35:10 PM (GMT +05:30)



VWD: Signal A,
 205 nm Results

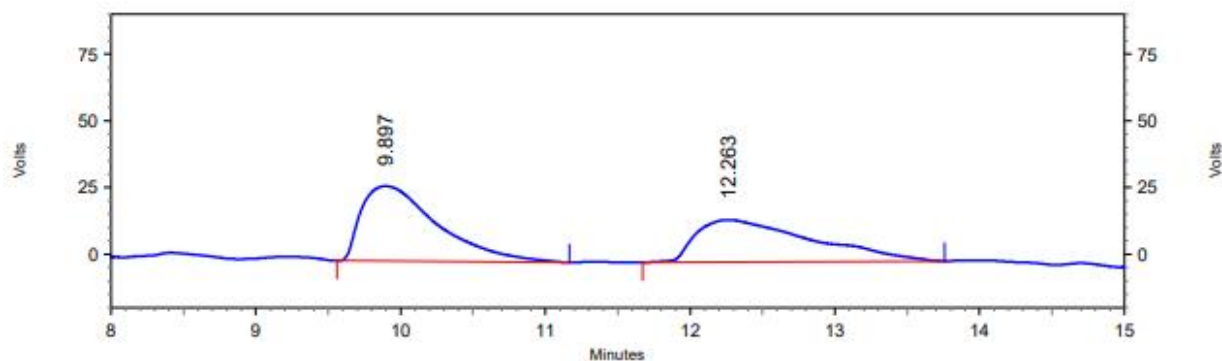
Retention Time	Area	Area %	Height	Height %
9.847	28331734	100.00	663540	100.00
Totals	28331734	100.00	663540	100.00

Figure A5.41. HPLC chromatogram and analysis plot showing the resolved peaks for untreated S-epichlorohydrin (SEP)

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Area % Report

Data File: D:\KISHOR\Cavya\17072024\EP RS.rsl\EP RSEP10.met2024-07-17 15:55:54 (GMT +05:30).dat
Method: D:\PROJECTS\02MAR15\Method\Amol\3% IPA and 97% Hexane_230 nm_1 ml_60 min.met
Acquired: 7/17/2024 3:56:35 PM (GMT +05:30)
Printed: 7/17/2024 5:34:03 PM (GMT +05:30)



VWD: Signal A, 205 nm Results

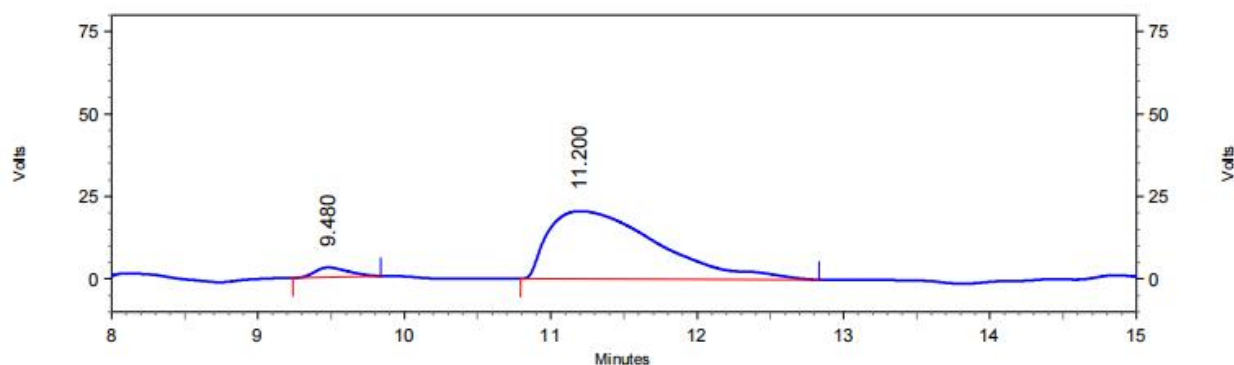
Retention Time	Area	Area %	Height	Height %
9.897	17294157	54.21	471444	64.09
12.263	14605414	45.79	264200	35.91
Totals	31899571	100.00	735644	100.00

Figure A5.42. HPLC chromatogram and analysis plot showing the resolved peaks for separation of rac-epichlorohydrin (EP) by **5.1-R**, ee = 28.2 %.

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Area % Report

Data File: D:\KISHOR\Cavya\23072024\EP-2REP1.rsl\EP-2REP1EP10.met2024-07-23 09:41:16 (GMT +05:30).dat
 Method: D:\PROJECTS\02MAR15\Method\Amol\3% IPA and 97% Hexane_230 nm_1 ml_60 min.met
 Acquired: 7/23/2024 9:41:47 AM (GMT +05:30)
 Printed: 7/23/2024 12:30:39 PM (GMT +05:30)



VWD: Signal A, 205 nm Results

Retention Time	Area	Area %	Height	Height %
9.480	760950	4.07	49140	12.50
11.200	17952404	95.93	343837	87.50
Totals	18713354	100.00	392977	100.00

Figure A5.43. HPLC chromatogram and analysis plot showing the resolved peaks for separation of rac-epichlorohydrin (EP) by **5.2-R**, ee = 75 %