Molecular selectivity by Host-Guest methods

by

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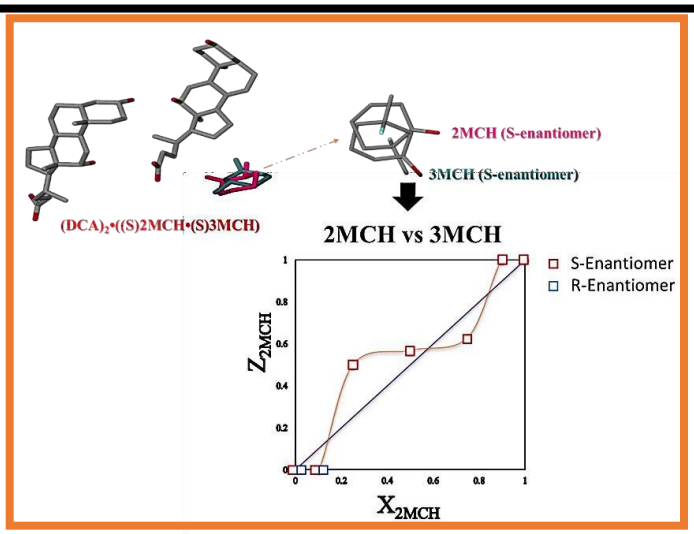

« On voit que, pour arriver à la solution de ces deux questions, il fallait d'abord bien connaître l'analyse et la nature du corps susceptible de fermenter, et les produits de la fermentation ; car rien ne se crée, ni dans les opérations de l'art, ni dans celles de la nature, et l'on peut poser en principe que, dans toute opération, il y a une égale quantité de matière avant et après l'opération ; que la qualité et la quantité des principes est la même, et qu'il n'y a que des changements, des modifications. »

"We see that, in order to arrive at the solution of these two questions, it was first necessary to know the analysis and the nature of the body likely to ferment, and the products of fermentation; for nothing is created, neither in the operations of art, nor in those of nature, and one can posit in principle that, in any operation, there is an equal quantity of matter before and after the operation ; that the quality and quantity of the principles is the same, and that there are only changes, modifications."

Antoine Lavoisier

DECLARATION

I, Jacky Sorrel Bouanga Boudiombo, declare that the contents of this dissertation/thesis represent my own unaided work, and that the dissertation/thesis has not previously been submitted for academic examination towards any qualification. Furthermore, it represents my own opinions and not necessarily those of the University of Cape Town.

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I confirm that I have been granted permission by the University of Cape Town's Doctoral Degrees Board to include the following publication(s) in my PhD thesis, and where co-authorships are involved, my co-authors have agreed that I may include the publication(s):

1. Bouanga Boudiombo, J.S., Su, H., Bourne, S.A., Nassimbeni, L.R. Separation of trimethoxybenzene isomers by bile acids *Cryst. Growth Des.* 2018, 18(1), 424–430.
2. Bouanga Boudiombo, J.S., Su, H, Bourne, S.A., Weber, E., Nassimbeni, L.R. Separation of lutidine isomers by selective enclathration. *Cryst. Growth Des.* 2018, 18(4), 2620–2627.
3. Bouanga Boudiombo, J.S., Su, H, Ravenscroft, N., Bourne, S.A., Weber, E., Nassimbeni, L.R. Preferential enclathration of lutidine isomers by diol-hosts. *J. Mol. Struct.* 2019, 1181, 636-644.
4. Bouanga Boudiombo, J.S., Su, H, Ravenscroft, N., Bourne, S.A., Nassimbeni, L.R. *Cryst. Growth Des*., 2019, 19(7), 3962-3968.
5. Bouanga Boudiombo, J.S., Su, H, Ravenscroft, N., Bourne, S.A., Weber, E., Nassimbeni, L.R. *CrystEngComm*, DOI: 10.1039/d0ce00510j

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- ***The University of Cape Town, for increasing my knowledge and***
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- ***Any person who contributed to the accomplishment of this thesis directly or indirectly, may God bless you.***

▪ DEDICATION

To my father, I hope this thesis is up to the challenge you set to me years ago.

To my mum, family and friends…

PUBLICATIONS AND CONFERENCES

Part of this thesis has been published as follow:

- Title: Separation of trimethoxybenzene isomers by bile acids.
  Bouanga Boudiombo, J.S., Su, H, Bourne, S.A., Nassimbeni, L.R. *Cryst. Growth Des.* 2018, 18(1), 424–430.
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  Bouanga Boudiombo, J.S., Su, H, Ravenscroft, N., Bourne, S.A., Weber, E., Nassimbeni, L.R. *J. Mol. Struct.* 2019, 1181, 636-644.
- Title: Separation and resolution of methylcyclohexanones by enclathration with deoxycholic acid
  Bouanga Boudiombo, J.S., Su, H, Ravenscroft, N., Bourne, S.A., Nassimbeni, L.R. *Cryst. Growth Des*., 2019, 19(7), 3962-3968.
- Title: Selective enclathration of xylenols: synergistic effects of mixed hosts.
  Bouanga Boudiombo, J.S., Su, H, Ravenscroft, N., Bourne, S.A., Weber, E., Nassimbeni, L.R. *CrystEngComm*. DOI: 10.1039/d0ce00510j.

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  Title: Molecular selectivity by host-guest method (poster presentation).
- Annual Science Postgraduate Symposium: 11 September 2018.
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- Indaba 9 conference: 2 - 7 September 2018.
  Separation of trimethoxybenzene isomers by bile acid (poster presentation)
- SACI/RSC Western Cape Young Chemists' Symposium: 17 May 2019.
  Title: Separation of lutidine isomers by selective enclathration
- Department of Chemistry PhD symposium: 28 August 2019.
  Title: Separation of Isomers by Selective Enclathration.

ABSTRACT

The Host-Guest inclusion crystallization method has long been used for the separation of closely related compounds. Especially for the separation of isomers which presented difficulties in techniques like distillation or chromatography. In this study, different host systems were used to separate isomers of trimethoxybenzenes, lutidines, methylacetophenones and xylenols.

Isomers are compounds with the same molecular formula but different arrangement of their atoms. They are often produced as mixtures when synthesised in large quantities by various industries and are more valuable as purified single components. Thus, it is important to separate them into their individual components. The process of Host-Guest method is dependent on the phenomenon of molecular recognition between the host and guest molecules, and this, in turn, relies on the sum of non-bonded, secondary interactions which impinge on the final crystalline product. This is especially the case for enantiomers which are isomers with the same boiling points and melting point. However, enantiomers differ by their ability to diffract polarised light. Although countless methods have been used for their separation, one method that has been proven to be certainly successful on this path was the “family method”.

The “Dutch resolution method” or the “family method” makes use of the crystallization technique by mixing similar host compounds to separate enantiomers. However, the improvement of the end results was not understood. In fact, the whole process has been done just on results and no analysis of the actual activity occurring at the molecular level was investigated. In this research, the Host-Guest chemistry method was applied with the aim of separating several isomers compounds in the intention of understanding the selectivity characteristics of a particular host.

For the purpose of the analysis, structural isomers with close boiling points were selected. Competition experiments were set to survey which of the isomers were a better fit for a particular host. After analysis of the different crystal material obtained from crystallization experiments with NMR techniques, various trends were observed. X-Ray crystallography was employed to elucidate the crystal structures of the different compound formed by Host-Guest chemistry. The new complexes were further analysed by thermal analysis (TGA, DSC), kinetics of desolvation, Hirshfeld surface analysis, and activation energy of desolvation-analysis techniques.

During the separation of the trimethoxybenzene (TMB) isomers, cholic acid and deoxycholic acid' hosts were used in chapter 3. It was found that each host separated the isomers differently. That was independent of the closeness of their molecular structures. The difference in selectivity was attributed to the arrangement of each host in the structure obtained with the guest compounds.

Separation of lutidines was carried out in chapters 4 and 5. The first separation consisted of the study of the fifteen pairwise combinations of the isomers with 3,3′-bis(9-hydroxy-9-fluorenyl)2−2′- binaphthyl which is presented in chapter 4. The second analysis was carried out with host 2,2'bis(1-hydroxy-4,5-dihydro-2,3:6,7-dibenzocycloheptatrien-1-yl)-biphenyl. Nevertheless, both hosts preferred 3,4-lutidine. Four additional hosts were used to simulate the "Dutch resolution method" in chapter 5. Further analysis of torsion angles was performed over the five hosts for the complexes formed with 2,4-lutidine and 3,5-lutidine. The host characterized by unbridged phenyl moieties and the one characterized by bulky tert-butyl groups was found to prefer 3,5-lutidine.

In chapter 6, deoxycholic acid resolved the 2-methylcyclohexanone (2MCH) but not 3-methylcyclohexanone (3MCH) during the separation of methylcyclohexanone isomers. However, during the competition experiment, it was found that when 2MCH was mixed with 3MCH, the latter was resolved as an S-enantiomer. Kinetics of desolvation studied resulted in the determination of the activation energies of the Host-Guest complexes and was like the trend observed by ^{1}H NMR analysis.

Chapter 7 was focused on the synergistic effect of mixed hosts system. This was to emphasize the impact that a mixture of compounds with similar structural composition may provide. Competition experiments were done with the 15 pairs of xylenol isomers with 4,4'-isopropylidene Bisphenol. Three of these pairs were selected for further analysis with two similar bisphenol hosts. One interesting structure was obtained with 4,4-isopropylidene Bisphenol and 4,4'-(9-Fluorenylidene) Bisphenol with a guest mixture. This is an unusual result as crystal structures comprising two hosts with two guests are rare.

GLOSSARY

Terms/Acronyms/Abbreviations	Definition/Explanation
H	**Host compound**
DCA	**Deoxycholic acid**
CA	**Cholic acid**
LUT	**Lutidine**
XYL	**Xylenol**
MCH	**Methylcyclohexanone**
TMB	**Trimethoxybenzene**
API	**Active pharmaceutical ingredient**
HSQC	**Heteronuclear single quantum coherence**
NMR	**Nuclear magnetic resonance**
DMSO-d6	**Deuterated dimethyl sulfoxide**
DSC	**Differential Scanning Calorimetry**
TGA	**Thermogravimetry analysis**
a, b, c	**Unit cell axes**
α	**Angle between b and c unit cell axes**
β	**Angle between a and c unit cell axes**
γ	**Angle between a and b unit cell axes**
V	**Unit cell volume**
Z	**Number of formula units per cell**
T_{on}	**Onset temperature**
D_{calc}	**Calculated density**
GOOF	**Goodness of fit**
R	**Universal gas constant**
E_a	**Activation energy**
T	**Temperature**
kJ mol^{-1}	**Kilojoules per mole**
β	**Heating rate**
bp	**Boiling point**

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Chapter 1. **Introduction**

The present chapter focuses on the background of supramolecular chemistry and the different techniques used to separate compounds. In this section, concepts like self-assembly and molecular recognition have been subsequently reviewed. The problem statement, the rationale of the study, the aim, and the thesis layout have also been defined.

1.1 Background

Supramolecular chemistry is a new branch of chemistry that focuses on the study of entities connected through non-covalent bonding. Although it was introduced by the Nobel Prize winner Jean-Marie Lehn as "*the chemistry beyond the molecule*" in 1978[1,2], supramolecular chemistry obtained its origins earlier when Axel Cronsdtedt described zeolites as boiling stones in 1756[3]. However, one of the first recognized supramolecular structures was chlorine hydrate discovered by Sir Humphrey Davy in 1801 which was then followed by the discovery of its formula by Michael Faraday in 1823[4]. The highest recognition for supramolecular chemistry was given to Petersen, Cram and Lehn when they shared their Nobel Prize in 1987[1] for their contribution in synthesizing molecules with similar characteristics as the vital chemical functions of entities in living organisms[1,5]. Since then, several works were carried out which promoted the features and diversity of supramolecular chemistry showing its application in organic, medicinal as well as inorganic chemistry and materials.

Also referred to as the "*chemistry of molecular assemblies*" or "*of the intermolecular bond*", supramolecular chemistry has been given several names like "Lego chemistry" as well as "*the chemistry of the non-covalent bond*"[6–8]. It focuses on the studies of intra and intermolecular interactions within two or more molecules[9]. In other terms, supramolecular chemistry focuses on the formation of supramolecules and the interaction patterns observed within these structures[10]. This leads to the formation of different synthons which could be obtained by the hydrogen bonding patterns formed by atoms commonly used like nitrogen, oxygen, and carbon [11–13]. Figure 1 shows the formation of supramolecules from molecular precursors.

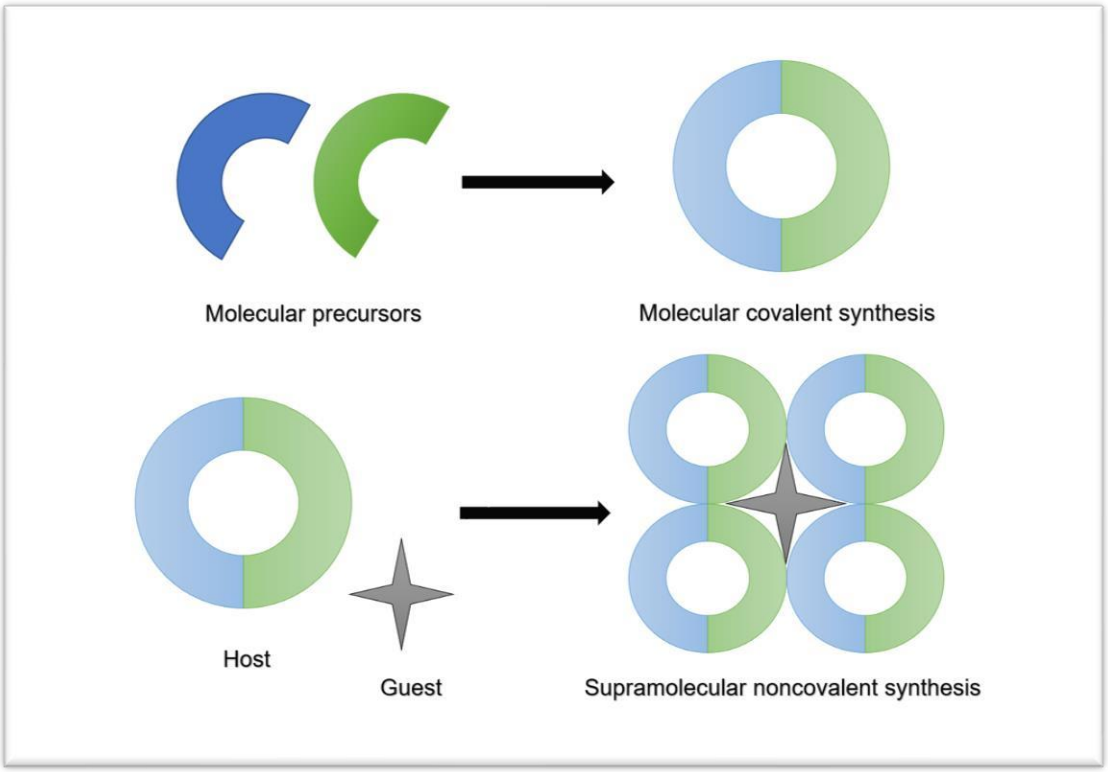

Figure 1-1: Formation of supramolecular noncovalent synthesis from molecular precursor.

Molecules consist of atoms linked to one another by relatively strong intramolecular interactions. Conversely, supramolecules (supermolecules) are compounds consisting of molecules held together by various noncovalent interactions such as hydrogen bonding, Van der Waals forces, electrostatic interactions and hydrophobic interactions, etc[14–16]. It is usually observed that these supramolecules may display enhanced reactivity by synergistic effects of the individual components. This is directly applied in the construction of co-crystals of active pharmaceutical ingredients[17]. According to Ariga and Kunitake[18] "*good organisation and a well-selected combination of supramolecular elements lead to systems with incredible performance*".

1.1.1 Self-assembly

As previously defined above, supramolecular chemistry is the chemistry beyond molecules and serves as a bridge to physics, biology, and chemistry[19,20]. Molecules tend to self-assemble in terms of how easily they can reach their most stable conformations[21–23]. This self-assembly

process is usually reflected in biology where the arrangement of molecules is expressed by their functions in the body. Self-assembly process prompts to several structures and superstructures observed at the sub-cellular and cellular levels. In other terms, the continuous arrangement of cells in the human system is an amalgamation of components depending on one another. When the reciprocal recognition of cells does not take place, fatal consequences may derive, and this is usually encountered with cancerogenic cells[24]. The indicated process shows a practical representation of self-assembly defined as the ability of molecules to reorganize themselves depending on many features like their functional groups, shapes, or sizes. Furthermore, self-assembly is an alterable and effortless process with minimum by products whose application is extended in various domains from the formation of multilayers to supramolecules (Figure 2)[25–27].

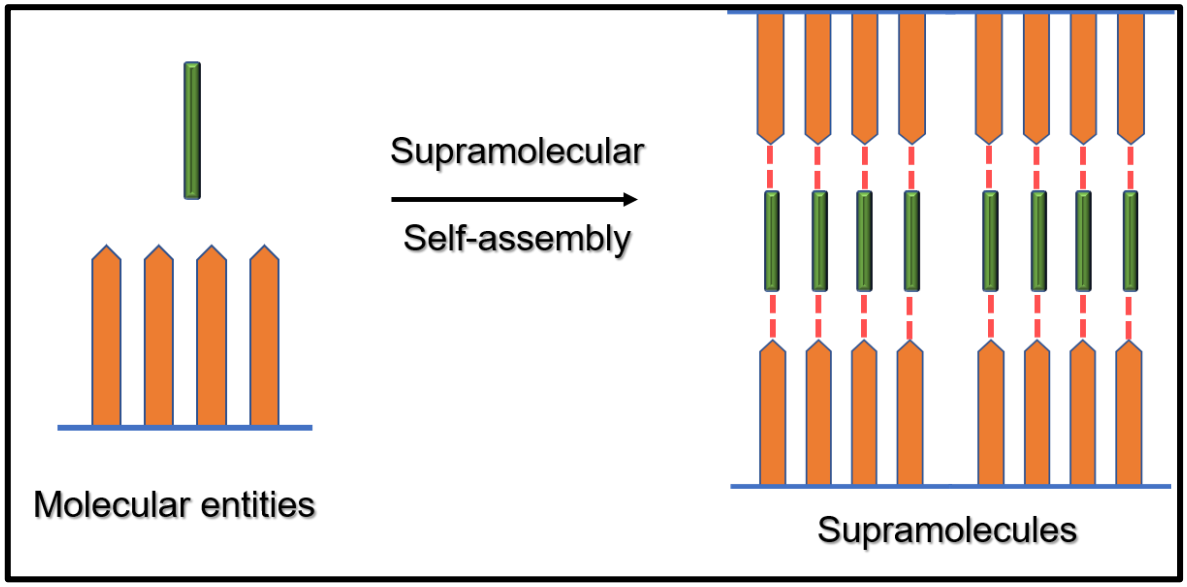

Figure 1-2: Formation of supramolecular entities by self-assembly of hydrogen bonding reactants.

Whitesides[28] defines self-assembly as the "*spontaneous assembly of molecules into structured, stable, non-covalently bonded aggregates*" representing the most thermodynamically favourable form. Besides, in supramolecular chemistry, Lindoy and Atkinson[29] define self-assembly as "*the process by which a supramolecular species is formed spontaneously from its components*." This presents an important order in supramolecular chemistry since chemists can afford to produce different species by the analysis of various structures from different components. This takes place as every entity would have a uniqueness leading to a specific

structural arrangement. This awareness was emphasized by Gale and Steed[3] who specified that the fundamental concept within self-assembly is the information contained within a supramolecule. This information may dictate how they will be interlinked, how to avoid errors during their synthesis but also to promote the resulting supramolecular species to be efficient. One should regard self-assembly as the self-organization of molecules in a system[28,30,31]. These aspects are of great importance to the crystal engineering team since they rely on these features to strategize as well as predict the resulting supramolecular compound from their starting material[32,33]. Therefore, the type of interactions to be used would be adapted from the features of the guest and host molecules employed.

1.1.2 Molecular recognition

Supramolecular chemistry focuses on the formation of supramolecular complexes made from smaller molecules linked by reversible noncovalent interactions[4]. When combined these molecules result in complexes with improved chemical properties since they have different chemical and physical characteristics. For these compounds to combine with one another, a process of recognition is likely to take place as some of the individual components must follow certain complementary characteristics as observed in Figure 3. When these characteristics are not observed, the ability for these components to combine is reduced.

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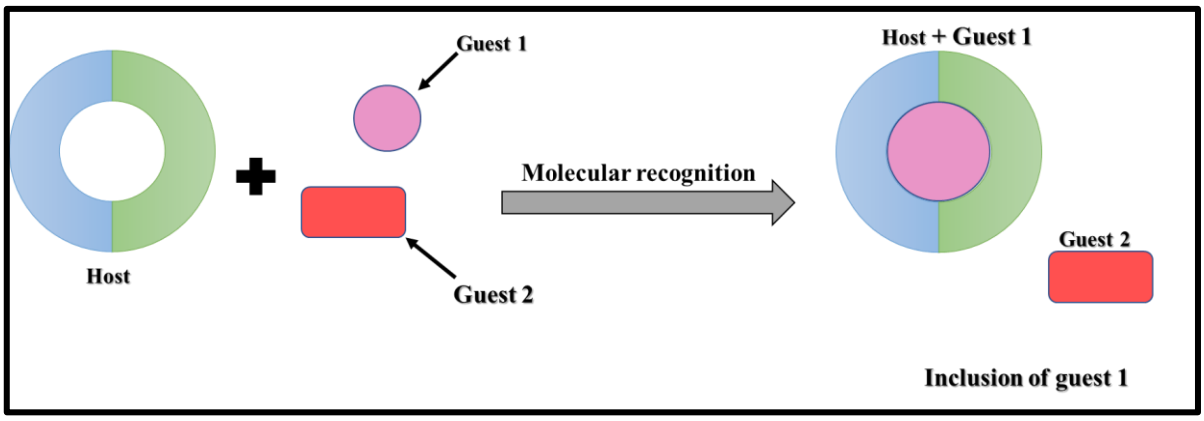

Figure 1-3: Process of molecular recognition from the selection of a better fit guest 1.

Molecular recognition is based on the host-guest assembly concept. In this area of study, a host molecule is considered as having convergent binding sites while the guest displays divergent

sites[3]. The availability of divergent sites entices the guest to combine in a particular manner with any host molecule. According to Ariga and Kunitake[18], molecular recognition results from a specific interaction occurring between components. This takes place through a reaction between selected partners, whereby the host compound found its best partner (best guest) which refers directly to the mechanism of molecular recognition. Additionally, Lindoy and Atkinson[29] specified that "*the degree of electronic and steric complementarity between host and guest, in general dictates the magnitude of any molecular recognition that occurs in a given supramolecular system*".

The application of molecular recognition is fundamental throughout this thesis, where the focus of the study is on the separation of compounds by host-guest complexes formation. This is observed when the host would have a preference toward a selected guest during the competition experiment. This would be based on the molecular recognition pattern which is then investigated to understand the selectivity. Another aspect of a direct application of molecular recognition occurs during the enantioselectivity analysis. In this process, a chiral host is required which is combined with a racemic modification during the crystallization process. From the features observed in the given host, it could have a particular attraction toward the R or the S-enantiomer. The present field of study is of great interest in the pharmaceutical industry where certain drugs are racemic and may cause serious damage to health if they are not separated from their R- or S-enantiomer. The following process may result in some of those racemic modifications being toxic due to the presence of the undesirable enantiomer.

1.2 Crystal engineering

Crystal engineering is a tool used in the formation of new supramolecules with control features (Figure 4)[34,35]. Crystal engineers identify specific topographies of the final compound that should be produced and acknowledge the criteria that lead to these specific patterns by choosing the correct starting materials[8,36]. As an analogy with organic chemistry synthesis, a crystallographer uses several types of reagents and reaction processes in the aim of producing crystalline compounds with required functions[37]. The most appealing aspect of the formation of supramolecules by crystal engineering is the production of a different compound by slightly changing temperatures, solvent, or also the environment of crystallization. Such changes in

the conditions of crystallization lead sometimes to different crystal compounds which is the case of polymorphs or solvates with different stoichiometries.

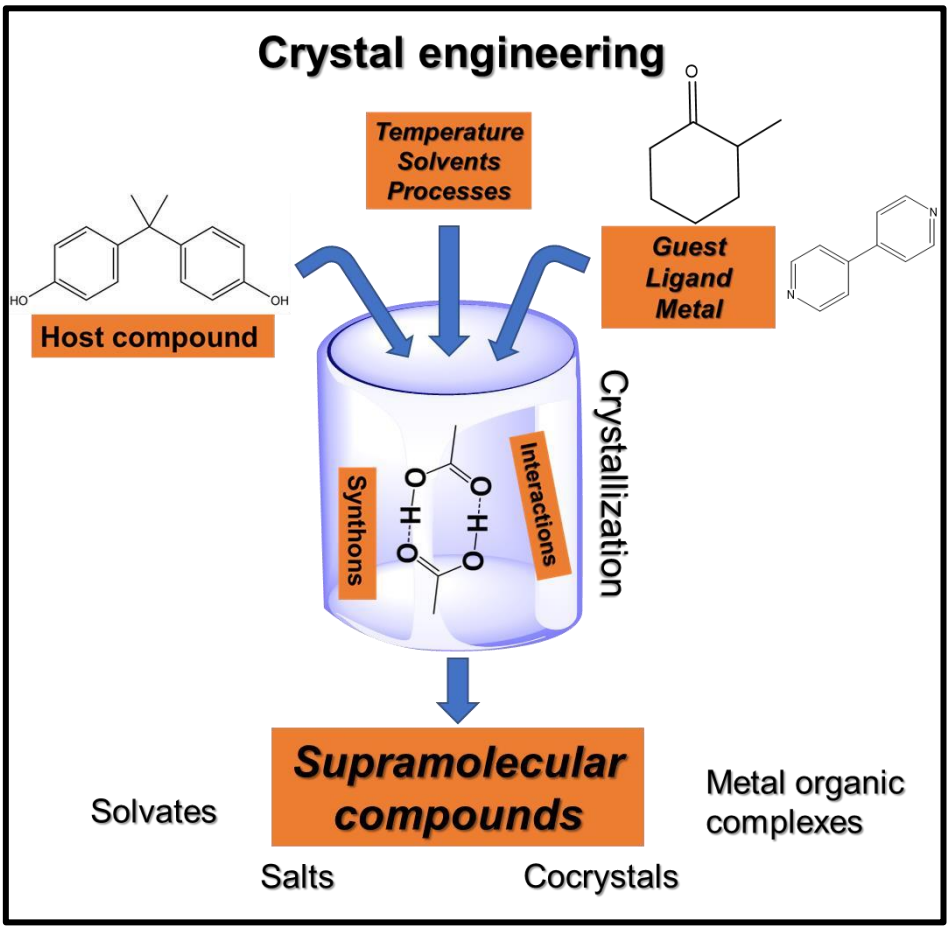

Figure 1-4: Crystal engineering outline

According to Braga[33], "*the aim of crystal engineering is that of controlling collective crystal properties by controlling the way molecular building blocks are assembled in the desired (designed) superstructure*". Crystal engineers synthesize new crystalline solids with a predefined aggregation of molecules, ions, or metals[38]. The predefined aggregation is attained through adequate synthons made from hydrogen bonding, Van der Waals interactions, halogen bonding, and other interactions[39–46]. Even though these different tools have been used to build up several supramolecules, it is not always possible to direct the final structure of a crystal component resulting from the handling of the different elemental parts. Nevertheless, studies from several researchers like Etter[47], Wuest[48], and Desiraju[49] have set an important platform for crystal engineering. Their work has been continually promoted by Zaworotko[50], Braga[33],

Aakeroy[51], and Metrangolo[52], and many others. Crystal engineering is now well known for its use in several fields for the construction of targeted pharmaceutical materials[53,54], organic conductors[55] and, metal-organic frameworks[56]. Recently, this resulted in the award of the Nobel prize in Chemistry, 2016, won by Jean Pierre Sauvage, Sir J Fraser Stoddard and Bernard L Feringa, for their design of molecular machines. These molecules have controllable movements that can perform a task when energy is added[57].

1.2.1 Supramolecular synthon in crystal engineering

Building supramolecular compounds result from an important screening of features. One of the necessities used for the rational design of a targeted network in crystal engineering are synthons[58]. A supramolecular synthon is "*a structural unit within a supermolecule which can be formed and/or assembled by known or conceivable synthetic operations involving intermolecular interactions*"[59]. Supramolecular synthons are a result of hydrogen bonding patterns formed by atoms commonly used like nitrogen, oxygen, and carbon (Figure 5). Due to synthons, molecules may change their conformation to readjust themselves to form interactions. The change of conformation results from the molecules looking for their most stable conformations to favour different interactions that may arise during the formation of supramolecules.

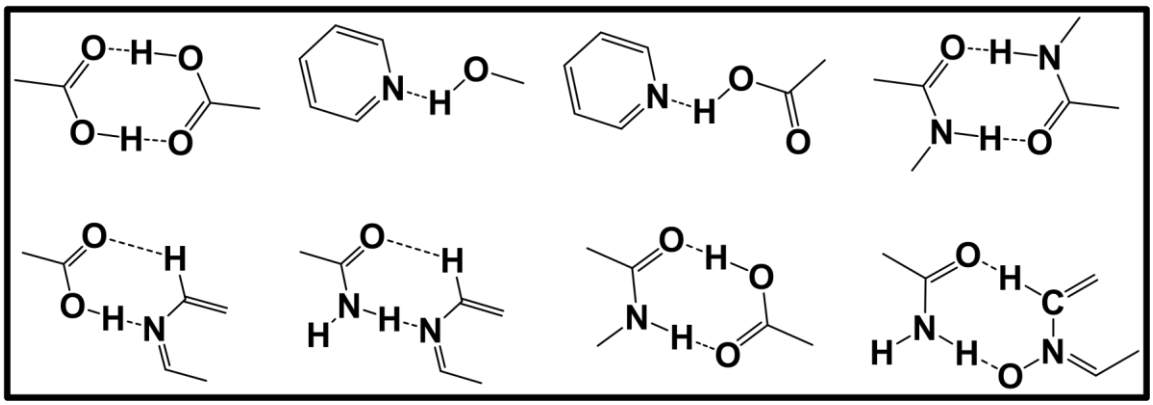

Figure 1-5: Example of some supramolecular synthons found in supramolecular chemistry

Supramolecular synthons are considered to contain information leading to molecular recognition[60]. Synthons are the smallest structural entities where the information essential in the recognition of molecules to yield crystals is encoded[59,61,62]. Therefore, during the resolution

of enantiomer by crystallization (separation of enantiomer), a chiral host would be needed as a starting material to perform the separation process[63,64]. This process was applied during the Dutch resolution method whereby racemic mixtures are separated through the formation of diastereomeric salts [65,66]. Also called the family method, the "Dutch resolution" consists of the use of structurally close host compounds combined in pairs or more to improve the selectivity toward a particular enantiomer. The indicated procedure could also be extended in the choice of host compounds to form adequate host-guest structures. In this case, a crystal engineer would focus on the robustness and rigid aspect of the host prepared by synthesis[67]. In addition, crystal engineering uses organic chemistry mechanisms to create adequate compounds for specific host-guest complexes.

1.2.2 Interactions in crystal engineering

1.2.2.1 Hydrogen bonding

Hydrogen bonding is the key concept in crystal engineering as most of the newly formed supramolecules show evidence of hydrogen bonding interactions and furthermore present favourable characteristics[33,68]. As described by Atwood and Steed[4], "*strength and directionality render hydrogen bond a theory of critical importance in establishing supramolecular structure*". Hydrogen bonding is an intermolecular interaction with strength ranging from 1-40 kJ/mol[1]. It is usually expressed in its simplest form as D-H•••A where D represents the atom donor and A is the receptor atom[12,13].

Table 1-1: Properties of hydrogen bonding interactions

Strength	Examples	D•••A/Å	H•••A/Å	D-H•••A/°
Weak	C-H•••O	3.0-4.0	2.0-3.0	110-180
Strong	O-H•••O-H	2.6-3.0	1.6-2.2	145-180
	O-H•••N-H	2.6-3.0	1.7-2.3	140-180
	N-H•••O=C	2.8-3.0	1.8-2.3	150-180
	N-H•••O-H	2.7-3.1	1.9-2.3	150-180
	N-H•••N-H	2.8-3.1	2.0-2.5	135-180
Very strong	$[F\text{-}H\text{-}F]^-$	2.2-2.5	1.2-1.5	175-180

Adapted from Desiraju and Steiner [67]

Hydrogen bonds are known to have a structurally strong and directional characteristic compare to other weak interactions used in crystal engineering. The mentioned characteristic may have a reversible state since these interactions could be broken[12,45,49,69].

1.2.2.2 Halogen bonding

Comparable to hydrogen bonding, halogen bonding has been used to build up several supramolecular molecules. With scientists' attention growing recently for this type of intermolecular interaction, halogen bonding was found to have similar characteristics to hydrogen bonding, for example, the specificity, strength, and directional aspect to form supramolecules. Halogen bonding is characterised by a donor atom which is usually an electron-withdrawing substituent while the acceptor atom is usually less electronegative or maybe an anions[3]. Figure 6 shows different hydrogen and halogen bonding observed in a structure of mefenamic acid with 3-bromopyridine.

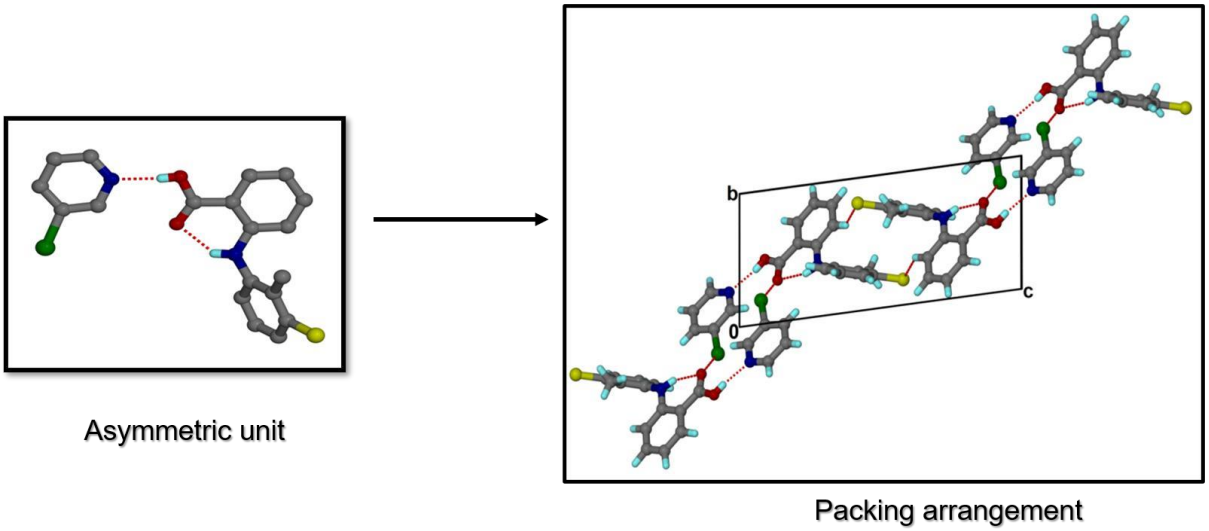

Figure 1-6: hydrogen and halogen bonding observed in the asymmetric unit of a complex formed with mefenamic acid with 2-bromo-pyridine.

1.2.2.3 Cation-π and anion-π interactions

Cation-π and anion-π interactions result from benzene rings interacting with a cation or an anion. The benzene ring is an electron-rich molecule with an overall charge distribution formed from the continuous build-up of negative charge. A cation is likely to be attracted to a benzene ring which may lead to a weak bond to take place[18,29,69]. However, repulsion is expected when an anion is in the environment of the benzene ring, due to the negative charge surrounding the benzene ring when it is close to an anion. On the other hand, some phenyl moieties tend to be electron deficient which then results in an interaction with anions present in the environment [3]

1.2.2.4 van der Waals interactions

van der Waals interactions are an accumulation of inductive and dispersive interactions. The present forces are weak with additive effect ranging from long to short-distance interactions. These interactions are less specific but they play an important role in building up supramolecules because they apply to all molecules. The van der Waals interactions result between molecules where the resulting combination of the forces interacting between them are larger than the sum of their electron clouds[29]. Van der Waals interactions involve several forces like dispersion forces, dipole-dipole interactions and other electrostatic effects.

1.2.2.5 π- π interactions

These interactions happen between aromatic rings when they are close to one another. Additionally, π -interactions result from short-range pi-systems and they tend to help in the packing of several supramolecular compounds. According to Steed & Atwood[3], π-π interactions arise when one of the interacting rings shows a relatively high electron density. They have been grouped into two general sets: the face to face and edge to edge interactions. The former occurs when we have two aromatic faces interacting in parallel with one another while the latter involves a weak hydrogen bonding between electron-deficient hydrogen and the electron-rich pi-cloud.

1.3 Separation Methods

1.3.1 Molecular sieves/zeolites

Zeolites and molecular sieves are compounds characterised by channels of specific sizes allowing the selectivity of a compound. Zeolites, are synthetic or natural hydrated aluminosilicate crystalline complexes with define apertures. On the other hand, when the silicon aluminium backbone is changed to other atoms, the complexes formed is called a molecular sieve[70]. One of the most interesting aspects of these compounds is their selectivity of molecules depending on their dimensions. This aspect allows some compounds of a specific shape to be retained into the crystal interior while the other molecules of different shape are not adsorbed[70].

Zeolites are useful adsorbents because they contain large void fractions and due to their hydrophilic properties[70]. Zeolites are used for the separation of isomers with one of its application seen in the separation of xylene isomers. Cheng *et al.* used a Ba^{2+} and a K^{+} ion-exchanged X zeolite to separate xylene compounds. To this end, a molecular constitution and the electrostatic effects led to capacities of ortho-xylene being the preferred isomer.

1.3.2 Chromatography

Chromatography was a method initially used to separate coloured plant pigments[70]. This method has been expanded to a much larger number of compounds, for example, within the pharmaceutical industry it is an important technique to separate and purify pharmaceutical drugs. Chromatographic methods are defined as physical methods whereby, during contact with a stationary phase and a mobile phase, substances are separated by partitioning[72]. According to Skoog *et al*.[73] "*Chromatography is a technique in which the components of a mixture are separated based upon the rates at which they are carried through a stationary phase by a gaseous or liquid mobile phase*". These methods are generally classified into two different categories depending on the type of mobile phase and could be a gas, liquid or maybe a superficial fluid. The mobile phase is employed depending on the type of samples analysed.

1.3.3 Distillation

Distillation is a separation technique based on the boiling point of the components to be separated. Although distillation is one of the most classic methods used to separate substances, it is still of vast importance in large scale separation of various substances like petroleum and ethanol. In this perspective, it is greatly used in a wide range of industries[74].

Early application of distillation was used for relatively crude vaporization and condensation techniques. The first relevant application of distillation was observed as the determination of alcohol concentration in beverages. This application has been expanded to the chemical industry in the twentieth century where it has been successfully used to separate crude oil. Nowadays, distillation has been extended to other techniques to improve its outcomes. In the petroleum industry, some companies use the extractive distillation which results in the addition of an additional solvent to enhance the relative volatility of the constituents to isolate. It is also employed for the separation of non-ideal mixtures[75]. Other various distillations (Flash evaporation, rotating circulation, vapour-reheat process, heat transfer using an immiscible liquid) are also used for the desalination of water. An additional method is the membrane distillation which is used for the treatment of water. In this method, pressure differences drive the process of distillation[76]. However, vacuum distillation is a technique applied for the separation of high boiling point liquids to avoid their decomposition[77]. The process is usually

practical during the separation of crude oils by controlling the temperatures as well as the pressure of the system[78].

1.3.4 Crystallization

Crystallization is a separation and purification method. It is considered a classic technique used to isolate several compounds depending on the difference in their physical properties. According to Ulrich & Stelzer[79], in the portfolio of industrial or laboratory separations, this method has been used in early ages to produce salt. This makes crystallization as one of the oldest methods used in chemical engineering[80]. Nowadays, it has been employed in the production of many materials such as in the industries of food, pharmaceutical, microelectronics and fine chemical industries[81,82]. The particularity of crystallization could be observed in pharmaceutical companies where the outcome of this method leads to the purified components with important characteristics. These characteristics may be the purity and the shape of the crystal which are quite important properties since these traits may enhance the bioavailability of some drugs. According to Chen *et al.*[83] "*The control of crystal size, shape, and crystal form is crucial as they can influence downstream operations such as filtration, drying, and milling as well as influence the physical and chemical properties of the solid such as dissolution rate and solubility*."

Crystallization has also been described as a phase change where a crystalline component is separated from a solution. This solution derives from the homogenous mixture of one or more components to form one phase. In general, the crystalline component is obtained by the evaporation from the solution or the melts of these compounds[84].

1.4 Host-guest chemistry

1.4.1 Host-guest chemistry: the concept of inclusion compounds

Host guest chemistry is a part of supramolecular chemistry focused on the interaction of large molecules, called hosts, with small molecules called guests. According to Steed *et al.*[85] Host-guest chemistry is "*the study of large 'host' molecules that are capable of enclosing smaller*

'guest' molecules via non-covalent interaction". By binding together, these molecules formed inclusion compounds.

Originally, inclusion compounds were termed as clathrates but as time went by, clathrates were a subset of this group of compounds. Nowadays, clathrates are defined more specifically as inclusion compounds where the guest molecules are completely entrapped in a void. Moreover, instead of lying in a channel, the guest is entirely enveloped by the host. This clearly emerged from the name of this type of compounds from the Latin word 'Clathrus', directly translate to "*surrounded on all sides*"[85].

In general, inclusion compounds can be defined as complexes where guest molecules would be found in hollows provided by host molecules. The host molecule would contain voids in the crystal lattice. This is shown in Figure 7 where the cavities of cholic were observed when it formed a complex with 1,2,4-trimethoxybenzene.

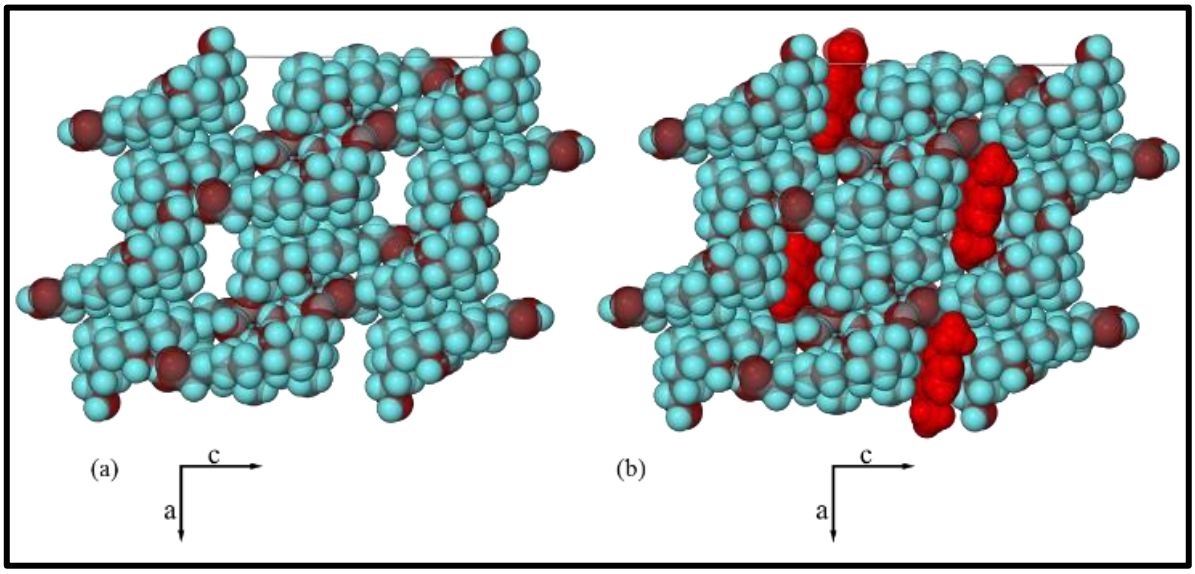

Figure 1-7: Inclusion compound of cholic acid with 1,2,4-trimethoxybenzene showing the hollows provided by the host molecules where the guest is found in red (b).

The then spaces could be in the form of cages, pockets, channels, and layers. Unlike the common covalent bonds between atoms which form a molecule, in this case, the guest would mostly focus on the suitability of its goodness of fit towards the spaces provided by the host.

This complementarity could be expressed by the interactions of the guest toward the host by the supramolecular interactions. Here, the strength of a particular complex would be taken into consideration. Complexes, where guest molecules are closely fitted, or have strong interactions with hosts, within the space provided by the host, would present stronger strength and stability compared to a less closely fitted guest presenting weaker interactions.

Inclusion compounds are arranged into two groups depending on where the guest is located.

- Molecular inclusion: in this type of molecules, the cavities are found within the host, and therefore the guest is encapsulated within the host cavities (see Figure 8).

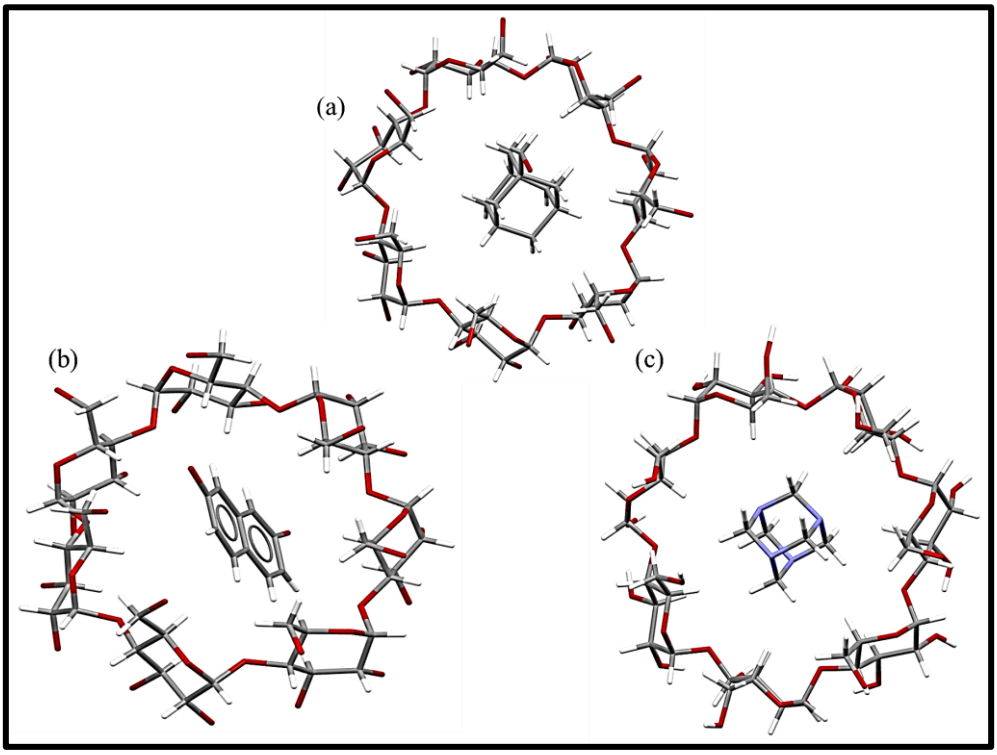

Figure 1-8: Inclusion compound of ***β***-Cyclodextrin with (a) 1-hydroxymethyl-adamantane [86] (b) 2,7dihydroxynaphthalene [87], (c) hexamethylenetetramine [88] (the water molecules where not included in this representation.

- Crystal lattice inclusion: voids are created by the imperfect packings of several host molecules which leave spaces between them. These are filled by the guests (see Figure 9).

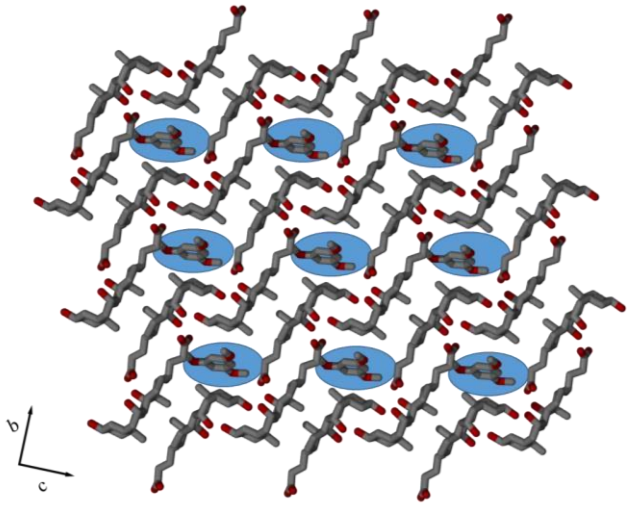

Figure 1-9: Inclusion compound of deoxycholic acid (DCA) with 1,3,5-trimethoxybenzene (TMB135) along [100] showing the guest (TMB135) located in the void provided by the packing of DCA.

The general scheme for the formation of Host-Guest compounds is as follows:

$$H\ (s, \alpha) + nG(l)/(g) \longrightarrow H{\cdot}Gn\ (s,\beta)$$

With H·Gn been the inclusion compound and α the non-porous

phase of the apohost β the phase of the inclusion compound

with host-guest ratio of n l the liquid phase g the gas phase s

the solid phase.

1.4.2 Selectivity in host-guest chemistry

Selectivity in host-guest chemistry relies on the level of complementarity between host and guest (see Figures 6 and 7). This depends on the aspect whereby one guest molecule is better accommodated in the space provided by a particular host. This accommodation could be related to the different interactions that the guest has with the host. Thus, the space provided by the host may better suit one guest instead of another. When considering the interactions, one will note the strength of hydrogen bonding, electrostatic, stacking or sometimes van der Waals interactions. These interactions may stabilize the complex formed with a particular

guest leading to its selectivity. This is demonstrated throughout this study, and finding the different tools to justify this selectivity was part of this research. Figure 10 presents the process of selectivity observed with a host and two different guests while Figure 11 is an illustration of three different selectivity curves that can result from the process of selectivity.

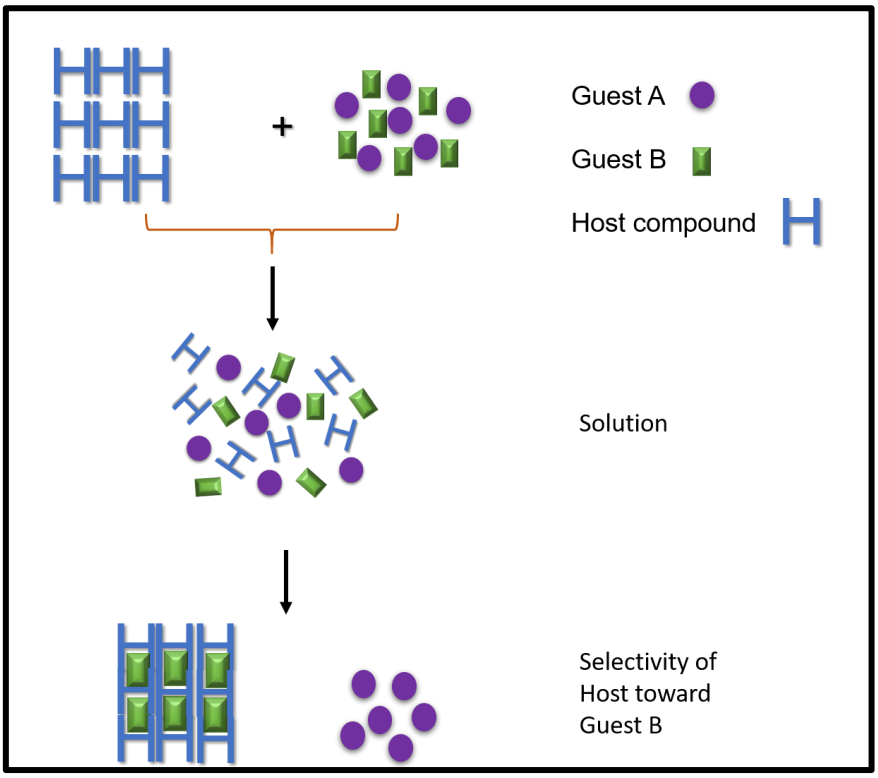

Figure 1-10: Selective inclusion process by molecular recognition.

For interaction between a host and a guest to take place, the host must present the appropriate binding sites. This could be the same number of hydrogen bonding sites or some chemical properties that may facilitate the binding effect. The host may be a base while the guest is an acid[85]. This results in the host having a particular preference which can arise from the complementary aspect of the host toward the guest. Additionally, the preorganisation of the host conformation with the cooperativity of the bonding groups of the two components should be considered[89].

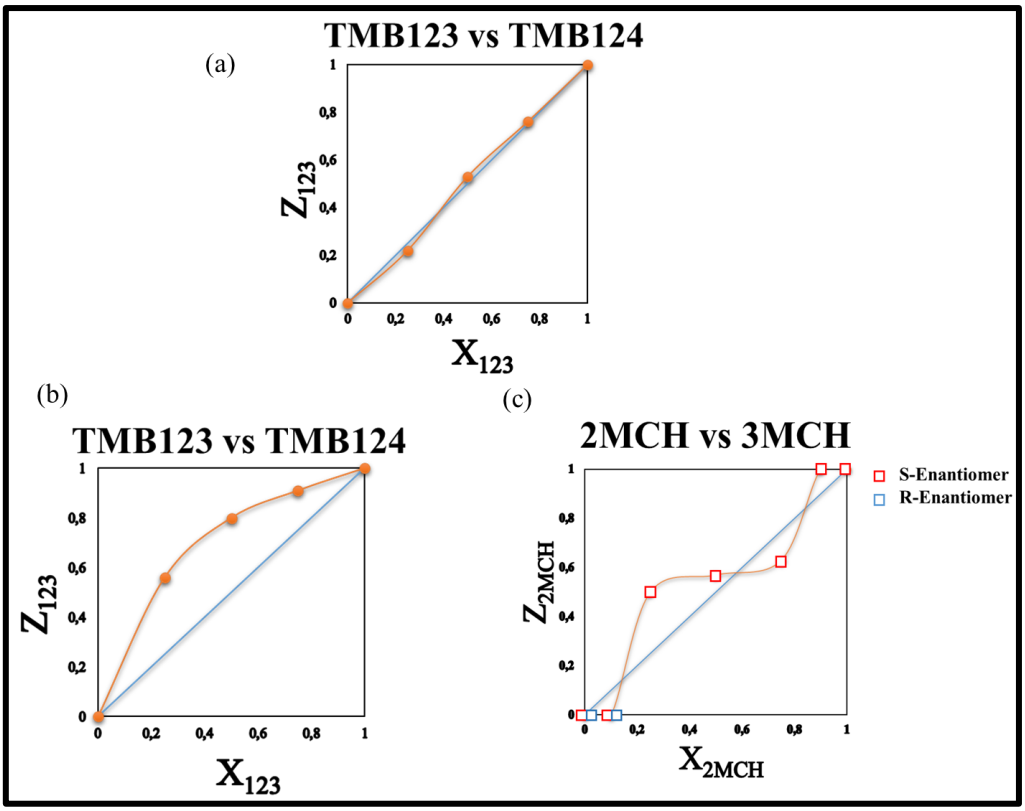

Figure 1-11: Selectivity pattern observed in three competition experiments of: a) cholic acid with 1,2,3trimethoxybenzene and 1,2,4-trimethoxybenzene showing no selectivity[90], b) deoxycholic acid and 1,2,3-trimethoxybenzene and 1,2,4-trimethoxybenzene showing preference for a particular guest[90], and c) deoxycholic acid with 2-methylcyclohexanone and 3-methylcyclohexanone showing a preference dependent on the guest present[91].

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Complementarity in host-guest chemistry relies on the components involved in complexation which must have binding sites that are complemented by one another. In other terms, complementarity focuses on the arrangement proposed by the host molecule. Due to this arrangement, the fitness of a certain site of a particular guest molecule would then complement and form a compound. The complementarity mostly takes into consideration the different interaction that might take place, or that might induce the binding process of the host toward the guest molecule. According to Wittenberg & Isaacs,[90] "*the complementarity between host and guest is the major factor governing mutual recognition between molecules*".

In cooperativity, compounds come together to have better stability. In this case, the host compound with several interconnected binding sites may yield a more stable complex compared to the one where the sites are not interconnected[85]. In their review on assessing the cooperativity of supramolecular complexes, Von Krbek, Schalley, & Thordarson,[91] proposed

that cooperativity could be defined as a process characterised by the interactions where the free energy in the followed step increases (positive cooperatively) or decreases (negative cooperativity)[92]. Additionally, they then concluded that in supramolecular chemistry, cooperativity could be summarised by three different aspects. These are the cooperative aggregation of supramolecular polymers, the allosteric cooperativity which is found in host-guest complexes and lastly chelates cooperativity in multivalent complexes. Their review also reported a less known process called the inter annular cooperativity.

According to Steed *et al.*[85], "*a host is said to be preorganised when it requires no significant conformational change to bind a guest species*". In the preorganisation process, a host tends to adopt a certain pattern which does not really require a guest molecule to be formed. The pattern may therefore provide some channel which is usually observed in the bile acids studied in chapter three and four. Additionally, Wittenberg and Isaacs,[90] attested that for the complex between the host-guest to form, the entropic and enthalpic components of the energy must be overcome by the host. In general, host requiring less changes are necessary to form a stable structure with the guest molecule.

1.5 Isomerism and its importance

Isomerism is the existence of at least two different compounds from the same atomic composition but diverge in their chemical and physical behaviour. Isomerism derives from the Greek word "*isos*" and "*meros*" which translate to "equal parts". The various compounds obtained from isomerism are called isomers and can be classified in two general groups named constitutional and stereo isomers. Constitutional isomers are a group of compounds differing in their structural arrangements of the same atoms (Figure 12). These could be based on the arrangement of the position of the atoms, functional arrangement, metamerism, tautomerism and also the arrangement in the ring. On the other hand, stereoisomers differ in the spatial arrangement (geometric) of the atoms and also their arrangement in 3D space (optical).

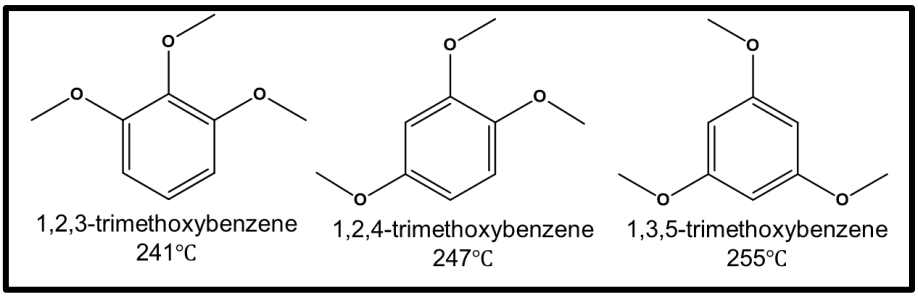

Figure 1-12: Example of functional isomers with their boiling point.

Isomerism can be found in many industries like petroleum industry, medical industry, agricultural and pharmaceutical industry. In the medical and pharmaceutical industry, isomerism plays an integral role due to the importance of medical substances in human metabolism. The most influential isomers in these domains are the stereoisomers which have sometimes been difficult to separate. This is due to their differences usually lying on the spatial arrangement of some atoms which may only be observed by the way they interact with polarised light. The pioneer on the separation of these isomers was Louis Pasteur who came to successfully separate the left from the right of sodium ammonium tartrate[93,94].

Enantiomeric separation plays an important role in the pharmaceutical industry because of the physical and biological effect of racemic drugs in the human body. Due to their arrangement in space, each stereoisomer may have a different effect on the metabolism. Around 1958 in England, thalidomide (figure 14) was a medicine taken by pregnant women for their morning sickness. Unfortunately, they were dispatched as a mixture of an S and R enantiomer while the R-thalidomide was sedative, its S-form was discovered to have teratogenic properties[95,96]. Several studies were carried out over numerous drugs which present the importance of racemic separation in the pharmaceutical industry.

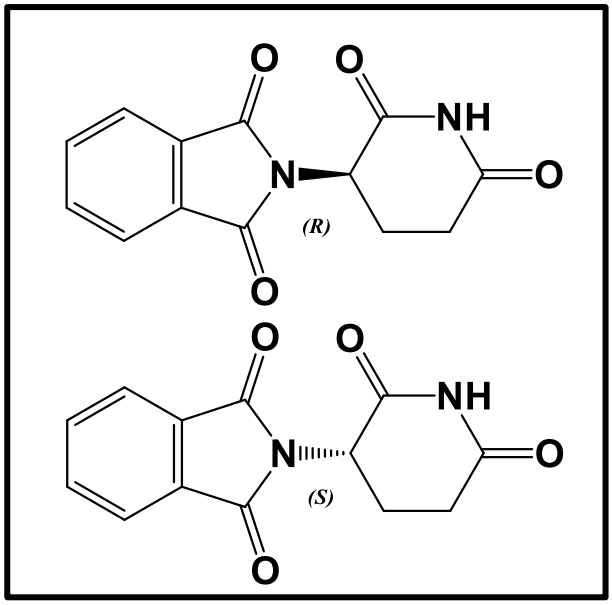

Figure 1-13: Thalidomine isomers

There are several methods for the separation of isomers from which one of the most used in pharmaceutical chemistry is the different chromatographic methods. The other methods like distillation and complexation are employed as well. The crystallization method, however, is the most advantageous among these methods because of its economic and reduced biproducts attained. The method of enclathration has been exploited in the separation of xylenes, picolines and lutidines which are important derivates of crude oil. An interesting method used for the separation of stereoisomer is the Dutch resolution method or the family method. This process consists of the formation of salts by utilizing more than one host compound to increase the result of the racemic separation. In this case, it was observed that a stereoisomer has a low percentage of resolution when one host compound was added to the racemic mixture. On the other hand, the addition of an appropriate host compound with a close backbone led to an increase on one isomer through the formation of salts[97].

1.6 Compounds used in the study

In host-guest chemistry, the choice of host for the formation of supramolecules is significant. A host must have appealing characteristics or behaviour so to be considered for crystallization. Particularly in selectivity, the bulkiness of a host compound may express its stability in the formation of a crystal system. The host may also present different interactions. One should look at the different hydrogen bonding synthon that could be obtained when bonding with

some guest molecules. This may be of great importance in proving a preferential selection of one guest toward another one. Additionally, some compounds may rearrange themselves to form channels which are independent of the presence of the guest molecules. The channels formed after complexation could be a better fit for a specific guest. In the case of racemic compounds, one must choose a chiral host for the host-guest selectivity process. The first group of hosts that will be dealt with in our study are two different bile acids: cholic acid and deoxycholic acid.

1.6.1 Bile acids host

In general bile acids are substances resulting from hepatocyte from the cholesterol. They are plate-like compounds consisting of hydrophilic and hydrophobic layers and they can be found in mammals (Figure 13). These characteristics make these compounds been interactive with oil-water interfaces but also readily available as host compounds. Bile acids have a rigid skeleton, and they are formed with a steroidal backbone consisting of three six-member rings (ABC) with an additional five-membered ring (D). The A and B ring shapes are cis fused while C and D are trans-fused. Bile acids have been studied extensively by scientists for their inclusion behaviour.

Miyata *et al*.[98], studied their inclusion behaviour with several compounds like alcohols, amine and amides. In their studies, they found that these compounds could adopt several conformations as the functional groups attached to the backbone is altered. Since they possess chiral centres, these compounds were also used in the racemic separations of several guests. In our study, Deoxycholic acid was used in the separation of (R,S) 2-methylcyclohexanone where the resulting compound led to a host-guest structure with only the S-enantiomer included.

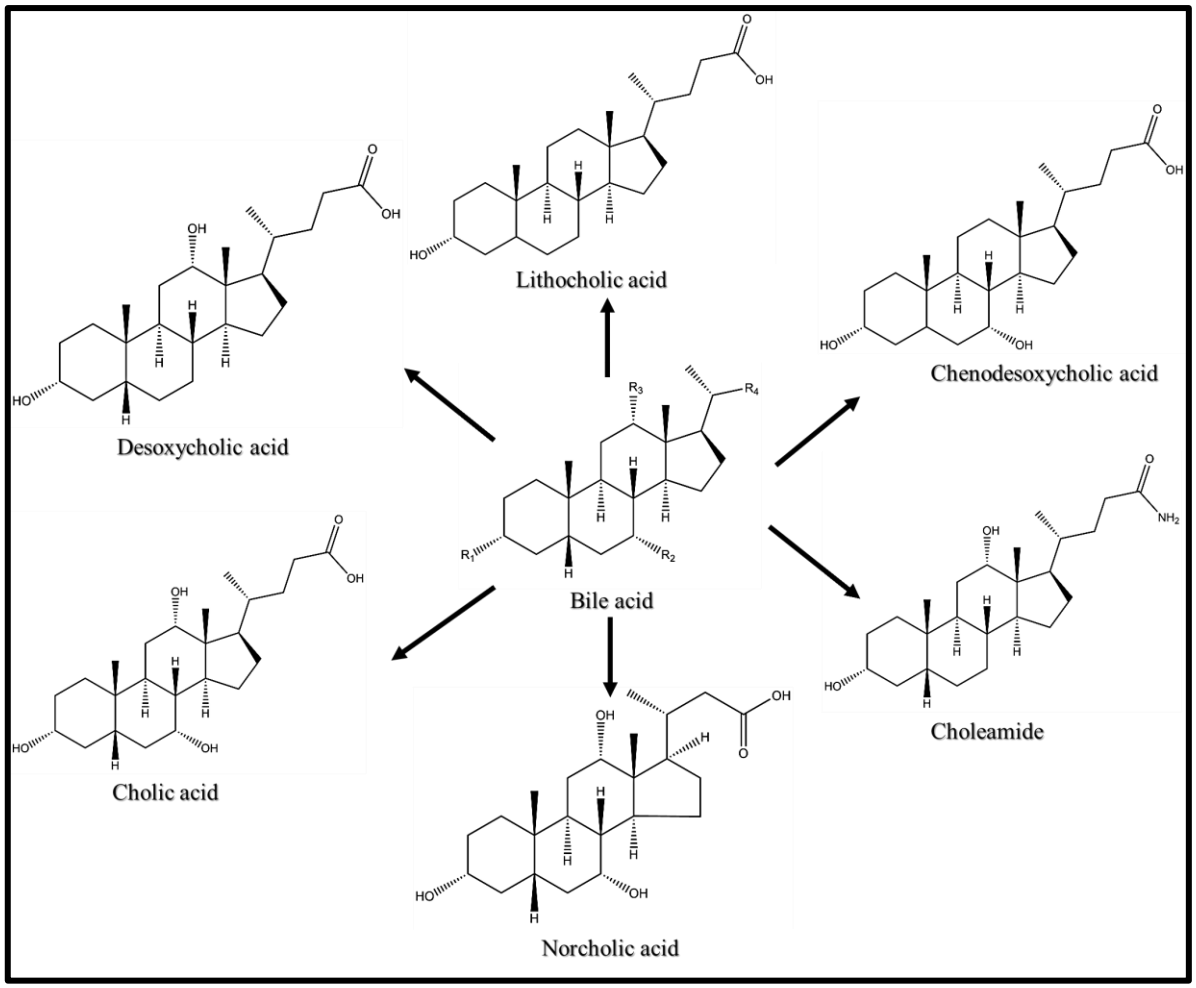

Figure 1-14: Some derivatives of bile acids.

Cholic acid and Deoxycholic acid have been studied in crystal engineering and they have shown interesting characteristics in their packing arrangement. As the popular bile acids, they have been shown to form more than 200 inclusion compounds with many organic guest molecules. One of the features that makes them so popular is that they tend to reorganise themselves depending on the guest. Bile acids self-assemble themselves into bilayers leaving small cavities which accommodate different guest[98–100]. Cholic acid was shown to form more than nine frameworks which completely depended on the guest included[58]. Additionally, Cholic acid has also shown to be selective into binary guest mixtures upon recrystallization[58]. Deoxycholic acid has been greatly used for racemic separation in many studies. Pentylamines and trans-3-amino-4-hydroxycyclopenten were resolved by deoxycholic acid along with racemic camphorquinone and racemic endo-(+)-3-bromocamphor[101,102]. Among several other relevant studies on these two bile acids, one of the characteristics that make them so popular

in supramolecular chemistry are their rigid framework, different chemical functionalities as well as their well-defined geometries[103].

1.6.2 Diol hosts

Design of a clathrate host with distinct rigidity and bulkiness (to avoid close packing) paired with hydrogen bonding properties tend to provide an adequate network pattern for the accommodation of guest molecules[104,105]. In this context, organic chemists use the wheel-and axle, dumb-bell-shaped, scissor-type and roof-shaped molecules to build special host compounds. An efficient characteristic was the introduction of biaryl units with 9-hydroxy-fluorenyl moieties within the host. The efficiency of this addition has been proven to be useful in the formation of the compound for separation processes as well as co-crystallization [106,107]. Diol hosts are interesting structures since the use of two or four hydroxyl groups lead to various patterns of networks (Figure 13). The diversity in the molecular assembly may also be altered by the addition of an atom or a moiety which may strengthen the backbone of the host compound by limiting its rotation to facilitate the bonding process with the guests[100].

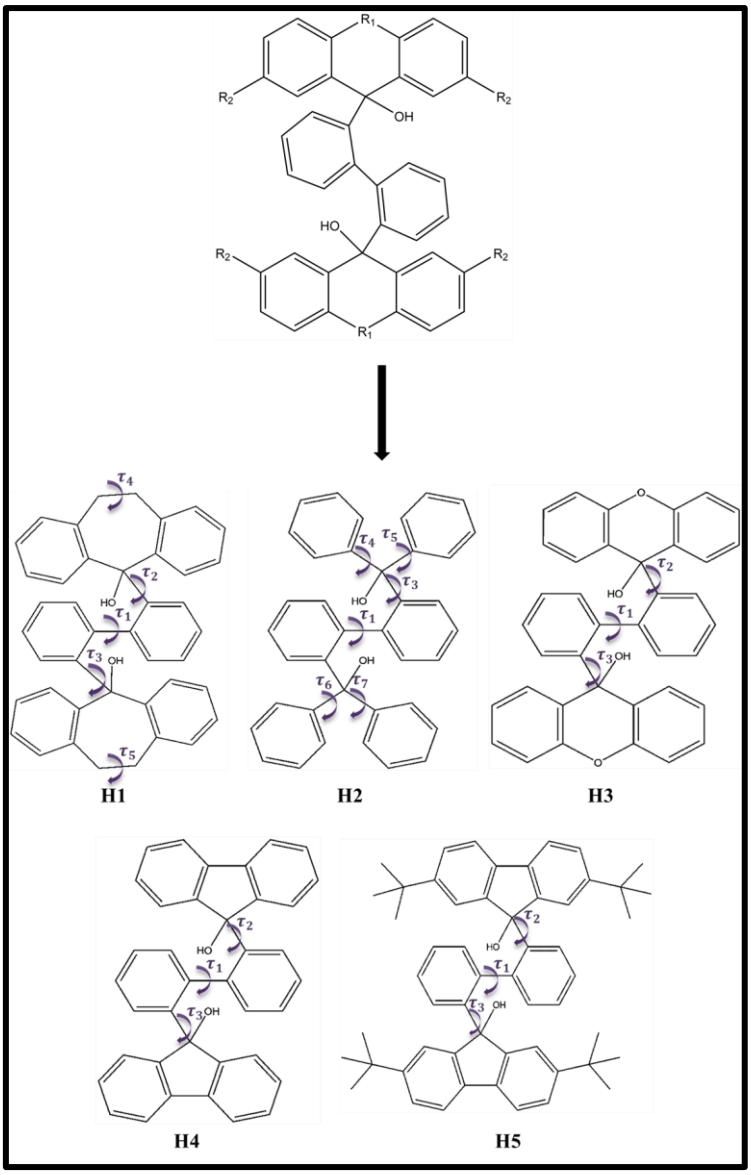

Figure 1-15: Example of diol hosts used for separation.

Researchers have been using diol hosts to separate different type of isomers. In this research, 2,2'bis(1-hydroxy-4,5-dihydro-2,3:6,7-dibenzocycloheptatrien-1-yl)-biphenyl was employed to separate isomers of lutidines. Then, similar compounds which present the same backbone have been employed simultaneously to improve their separation when the main host did not present a strong affinity toward one isomer. Sykes *et al.*[108] used 9,9′-(ethyne-1,2-diyl) bis (fluoren-9-ol) (H1) and 9,9′-(1,4-phenylene)-bis(fluoren-9-ol) (H2) to separate the methyl and dimethylpiperidines. 9,9'-(ethyne-1,2-diyl) bis(fluoren-9-ol) was also used to separate a series of alcohols with close boiling points. During this process, the host showed a preference toward 3-pentanol while the 1-butanol was less favoured.

1.6.3 Bisphenol hosts

Rational design of host compounds has been an important aspect for a crystal engineer. Suitable host with particular favourable characteristics to bond with different guests has been challenging[40,50,56]. Bisphenol compounds tend to satisfy some of the characteristics of a good host, and they were found to be useful in the formation of inclusion compounds[109]. With a propeller-like geometry, bisphenols are compounds consisting of two phenolic hydroxyl groups (see Figure 15). These groups are useful in the building of supramolecular compounds since they provide directional Hydrogen-bonding sites. Additionally, they were also observed to form supramolecular networks leading to a range of chains, ladders, cyclic oligomers and other assemblies[82,110]. Due to the usefulness of the phenolic groups, several bisphenol molecules have been synthesised by varying the linkers of the two phenolic rings. The linkers vary from phenylene, to cyclohexane or methylene groups. One of the most popular bisphenols used is bisphenol A (BPA). Bisphenol A is a commercially available compound used in the synthesis of polymers[111,112]. Therefore, the complex is readily available for the synthesis of supramolecules with several guests.

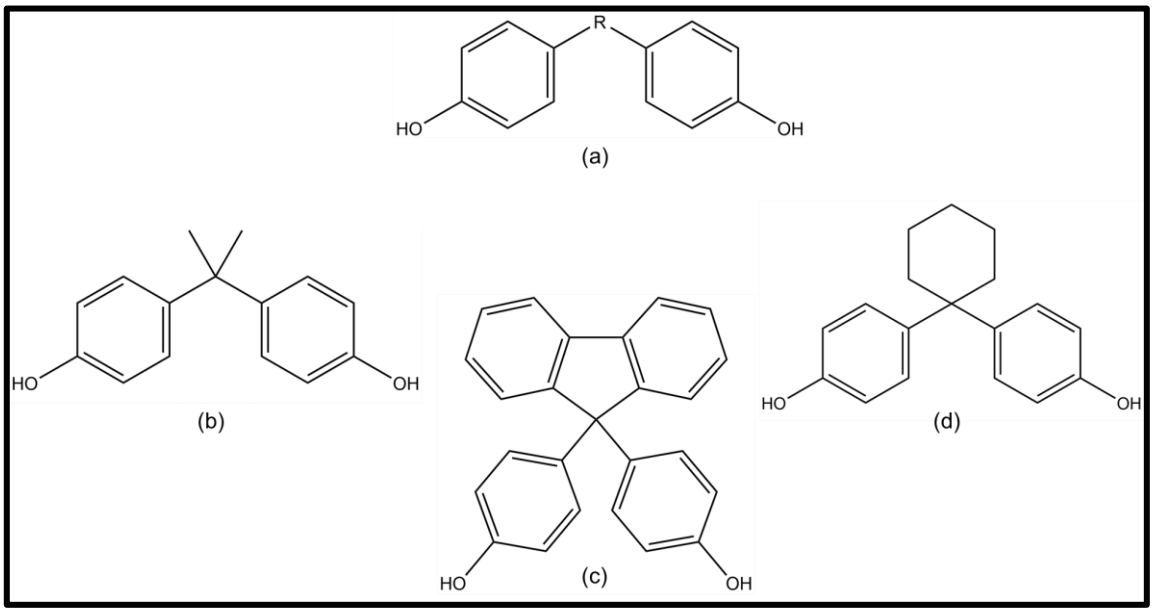

Figure 1-16: Bisphenol hosts compound used in the study a) Bisphenol backbone, b) 4,4'-isopropylidene bisphenol; c) 4,4'-(9-fluorenylidene) bisphenol; d) 4,4'(cyclohexylidene) bisphenol.

Bisphenols have been studied due to their ease in forming new crystal material. Tominaga *et al.*[113] report the structures of bisphenol molecules with adamantane. Additionally, Nath and Baruah prepared host-guest compounds from imidazole and bisphenol compounds. In our research, we used 4,4-Isopropylidene bisphenol (BPA), 4,4'(9-fluorenylidene) bisphenol and 4,4, (cyclohexylidene) bisphenol. Goldberg, *et al.*[114] reported the separation of m- and p- cresol by 1,1-di(p-hydroxyphenyl) cyclohexane and 2,2-bis(4-hydroxyphenyl) propane. It was found that the two hosts separated the two isomers following a different trend. While 2,2-bis(4hydroxyphenyl) propane preferred p-cresol over m-cresol, 1,1-di(p-hydroxyphenyl) cyclohexane chose the opposite trend. Nonetheless, the two hosts separated the two cresols effectively. Caira *et al.*[115] also reported the separation of phenylenediamine isomers by 1,1di(p-hydroxyphenyl) cyclohexane. In their study, the preferred guest was the para substituted phenyldiamine. Clements and Le Roex[116] reported the inclusion of the host 4,4'(9fluorenylidene) bisphenol with small guest molecules and three organic spacers pyrazine, piperazine and 1,4-diazabicyclo [2.2.2] octane. During a competition experiment, the host was found to be more selective toward acetone compare to tetrahydrofuran.

1.7 Problem statement and Rationale of the study

The separation of compounds is an important process in numerous industries such as pharmaceutical, petroleum and medicinal sectors. Therefore, researchers are continuously looking for different methods and alterations to improve the outcomes of separation. Even more, it was observed that during a racemic resolution, there was an improvement in selectivity toward an enantiomer when more than one host of similar backbones were used. Unfortunately, there was no direct reason why the selectivity was improved when an extra host compound is added in the system. Therefore, it is important to explore the different crystal compounds, the environment of crystallization of several combinations of host and guest compounds. This would allow the deduction of specific characteristics that may be useful to the crystal engineers to select the correct combination of hosts for separation purpose.

1.8 Aims and objectives

The general aim of this project is to separate different type of isomers which have close chemical and physical characteristics by host-guest chemistry method. Upon separation, a thorough study of the structural aspect of the resulting compound would be done to explain the preferences. In this line, the different objectives are as follow:

1. Careful choice of the host compound to be used for selectivity.
2. Careful choice of guest's systems by surveying the literature.
3. Surveying the selectivity process occurring when two guests are mixed with a particular host.
4. Analysing the obtained crystal by NMR to evaluate if one guest was preferred compared to another one.
5. Analysing the crystals obtained from a single/mixed guest crystallization by X-ray diffraction and thermal analysis.
6. Surveying the crystal structures obtained to investigate the features that lead to a particular selectivity
7. To evaluate the synergistic effect of the addition of an extra host with a similar backbone.
8. Analyse the kinetics of decomposition of the host-guest compound (TG and DSC).
9. Analysing the packing of the host-guest crystal structure and reconciling this with the thermal and kinetic results.
10. Using computational sciences to help to explain the behaviour of the host and the guests. The different interactions and packing arrangement would be determined by computational science.

1.9 Scope and delimitation of the study

The following research focuses on the separation of isomers which have close physical properties. Isomers with boiling points that are close to one another rendering them difficult to be separated by common separation methods like distillation and chromatography. Additionally, resolution of racemic mixtures has shown to be a difficult process because these isomers differ only by the way they react to polarised light. Results of their separation were found to be improved as more than one host was added to the crystallization process. An

attempt to explain this increase of selectivity would also be covered to better understand the characteristics of host and guest compounds that facilitate the preference.

1.10 Thesis layout

This research work comprises eight chapters; Chapter 1 presents the general introduction of the study while chapter 2 describes the various instruments/equipment and experimental procedures used to accomplish the aim and objectives of the study. Moreover, the results of this study were subsequently presented and discussed from chapter 3 to chapter 7. Furthermore, chapter nine discloses conclusions of the main findings as well as the recommendations for future investigations. All experiments in this study were conducted by the author/candidate in our research laboratories. This thesis was elaborated in the form of publication as follows:

Chapter 3: Deals with the separation of trimethoxybenzene isomers using cholic acid and deoxycholic acid. Analysis of the packing behaviour of the different structures was elaborated in the sense of finding what makes the two similar hosts behave differently in the way they select the different guest compounds. One of the most interesting behaviours of the host molecules used was their characteristics of not forming complexes when they were mixed with some other compounds.

Chapter 4: In a way of dealing with the problem of solubility and the consistency of forming host-guest complexes encountered in chapter 1, choices of guest and host compounds were thoroughly screened. In this chapter, three different hosts compound with close backbones were selected to separate the isomers of lutidines. The study also attempted to improve the separation of lutidine isomers in the aim of mimicking the family method of separation. In this case, no emphasis was done in the different groups attached to the rigid backbone of the host compound. The effects of mixed hosts and vapor-phase competitions were briefly explored.

Chapter 5: This chapter is a continuation of chapter 4 since it deals with the separation of the lutidine isomers. In this case, a restriction was done over the selected additional host compound to be used and a much narrower analysis of the exact extension of these host molecules.

Chapter 6: In this chapter, deoxycholic acid was employed to separate as well as resolved the different isomers of methylcyclohexanones. Several competition experiments were done since the isomers in this section contained racemic mixtures. Analysis of kinetics behaviour of the structure of the different compound formed helped in understanding the selectivity behaviour of deoxycholic acid toward a particular guest.

Chapter 7: From the results obtained in chapter 6, six other isomers of crude oil, xylenols, were chosen to be separated by bisphenol hosts. In this section, an emphasis on the synergistic effect of the addition of similar hosts was analysed while an uncommon structure presenting two different host molecules was synthesised.

Chapter 8: Covers a conclusive summary of the research

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Chapter 2. **Methodology**

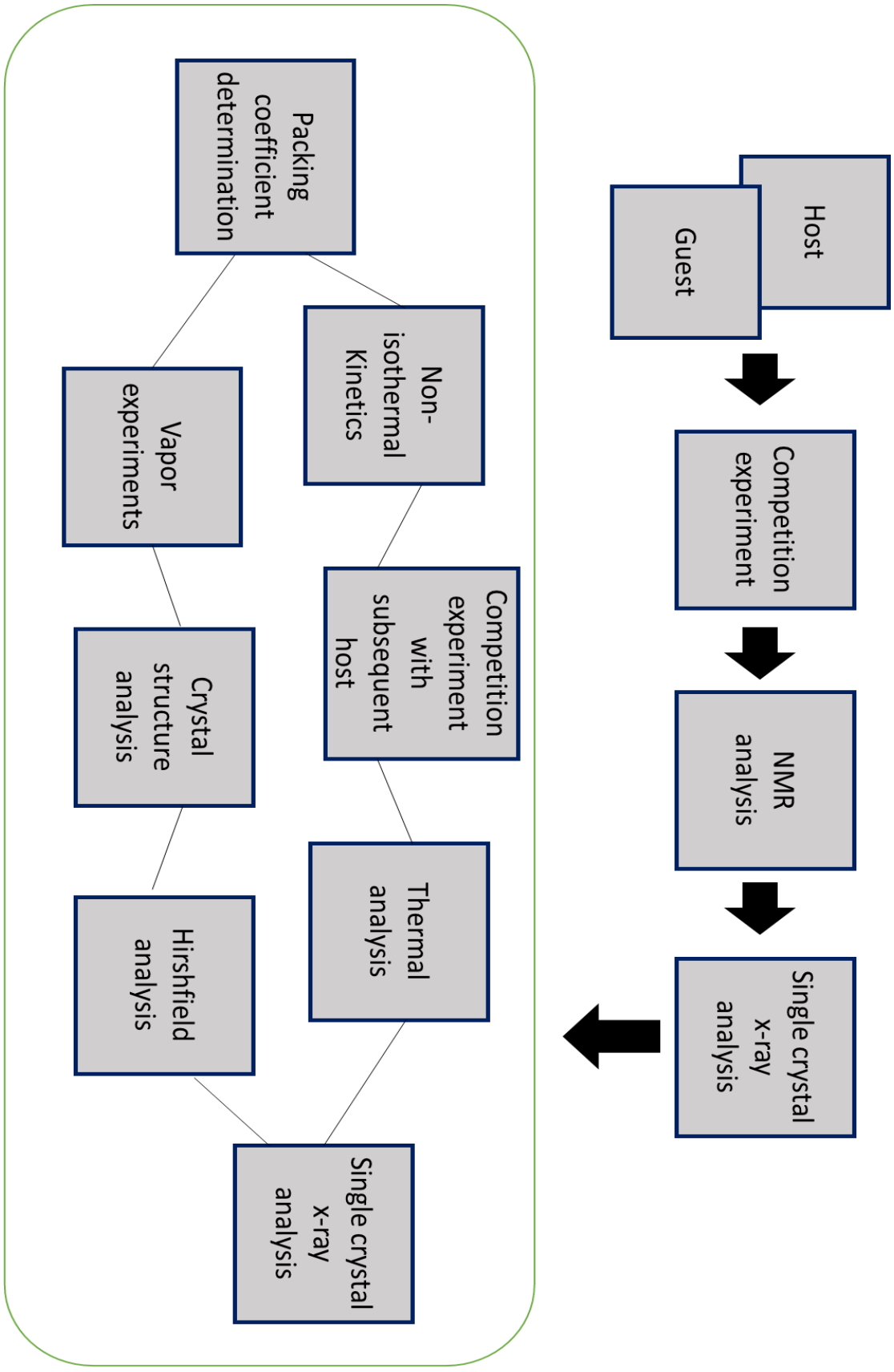
2.1 Introduction

This chapters presents the materials and techniques used during this the different analysis done. In, the materials section, the origin of the various compounds used are provided. The technique section of this chapter describes the different instrumentation as well as their method of use. used for the research. In addition of the instrumentation, the computational components employed to solve the various crystal obtained are given.

2.2 Experimental design

The following scheme present the experimental design that was used through the various research highlighted in chapter 3, 4, 5, 6 and 7. During the separation studies, the choice of the host for the separation of particular guest was first established by a survey done on the Cambridge Structural Database. This followed to pairwise competition from which the resulting crystals were collected for NMR analysis. When the crystals were of good quality, and when necessary, the single crystal X-ray analysis was then carried out. As described in scheme 1 and ensuing the arrow after the X-ray analysis, several additional analyses were carried like thermal analysis, non-isothermal kinetics, packing coefficient determination, crystal structure analysis, vapor experiments, competition experiment with subsequent host along with extra data collection by X-ray analysis.

Scheme 1: Experimental design



2.3 Materials

2.3.1 Host compounds

The Host used in Chapter 1, 4 and 5 are deoxycholic acid and cholic acid; 4,4-Isopropylidene Bisphenol, 4,4'-(9-Fluorenylidene) Bisphenol and 4,4'(Cyclohexylidene) Bisphenol. These host were obtained from Sigma Aldrich, and they were used without further purification.

The following hosts used in chapter 2 and 3 were synthesised by Weber and were used without further purification. The name of the of these compounds are: 3,3'-bis(9-hydroxy-9-fluorenyl)-2-2'-binaphthyl[1]; 2,2´-bis(5-hydroxydibenzosuberan-5-yl)biphenyl[2]; 3,3'-bis-(di-p-tolylhydroxymethyl)-1,1'-binaphthyl[3]; 2,2'-bis(diphenylhydroxymethyl)biphenyl[4]; 2,2'-bis(9-hydroxy-9H-xanthen-9-yl)biphenyl[2]; 2,2'-bis(9-hydroxyfluoren-9-yl)biphenyl[5]; 2,2'-bis(2,7-di-tert-butyl-9-hydroxyfluren-9-yl)biphenyl[6]. Below is an example of the synthesis of compound 2,2'-bis(9-hydroxyfluoren-9-yl)biphenyl[5]. this compound was synthesised by slowly adding a solution of nBuLi (53.1 ml, 85 mmol, 1.6N in n-hexane) under argon at 0 °C to 2, 2'-dibromobiphenyl (10.5 g, 38 mmol) in 70 ml of dry diethyl ether. The reaction was stirred for 2 h and a solution of fluorenone (13.8 g, 77 mmol) in dry diethyl ether was added dropwise. The mixed solution was further stirred for another 2h at room temperature and heated at reflux for 15h, and subsequently hydrolysed (NH4Cl solution). The precipitated product was filtered, the ethereal phase was separated off, dried with MgSO4 and evaporated to dryness in a vacuum. More product was precipitated when methanol was added to the oily residue and a yield of 13.8 g (70%) was obtained.

2.3.2 Guest compounds

All the guest compounds (trimethoxybenzenes, lutidines, methylcyclohexanones and xylenols were all purchased from Sigma Aldrich and they were used as received. The co-solvents like methanol, 2-propanol, 1-butanol, 1-pentanol, chloroform and ethyl acetate were purchased from Sigma Adrich and were used without further purification. The different figures present the molecular representation of the various guests.

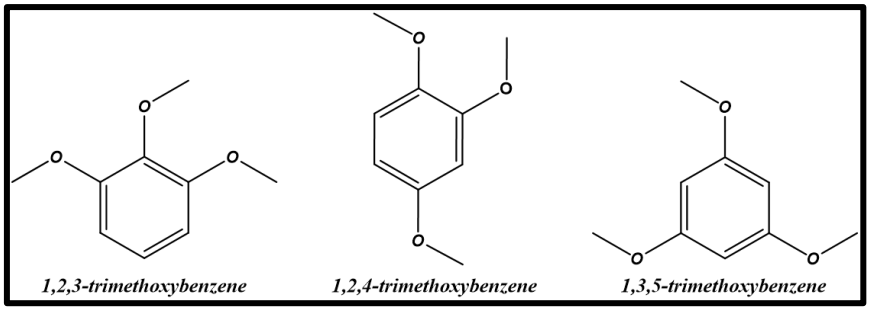


Figure 2-1: Isomers of trimethoxybenzene guests

Table 2-1: Code and boiling point of the tromethoxybenzene guest

Guest	Acronyms	Condensed formula	Formula weight (g mol^{-1})	Boiling Point (°C)
1,2,3-trimethoxybenzene	TMB123	$C_6H_3(OCH_3)_3$	168.2	241
1,2,4-trimethoxybenzene	TMB124	$C_6H_3(OCH_3)_3$	168.2	247
1,3,5-trimethoxybenzene	TMB135	$C_6H_3(OCH_3)_3$	168.2	255

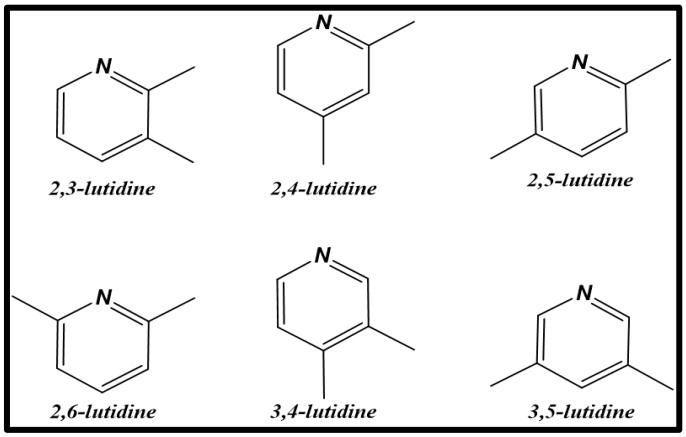


Figure 2-2: Isomers of lutidine guests

Table 2-2: Acronyms and boiling point of the lutidine guest

Guest	Acronyms	Condensed formula	Formula weight (g mol^{-1})	Boiling Point(°C)
2,3-lutidine	**2,3-LUT**	**C_7H_9N**	**107.2**	**163**
2,4-lutidine	**2,4-LUT**	**C_7H_9N**	**107.2**	**159**
2,5-lutidine	**2,5-LUT**	**C_7H_9N**	**107.2**	**157**
2,6-lutidine	**2,6-LUT**	**C_7H_9N**	**107.2**	**144**
3,4-lutidine	**3,4-LUT**	**C_7H_9N**	**107.2**	**163**
3,5-lutidine	**3,5-LUT**	**C_7H_9N**	**107.2**	**169**

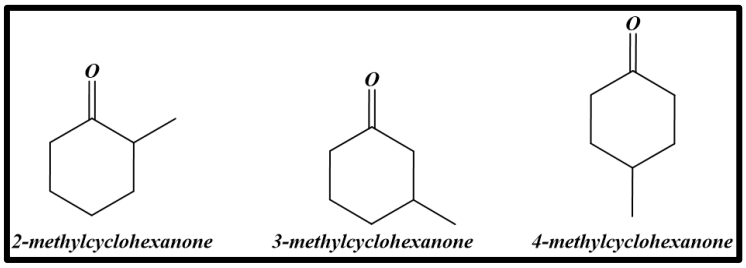


Figure 2-3: Isomers of methylcyclohexanone guests

Table 2-3: Acronyms and boiling point of the methylcyclohexanone guests

Guest	Acronyms	Condensed formula	Formula weight (g mol^{-1})	Boiling Point (°C)
2-Methylcyclohexanone	2MCH	$CH_3C_6H_9O$	112.2	162
3-Methylcyclohexanone	3MCH	$CH_3C_6H_9O$	112.2	169
4-Methylcyclohexanone	4MCH	$CH_3C_6H_9O$	112.2	169

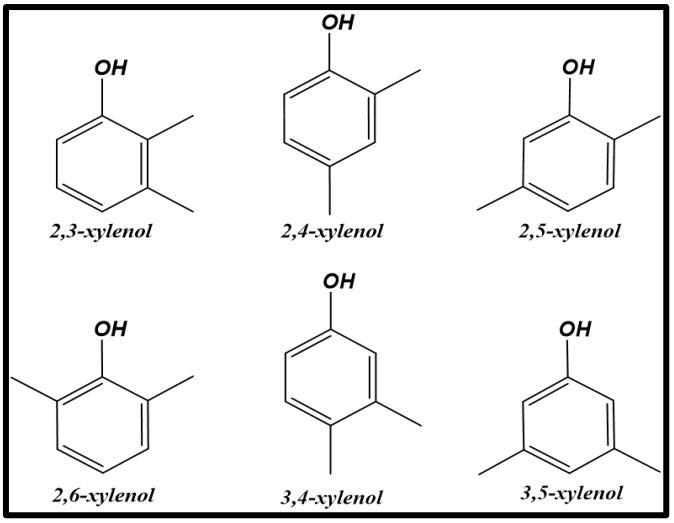


Figure 2-4: Isomers of xylenol guest

Table 2-4: Acronyms and boiling point of the xylenol guest

Guest	Acronyms	Condensed formula	Formula weight (g mol^{-1})	Boiling Point (°C)
2,3-xylenol	23XYL	$C_8H_{10}O$	122.2	217
2,4-xylenol	24XYL	$C_8H_{10}O$	122.2	212
2,5-xylenol	25XYL	$C_8H_{10}O$	122.2	212
2,6-xylenol	26XYL	$C_8H_{10}O$	122.2	203
3,4-xylenol	34XYL	$C_8H_{10}O$	122.2	227
3,5-xylenol	35XYL	$C_8H_{10}O$	122.2	222

2.4 Techniques

2.4.1 Crystallization

Crystallization is the process whereby molecules rearrange themselves to form new structured crystalline lattices[7,8,9]. In the current research study, a slow evaporation method was used to form crystals.

Single crystals of the inclusion compounds were obtained by dissolving the particular host or mixture of hosts in an excess of the relevant guest or binary guest mixtures. In cases where the guest compound was a solid, a co-solvent was used for dissolution of the mixture of the host and guest. The mixtures were stirred at a temperature of 60 °C to achieve complete dissolution. Higher temperatures of dissolution were used when necessary. Crystals were visualised after days, weeks or months after evaporation of the solutions at the ambient temperature.

2.4.2 Thermal analysis

Thermal analysis refers to a category of analytical chemistry techniques whereby physical and chemical changes of a sample are monitored as the sample temperature is either increased or decreased[124]. The methods used to analyse the crystals prepared during this study were differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA).

2.4.2.1 Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) is a technique used to measure the difference in energy between an experimental sample and an inert reference sample as a function of time and temperature [10–13]. Generally, the energy released or absorbed by the sample when heated or cooled is observed as endothermic or exothermic peaks. Therefore, results of DSC analysis provide information on melting point, reaction energy and temperature as well as crystalline transition temperature[11,13]. The instrument requires an empty standard aluminium pan as a reference, and a second pan for holding the sample. These are positioned in a furnace. Heat flow is measured by comparing the difference in temperature throughout both the test sample and the reference[11,13].

Differential scanning calorimetry (DSC) was performed using a TA Instruments DSC-Q200. During the analysis, selected crystals were retrieved from the mother liquor and placed onto filter paper. The solid was then dried and crushed into a powder. Approximately 1-3 mg of the resulting was transferred into the aluminium pan and then placed into the furnace for analysis. The software used for the analysis of the DSC curves was TRIOS[14].

2.4.2.2 Thermogravimetric analysis (TGA)

Thermogravimetric analysis is a method used to measure the change in mass of a material as a function of increased temperature [11,13,15,16]. The isothermal change can also be measured as a function of time in a known atmosphere. Generally, results yield a graph showing mass loss recorded in the sample versus temperature/time due to dehydration, decomposition or oxidation of a certain compound[11,13] (Charsley & Warrington, 1992; Haines, 2002). Thus, the data retrieved from the TGA results are the temperature at which a change in mass occurs, the temperature at which a solvent is released from a crystal lattice and also information on the kinetics of desolvation of the compound undergoing analysis[11].

Thermogravimetric analysis (TGA) was performed using a TA-Q500 thermogravimetric analyser. Results were analysed using Universal Analysis 2000 software[17]. The samples were crushed and blotted dry (3−6 mg) and weighed directly into open aluminium oxide TGA crucibles.

2.4.3 Single crystal X-ray diffraction

Single crystal X-ray diffraction is one of the most definitive methods for elucidating the crystal structures of compounds[18]. In general, the present instrumentation allows the determines the packing and conformation of molecules and the intermolecular interactions within a crystal.

Single crystal X-ray diffraction data were collected on a Bruker DUO APEX II diffractometer (Madison Wisconsin) for all structures using Mo Kα radiation (λ = 0.71073 Å)[19] at a temperature of 173 K. The intensity data were collected using the phi scan and omega scan techniques, scaled, and reduced with SAINT-Plus[20]. The correction of the collected intensities for absorption was done using the SADABS program. The crystal structures were solved and analysed with the aid of various computer software which is discussed further in the next section.

2.4.4 Computation

Xseed[21] was the graphical user interface used to analyse the data. This program utilises: SHELXS-97[22] to solve the structure to completion and SHELXS-97[22] which refined the structure. Additional computing programs were implemented to further interpret the results. These were:

- Conquest, which was used to screen and obtain information from the Cambridge Structure Database regarding the compounds used as well as for comparative analyses of data obtained during this study (CSD, version 5.36, Nov 2014)
- PovRay, which rendered graphics of the different structures[23];
- Platon: Program which calculates the structure molecular parameters[24].
- DENZO-SMN which was used to reduce and scale the data obtained from the Nonius Kappa CCD[25]
- XPREP which was used to read both the row data file and the parameter file obtained from the single crystal X-ray analysis and to prepare the input files for SHELXS. It was also used to determine the space group of a particular crystal[26].
- Mercury which generated information relating to the voids created by the solvents. A probe radius of 1.2 Â and an approximate grid spacing of 0.7 Â were used for the voids[27].
- Crystal explorer: The Hirshfield surfaces of some molecules were obtained from this program to determine the various intermolecular interactions present in their structures[28].
- POVLabel[23]: Used to edit the atomic labels of POV-Ray images
- Layer: This program displays the intensity data of a crystal as simulated procession photographs of the reciprocal lattice levels. The investigation of the systematic absences occurring are investigated.

2.4.5 Non-isothermal kinetics of inclusion compounds

The activation energies of desorption reactions were estimated by carrying out the host-guest decompositions at various heating rates, following the method of Flynn and Wall.[29] The results were used to produce a graph with axes -log β versus T^{-1}. After each experiment, the activation energy was calculated by using the slopes of the graphs where the slope= $(0.457E_a)/R$. This was obtained from the following equation:

$$dC/dT = A / \beta f(C) e^{-Ea/RT}$$

β is the heating rate,

C is the mass loss of the sample

and E_a is the activation energy.

This equation can be reduced to: d log β/d (1/T) = (0.457/R) E_a.

2.4.6 NMR Spectroscopy

Atoms are characterised by their ability to interact with light. Depending on the section of the light used for the study of compound, information regarding their ability to absorb or reflect light is an indicative of their nature. In nuclear magnetic resonance spectroscopy, the magnetic properties of atoms and the related energies of various nuclei are studied[30,31]. This result in the specific identification of the different components of a compound

In this study, approximately 5 mg of representative crystals were blotted dry, crushed and dissolved in 600 µL of the corresponding d_6-solvent and introduced into a 5 mm NMR tube for data acquisition. 1D ^{1}H and 2D ^{1}H–^{13}C HSQC NMR spectra were recorded on a Bruker 300 or 400 MHz spectrometer at 30 °C and processed using standard Bruker software (Topspin 3.5). The HSQC experiment was optimized for J = 145 Hz (for directly attached ^{1}H–^{13}C correlations). The spectra were referenced relative to the solvent signal at 7.26 ppm (for ^{1}H) and 77.16 ppm (for ^{13}C); appropriate signals were integrated to determine the relative proportions of the guests. The analysis was carried out on the crystals harvested from the mother liquors of the equimolar methylcyclohexanone binary mixtures. These crystals were dried using blotting paper but were not washed with any solvent to avoid any exchange of guests.

2.4.7 Competition experiments

The competition experiments were carried out to analyse the selectivity of a particular host for a guest. The analysis was carried out by exposing an equimolar mixture of a pair guests (mg) to a host compound. The ratio in this method was kept at 1:10 ratio in favour to the guest. This ration was kept in the aim of allowing the guest molecules to be completely in competition with one another. The addition of a specific amount of cosolvent was involve in the process to complete the dissolution process when solubility of the host was low. The present addition was kept the same for a particular family of isomers. The mixtures were then dissolved by gentle

warming and allowing crystallization by slow evaporation. The resulting crystals were recovered, blotted dry and subjected to NMR analysis.

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Chapter 3.

Separation of trimethoxybenzene isomers by bile acids.

3.1 Summary

The Host-Guest method is commonly used in the process of separating various components in crystal engineering. In this chapter, yet another successful separation of isomers was established with two hosts of our common family of bile acids: cholic acid and deoxycholic acid.

Cholic acid host (CA) was first selected for the separation of trimethoxybenzene (TMB) isomers. Competition experiment was carried out by setting crystallization of CA with equal mixture of the guest. H^1NMR was employed to determine the proportion of each component in the various crystals within an error of 3%. During the aforementioned procedure, it was found that CA preferred the 1,3,5-trimethoxybenze (TMB135) compared to the 1,2,3-trimethoxybenze (TMB123) and 1,2,4-trimethoxybenze (TMB124). The following trend was obtained for CA: TMB135 >
TMB123 ≈ TMB124. Four crystal structures named 1, 2, 3, and 4 resulted from this procedure. Crystal structures CA•TMB123 (**1**), CA•TMB124•3H_2O (**2**), and CA•TMB135 (**3**) emerged from an attempt to crystallize the cholic acid host with each isomer. The aim of this process was to analyse the different interactions involved between the host and single guest molecules that led into such selection. Additionally, the present idea was also set to comprehend the preference that cholic acid had toward the TMB135. Unfortunately, structures **1** and **2** came with some quandaries. Structure 1 had a disordered TMB123 so it could not be used for further analysis since the refinement was not satisfactory for the next step. Even though, structure **2** did not include TMB124 guest only in the vicinity of the structure, comparing comments were carried out with compound **3**. Unfortunately, the analysis was not completely conclusive, and this was attributed to the presence of water molecules in the complex. Crystal structure CA·TMB123/TMB124 (**4**) resulted from the mixture of isomers TMB123 and TMB124 with cholic acid. This complex was found during the competition experiment since CA did not show a particular preference toward any of the two isomers.

The separation of trimethoxybenzenes was secondly carried out by deoxycholic acid which presented similarities to cholic acid. The differences between the two components lied on the absence of hydroxyl group from the cholic acid. The competition experiments with DCA led to the following trend: TMB123 > TMB124 > TMB135. The present experimentation resulted in three additional structures named DCA•TMB123/TMB124 (**5**), DCA•TMB123/TMB135 (**6**), and DCA•TMB124/TMB135 (**7**). Unfortunately, the different structures were

characterized by disordered guest compounds. Crystallization of DCA with each guest gave the structures with the similar characteristics. Therefore, the complexes found during the competition experiments were used for further analysis.

To understand the difference in selectivity trend observed, a careful analysis was done over the different structures of the two bile acids. A paper from Miyata's group in 2006 focusing on the study of cholic acid and deoxycholic acid's patterns after forming inclusion compounds with various guest molecules, was used to further comprehend the selectivity[1]. In this paper, Miyata showed that during crystallization and after the removal of the guest molecules, cholic acid formed a different packing arrangement compare to deoxycholic acid. The packing arrangement also leads to different void spaces which may direct the respective preference. Analysis of the packing coefficient of the inclusion compounds in CA and DCA was carried out to further justify the selectivity of the two hosts. In general, a packing coefficient is the ratio of the volume of a guest with the volume of the cavity where it is in the crystal lattice. On the other hand, the packing coefficient of a crystal refers to the determination of the density of the crystal. Therefore, analysis of the packing coefficient leads to the understanding the best fitted guest compound in the various host-guest.

NB: The R_{int} for the structures with high R values are reported in the CIF files which have been deposited in the various journals.

3.2 Reference:

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Separation of Trimethoxybenzene Isomers by Bile Acids

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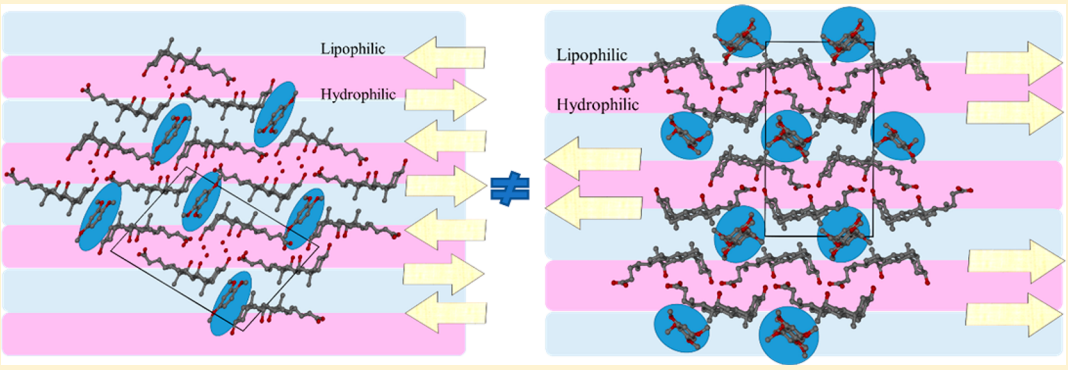
Supporting Information



ABSTRACT: Cholic acid (CA) and deoxycholic acid (DCA) have been employed to separate the three isomers of trimethoxybenzene (TMB). The selectivity preference is CA: TMB135 > TMB123 ≈ TMB124, while it is reversed for DCA: TMB123 > TMB124 > TMB135. Some of the crystal structures with CA as host suffered from partial disorder, while the DCA structures were grown from pairs of equimolar guest mixtures, and all contained both guests in different proportions. Packing analysis revealed the importance of layering of the hydrophilic and lipophilic regions of the structures with the TMB guests accommodated in the lipophilic layers.

INTRODUCTION

The separation of multiple components from a mixture is an important process in chemistry and chemical engineering and is dependent on the physical properties of the individual compounds. The most common techniques include distillation, absorption, extraction, and crystallization, and their success depends on the differences in the physical properties of the components, especially solubility, boiling point, and melting point.[1,2] However, in the case of constitutional and stereoisomers, their physical properties are often similar, making them difficult to separate by the usual methods. For example, the isomers ethylbenzene, *ortho*-, *meta*-, and *para*-xylene have normal boiling points varying from 136.2 to 144.4 °C, making separation by distillation impractical. When the melting points of the components are significantly different, fractional crystallization is sometimes employed, but the process may be frustrated by the formation of eutectic mixtures. For the separation of isomers, therefore, the method of selective inclusion by host−guest chemistry becomes attractive.

There are two main approaches: one may employ a traditional porous material such as a zeolite, in which the framework remains unchanged and whose selectivity is governed by the dimensions of the channels.[3−5] Alternatively, one may utilize organic or metal−organic compounds as hosts which, upon exposure to the mixture of isomers, form crystalline host−guest compounds and enclathrate one particular isomer preferentially. This process depends on the phenomenon of molecular recognition, which is the driving force arising from the various host···guest, host···host, and guest···guest secondary interactions that occur in the inclusion compound and are ultimately responsible for the packing of the various molecular components in the crystal structure. The method of enclathration is now well established and has been summarized in a number of important texts.[6−9] The topic of isomer separation by this technique has elicited considerable interest,[10,11] and recent publications point to a variety of target isomers. An important objective is the separation of xylenes because these isomers are used in the manufacture of polymers and plasticizers, and several different host compounds have been employed for their separation.[12−17] The separation of other groups of isomers such as the phenylenediamines,[18] picolines,[19] and lutidines[20] has been investigated, and the results have been summarized.[21]

In this work we employ the two most common bile acids, cholic acid and deoxycholic acid, to separate the three isomers of trimethoxybenzenes. The structural formulas and atomic numbering of the hosts and the guests are shown in Scheme 1.

Miyata[22,23] has reviewed the structures and inclusion compounds of the bile acids, and he names 36 such compounds depending on their different side chains and substituents. Their packing modes, polymorphism, and hydrogen-bonding networks have been described.

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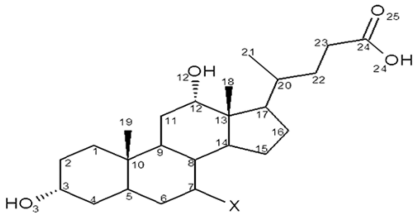
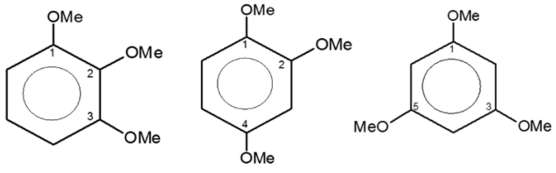
Scheme 1. Structural Formulae and Atomic Numbering of the Hosts and Guests



Cholic Acid, CA, X= O_7H
Deoxycholic Acid, DCA, X= H

Trimethoxybenzene: TMB



	TMB123	TMB124	TMB135
B.p.	241°C	247°C	255°C

EXPERIMENTAL SECTION

Materials. The compounds were obtained from Sigma-Aldrich, and they were used without further purification. Single crystals of the inclusion compounds were obtained by dissolving the respective host in the respective solvent (methanol, 2-propanol, 1-butanol, or 1-pentanol depending on the crystal quality obtained for X-ray analysis) and adding an excess of the relevant guest or guest mixture. The resulting solutions were then allowed to crystallize by slow evaporation at room temperature.

X-ray Crystallography. Single crystal X-ray diffraction data were collected on a Bruker DUO APEX II[24] diffractometer for all structures using Mo Kα (λ = 0.71073 Å) at a temperature of 173 K. The intensity data were collected using the phi scan and omega scan techniques, scaled and reduced with SAINT-Plus.[25] The correction of the collected intensities for absorption was done using the SADABS program.[26]

The structures were solved by direct methods using the SHELX-97[27] program package. The graphical interface used was the program X-SEED.[28] All C−H hydrogen atoms were placed geometrically and with a riding model for their isotropic temperature factors. The O−H hydrogen atoms were located in the final difference electron density map. Their bond lengths were fixed using the formulas suggested by Lusi and Barbour.[29]

NMR Spectroscopy. ^{1}H NMR spectra were recorded on a Bruker 300 MHz with DMSO as internal standard. Samples were blotted dry, crushed, and dissolved in deuterated DMSO-d_6. The appropriate signals were integrated to determine the relative proportions of the guests.

RESULTS AND DISCUSSION

Separation of Trimethoxybenzenes by Cholic Acid. The pairwise competition experiment of the three TMB guests are shown as selectivity curves in Figure 1. The technique for all such experiments was to expose 100 mg of host to a known mixture of the two TMB isomers such that the total guest to host ratio was in a molar excess of 10:1. Furthermore, for the preparation of compounds 3−7, 1.00 g of an alcohol solvent was added to achieve dissolution. This is detailed in Table 3. The solutions were allowed to evaporate slowly at room temperature, and the resulting crystals were harvested, and the relative molar ratio of the host to each guest was analyzed by

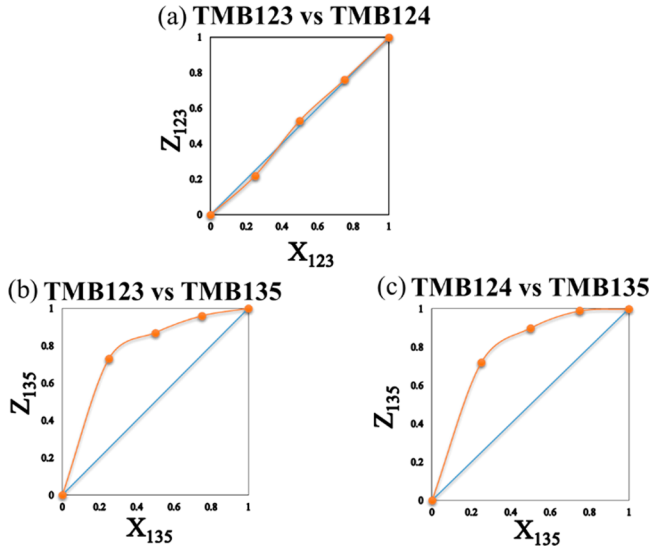


Figure 1. (a−c) Pairwise selectivity curves of the TMB guests with cholic acid, in which the fraction X of a given guest is plotted against its mole fraction Z in the crystal.

NMR. The normal boiling point of the guests being similar, we assumed no significant differences in their rates of evaporation. For the TMB123/TMB124 pair, Figure 1a, the mole fraction X_{123} in the mother liquor is plotted against Z_{123}, the mole fraction found in the crystal. The points fall close to the diagonal line, showing there is practically no discrimination of these two guests by the CA host.

If we define the selectivity constant as $K_{A:B} = Z_A/Z_B \times X_B/X_A$, then Figure 1b shows that for TMB123/TMB135 the selectivity curve the TMB135 guest is favored over the complete range, with an average value of $K_{TMB135/TMB123}$ = 7.7. Figure 1c, which displays the competition between TMB135/TMB124, is similar to Figure 1b, with an average selectivity constant of 8.4 over the range of X_{135} from 0 to 0.75, at which point we observe complete discrimination.

With regard to the structures which contain mixed guests, the crystals were derived from mother liquors which were prepared with equimolar quantities of the TMB guests (Table 3).

The structure of CA·TMB123 crystallizes in $P2_1$ with two CA and one guest TMB123 in the asymmetric unit. The aliphatic chain containing the carbonyl moiety is disordered from C22 and refined with site occupancy factor % of 80/20 for molecule A and 75/25 for molecule B.

In the case of C22, the H atoms were considered only for the chains with the major site occupancies. The hydrogen bonds of this and subsequent structures are recorded in the Supporting Information. Because hydrogens were placed with O−H bond constraints, we only declared O···O distances.

The structure of CA·TMB124·3H_2O is similar to that of the previous compound, except that it contains three additional waters of crystallization. The packing, viewed along [010] is shown in Figure 2. which displays the CA molecules accommodating the water molecules on their hydrophilic side and the TMB124 guest in constricted channels in the lipophilic layer. Figure 3a shows the same view with structure in van der Waals representation and with the guest molecules omitted, displaying channels running in the [010] direction. However, when the guest molecules are reinserted in the structure, Figure 3b, it is clear that the channels are constricted, and are

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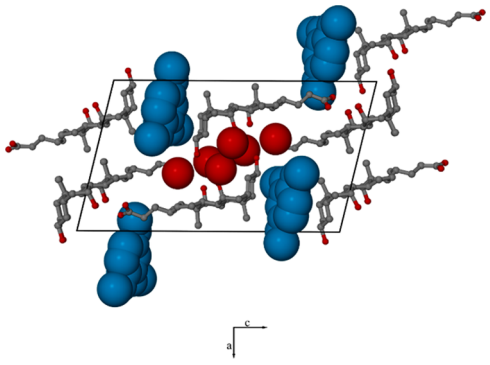

Figure 2. Packing of CA·TMB124·3H_2O viewed along [010] with the guest molecules (blue) and oxygen molecules from water (red) in van der Waals representation. (Hydrogen atoms were omitted for clarity.)

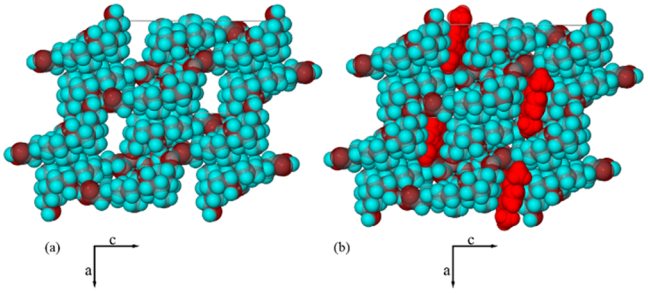

Figure 3. Packing of CA·TMB124·3H_2O in Van der Waals representation viewed along [010] (a) without guest and (b) with guest.

hourglass shaped, allowing the guests to reside in pockets which are narrowly interconnected.

The CA·TMB135 structure crystallizes in *P*1 with two hosts and one TMB135 guest in the asymmetric unit, $Z = 1$. The packing is similar to that of CA·TMB124·3H_2O in that the TMB135 guest resides in restricted channels running along [100]. The projections have been deposited in the Supporting Information as Figure 2S.

The crystal of CA with TMB123/TMB124 crystallizes in $P2_1$ with two independent molecules of CA, labeled with subscript A and B and one disordered TMB123/TMB124 guest molecule in the asymmetric unit shown in Figure 4a. The guest is disordered with the relative proportion of TMB123/TMB124 percentages at 53/47 as measured by NMR spectroscopy. The crystallographic refinement yielded the site occupancies of TMB123/TMB124 as 54/46, in good agreement. The packing is characterized by channels running along [010], Figure 4b, which are similar to those described for CA·TMB124·3H_2O, and Figure 4c is the projection shown with the guest.

Hirshfield Surface Analysis. In order to better understand the mechanism of guest selectivity, we analyzed the packing forces which stabilize the host−guest structures. We chose the two structures CA·TMB124·3H_2O and CA·TMB135, because neither structure suffers from disorder and therefore yielded reliable results. We employed the program Crystal Explorer[30] to generate fingerprint plots. These are displayed in Figure 5a,b, with the accompanying tables showing the percentages of each type on nonbonded contact. The figures display the interactions with the guest, either TMB124 or TMB135, as the target moiety. For both structures, it is clear that the H···H interaction are important, comprising more than 60% of the interactions in both structures.

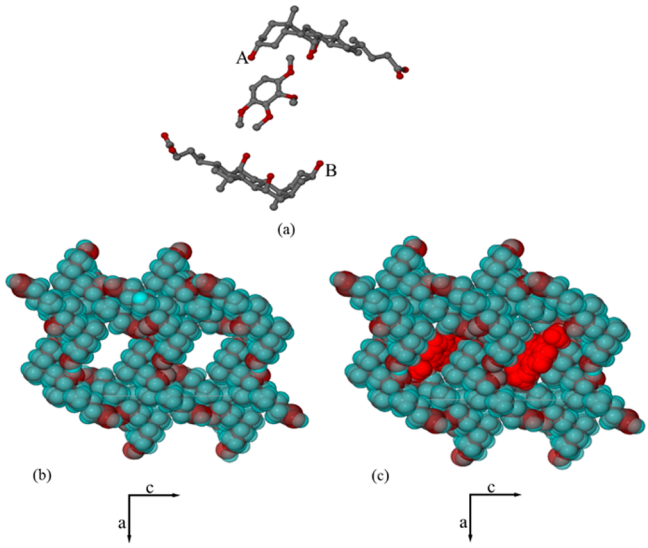

Figure 4. (a) Asymmetric unit of CA·TMB123/TMB124 (hydrogen atoms were omitted for clarity), packing of CA·TMB123/TMB124 in van der Waals representation viewed along [010] (b) without guest and (c) with guest.

However, the spikes labeled 1 in the figures display the H···H interactions peak at approximately 2.08 Å in Figure 5b and approximately 2.20 Å in Figure 5a, showing that CA·TMB135 is the closer packed structure. While there is no significant difference in the C···H interactions, labeled 3, there is a notable difference in the O···H interactions in favor of CA·TMB135, with 25.3% versus 18.0%, labeled 2 in both figures. This shows that there is a better fit between host and guest in CA·TMB135 than in CA·TMB124·3H_2O, in agreement with the selectivity profile shown in Figure 1c.

Separation of Trimethoxybenzenes by Deoxycholic Acid. The same procedure was employed for DCA as for CA to establish the selectivity of the three guests in pairs. Figure 6 displays the results, and Figure 6a shows that TMB123 is preferred over TMB124 over the complete range of guest mixtures, in which isopropanol was employed as solvent with $K_{TMB123:TMB124} = 4$. Figure 6b shows the selectivity curve for TMB123/TMB135 which also used isopropanol as the solvent and suffers from a solubility barrier, in that the first two points representing the mole fraction of TMB123 as 0.0 and 0.25 yielded crystals of pure TMB135 only.

The remaining curve from $X_{123} \geq 0.4$ shows a preference for TMB123 over TMB135 with $K_{TMB123:TMB135} = 4.5$. Figure 6c showing the selectivity between TMB124 and TMB135 with 1-butanol as solvent also shows a solubility gap as the previous example with $K_{TMB124:TMB135} = 2.6$. The solubility gaps in both the latter two figures are indicated by a double black arrow.

DCA crystal structures obtained with trimethoxybenzenes were similar (see Table 3 and Figure 7a−c), whether in a competition experiment of the guests or individual crystallization of the guest with the host. The three structures crystallize in $P2_12_12_1$ with one guest molecule and one host molecule in the asymmetric unit. The best model, that of the DCA·TMB123/TMB135 structure, arising from the three competitions experiments, is described as representative.

The DCA·TMB123/TMB135 crystal structure consisted of a 1:1 host to guest ratio. The guest was disordered with the relative proportion observed in NMR spectroscopy as 89/11 TMB123/TMB135. Additionally, the guest molecule showed

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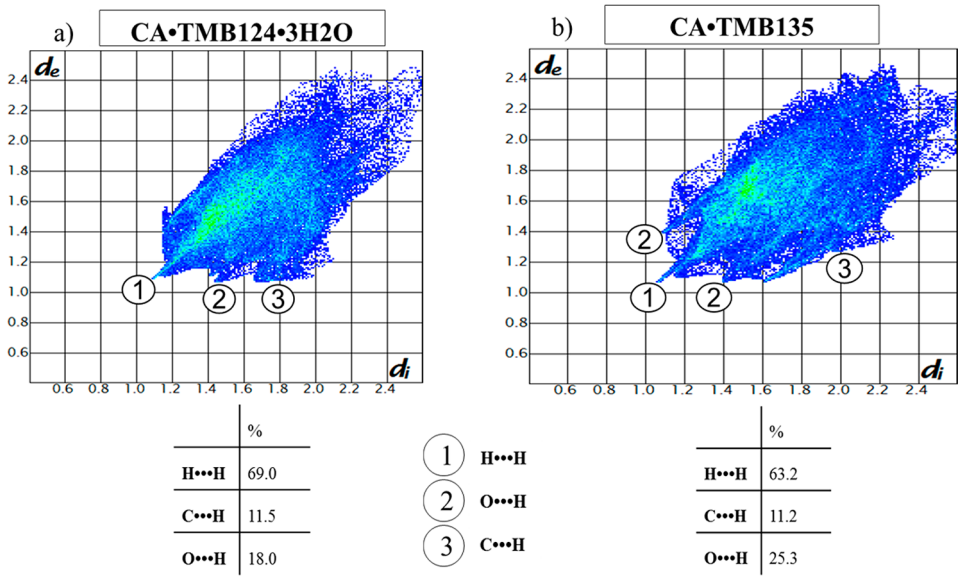

Figure 5. Fingerprint plots with the contribution of the different interactions present in CA·TMB124·3H_2O and CA·TMB135.

Table 1. Crystallographic Data for CA Inclusion Crystals

	1	2	3	4
compound	CA·TMB123	CA·TMB124·3H_2O	CA·TMB135	CA·TMB123/TMB124
formula asymm. unit	2($C_{24}H_{40}O_5$)·$C_9H_{12}O_3$	2($C_{24}H_{40}O_5$)·$C_9H_{12}O_3$·3H_2O	2($C_{24}H_{40}O_5$)·$C_9H_{12}O_3$	2($C_{24}H_{40}O_5$)·$C_9H_{12}O_3$
M [g mol^{-1}]	985.31	1039.35	985.31	985.31
data collection temp T [K]	173(2)	173(2)	173(2)	173(2)
crystal system	monoclinic	monoclinic	triclinic	monoclinic
space group	$P2_1$	$P2_1$	$P1$	$P2_1$
a [Å]	14.3455(2)	14.6160(10)	8.1221(6)	14.4231(18)
b [Å]	7.9011(10)	8.0112(6)	12.1749(10)	7.9118(10)
c [Å]	24.595(3)	24.8745(18)	14.1791(11)	24.615(3)
α [°]	90	90	105.157(2)	90
β [°]	105.367(3)	103.562(2)	91.590(2)	105.407(2)
γ [°]	90	90	93.2960(10)	90
volume [$Å^3$]	2688.1(6)	2831.4(4)	1349.76(18)	2708.0(6)
Z	2	2	1	2
D_c, calc. density [g cm^{-3}]	1.217	1.219	1.212	1.208
absorption coefficient [mm^{-1}]	0.084	0.087	0.084	0.084
$F(000)$	1076	1136	538	1076
θ range	1.72−28.43	1.43−28.41	1.49−28.43	1.49−26.40
reflections collected	31252	63561	28023	23622
no. data $I > 2\sigma(I)$	8653	14191	11061	5520
final R indices [$I > 2\sigma(I)$]	R = 0.1069, wR = 0.2844	R = 0.0403, wR = 0.0991	R = 0.0451, wR = 0.0991	R = 0.1237, wR = 0.3020
R indices (all data)	R_1 = 0.1490, wR_2 = 0.3254	R_1 = 0.0488, wR_2 = 0.1055	R_1 = 0.0591, wR_2 = 0.1067	R_1 = 0.2119, wR_2 = 0.3639

disorder by translation, represented along the [010] axis shown in Figure 8.

The packing of DCA·TMB123/TMB135 showed similarities with CA structures with trimethoxybenzenes. In this structure, the guest molecules were also observed to lie in channels. Figure 7a shows the structure in van der Waals representation with the guest omitted. As in CA·TMB124·3H_2O, when the guest was reinserted in the structure in Figure 7b, it also appeared as hourglass shaped constricted channels which are narrowly connected.

Comparison between Cholic Acid and Deoxycholic Acid Complexes. In the intention of elucidating the difference in selectivity observed in the complexes formed by CA and DCA with the trimethoxybenzene isomers, the packing of the structures was studied in detail. Figure 9a displays the packing of CA·TMB124·H_2O viewed along [010]. The host, CA, molecules are arranged in alternate hydrophilic (pink) and lipophilic (blue) layers. Adopting Miyata's convention, the CA molecules run in opposing directions in what is termed the shv# pattern.[31,32] The TMB124 guest is located in a cavity in the lipophilic layer, and the water molecules are located in the hydrophilic layers and are hydrogen-bonded to each other and the host hydroxyl moieties. The packing of the DCA·TMB123/TMB135 structure is shown in Figure 9b viewed along [100]. As before the hydrophilic and lipophilic layers are shown in pink and blue, respectively. In contrast with the CA structures, the DCA host molecules run in parallel directions in the shv pattern. The site of the mixed TMB123/TMB135 guests is located in the lipophilic layer.

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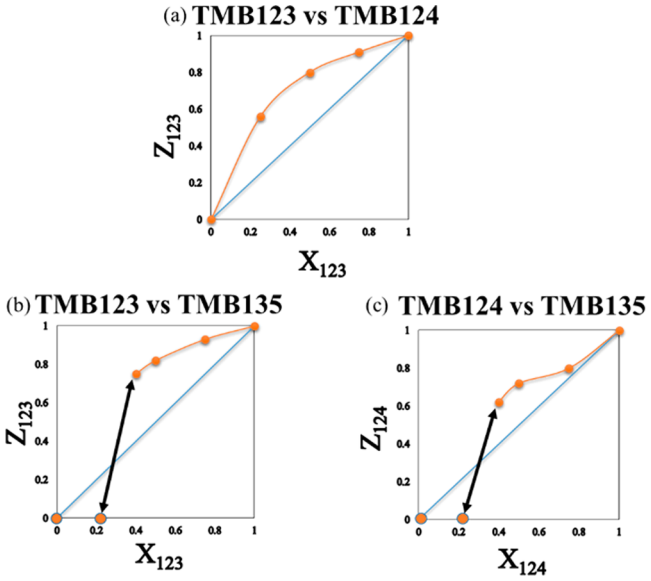

Figure 6. (a–c) Pairwise selectivity curves of the TMB guests with deoxycholic acid, in which the fraction X of a given guest is plotted against its mole fraction Z in the crystal.

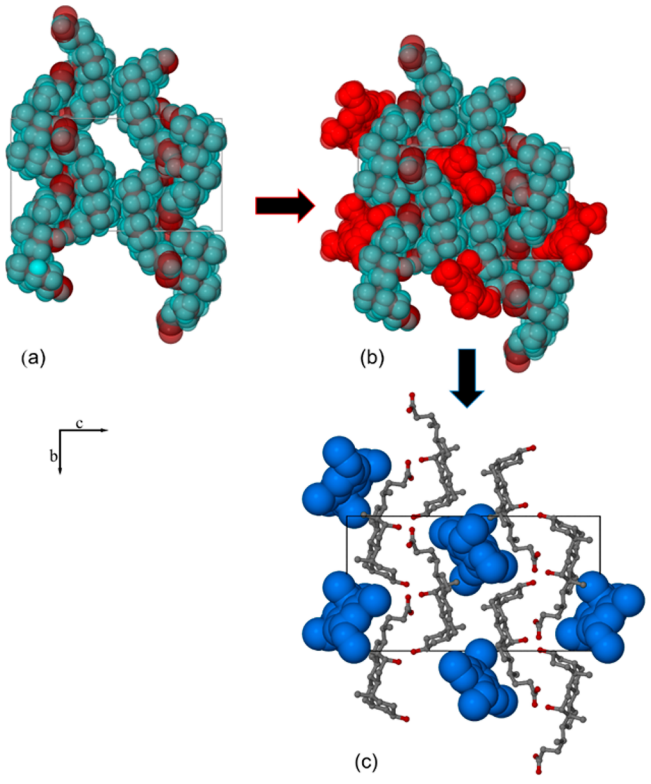

Figure 7. Packing of DCA·TMB123/TMB135 in van der Waals representation in (a) without guest, (b) with guest (red) along [100] and (c) with guest (blue) showing the location of the guests in the lipophilic cavities.

The study of the packing was further examined by analyzing the volumes of the TMB guest molecules, the volumes of the cavities, and the packing coefficient of the TMB guests in their respective cavities. These are reported in Table 3.

In the analysis of the selective inclusion of xylenes, Miyata[34] analyzed the complete selectivity curve of CA with known mixtures of *meta*- and *para*-xylenes and demonstrated that the

Table 2. Crystallographic Data for DCA Inclusion Crystals

	5	6	7
compound	DCA·TMB123/TMB124	DCA·TMB123/TMB135	DCA·TMB124/TMB135
formula asymm. unit	$(C_{24}H_{40}O_4)\cdot 1/2C_9H_{12}O_3$	$(C_{24}H_{40}O_4)\cdot 1/2C_9H_{12}O_3$	$(C_{24}H_{40}O_4)\cdot 1/2C_9H_{12}O_3$
M [g mol^{-1}]	476.65	476.65	476.65
data collection temp T [K]	173(2)	173(2)	153(2)
crystal system	orthorhombic	orthorhombic	orthorhombic
space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
a [Å]	7.3786(8)	7.3653(5)	7.2447(3)
b [Å]	13.8215(14)	13.8069(11)	13.5954(7)
c [Å]	25.960(3)	25.905(2)	26.3607(13)
α [°]	90	90	90
β [°]	90	90	90
γ [°]	90	90	90
volume [Å^3]	2647.5(5)	2634.4(3)	2596.4(2)
Z	4	4	4
D_c, calc. density [g cm^{-3}]	1.196	1.202	1.219
absorption coefficient [mm^{-1}]	0.081	0.081	0.082
$F(000)$	1044	1044	1224
θ range	2.78–27.91	1.57–27.87	1.54–28.35
reflections collected	19258	16573	40218
no. data $I > 2\sigma(I)$	5308	4753	6013
final R indices [$I > 2\sigma(I)$]	R = 0.0662, wR = 0.1784	R = 0.0698, wR = 0.1857	R = 0.0827, wR = 0.2599
R indices (all data)	R_1 = 0.0789, wR_2 = 0.1903	R_1 = 0.0931, wR_2 = 0.2045	R_1 = 0.0871, wR_2 = 0.2674

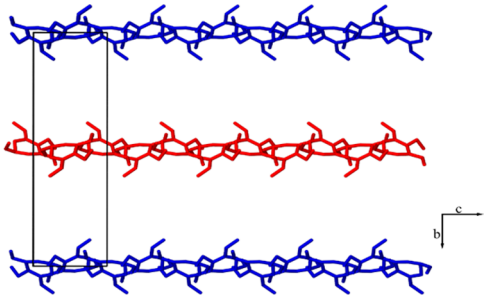

Figure 8. Disorder by translation of the guest molecules along [100] in DCA·TMB123/TMB135.

favored isomer *para*-xylene had the highest packing coefficient, PC_{cavity}. The results obtained in this analysis, however, are more difficult to interpret, in that structure 1, CA·TMB123, has disorder in the host, structure 2, CA·TMB124·3H_2O, is a trihydrate, and structure 3 is the only well resolved structure of a pure CA·TMB compound. It is difficult therefore to compare the packing factors of the guests in structures 1, 2, and 3. Suffice to say that they are similar ranging from 46.2% to 49.8%. Structure 4, which was synthesized from an equimolar mixture of TMB123 and TMB124, yielded the same guest proportion in the crystal, and their guest volume is correspondingly larger.

With the DCA structures 5 and 6, which yielded mixtures of the guests TMB123/TMB124 and TMB123/TMB135, the packing factors are ~63%. The final structure 7, which contained a mixture of TMB124/TMB135, allowed a % estimate of the guests from NMR (TMB124/74% and TMB135/26%), but the guest atomic positions could not be

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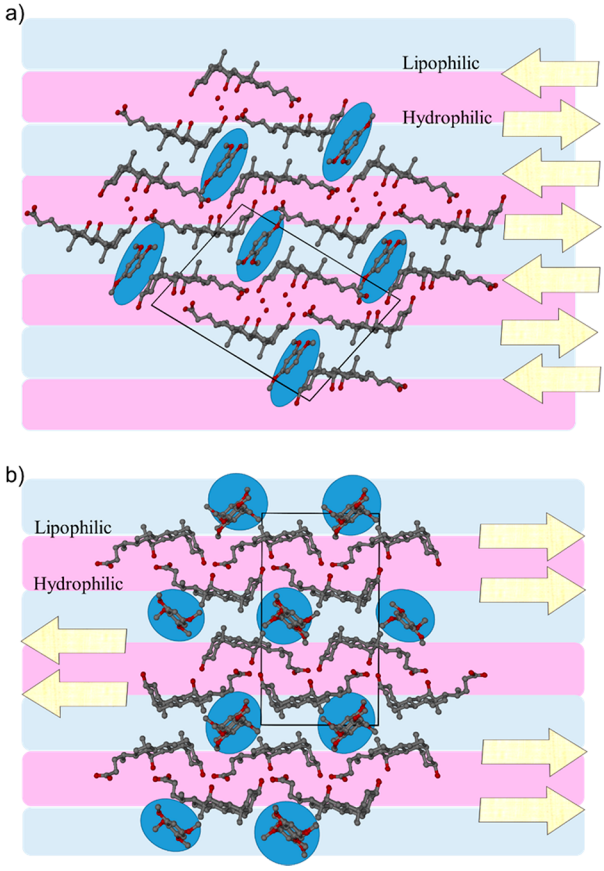

Figure 9. Bilayer structure of (a) CA·TMB124·3H_2O and (b) DCA·TMB123·TMB135. Lipophilic layers in blue, hydrophilic layers in pink (adapted from Nakano et al.[32]).

satisfactorily identified due to severe disorder. We therefore applied the program SQUEEZE from the PLATON suite of subroutines[32] to complete the refinement.

Additionally, due to the disorder observed in most structures, Crystal Explorer could not be applied to all structures in order to explain the selectivity preferences of each host. We note that the cavities arise from the different packing patterns (Shv versus Shv# respectively) as stated by Nakano et al.[32]

CONCLUSION

Analysis of the enclathration of the three isomers of trimethoxybenzene, TMB, by the bile acids cholic acid, CA, and deoxycholic acid, DCA, shows that the selectivity preferences are CA: TMB135 > TMB123 ≈ TMB124 and are reversed for DCA: TMB123 > TMB124 > TMB135. The crystal structures of the single guests with CA show the packing of the hosts to lie in alternative double layers which are either hydrophilic or lipophilic with the CA molecular axes running in opposing directions. In contrast, the DCA structures exhibit packing modes of pairs of parallel layers. For both hosts, the TMB guests are located in voids within the lipophilic layers.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.cgd.7b01423.

Table of hydrogen bonding, figures of packing diagram (PDF)

Accession Codes

CCDC 1579054−1579060 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

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Table 3. Cavity Volume, Volume Ratio of Cavity, Molecular Volume of Guest, and Packing Coefficient of Host Cavity in CA and DCA Inclusion Compounds

compound	preparation[f]	V_{guest} (Å^3)[a]	V_{cavity} (Å^3)[b]	V_{cell} (Å^3)	V_{cavity}/V (%)[c]	PC_{cavity} (%)[d]	structure comments
1	CA + TMB123 + 1-butanol	150.3	324	2688.1	24.1	46.4	CA host disordered (sof 78%/22%)[e]
2	CA + TMB124 + 1-pentanol	152.0	306	2831.4	21.6	49.8	CA·TMB124·3H_2O
3	CA + TMB123 + TMB135 + 2-propanol	152.3	329	1349.8	24.4	46.2	CA·TMB135
4	CA + TMB123 + TMB124 + methanol	176.7	327	2708.0	24.2	54.0	CA·TMB123 (53%)·TMB124 (47%)
5	DCA + TMB123 + TMB124 + 2-propanol	176.7	282	2647.5	21.3	62.6	DCA·1/2(TMB123·(80%) TMB124) (20%)
6	DCA + TMB123 + TMB135 + 2-propanol	176.7	280	2634.4	21.3	63.1	DCA·1/2(TMB123 (89%)·TMB135) (11%)
7	DCA + TMB124 + TMB135 + 1-butanol	176.7	266	2596.4	20.4	66.4	DCA·1/2(TMB124 (74%) ·TMB135) (26%)

[a]V_{guest}: volume of guest (Xseed[28]). [b]V_{cavity}: The volume of the cavity calculated with a sphere probe of radius 1.2 Å (Platon[33]). [c]V_{cavity}/V_{cell} (%): % volume of cavities in a particular the structure. [d]PC_{cavity}: % packing coefficient of guests in cavity. [e]Host disordered, only major component with sof = 78% was employed. [f]For compounds 3−7, the mother liquors contained equimolar of TMB guests.

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SUPPLEMENTARY DATA

Separation of trimethoxybenzene isomers by bile acids.

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INDEX

1.1S Tables

Table 1S: Geometrical data of the hydrogen bonds of CA crystal structures.

Compound	D•••A/Å	Symmetry operation
1		
O3A ••• O7A	2.726(5)	[-x+2, y+1/2, -z+1]
O7A ••• O24B	2.698(2)	[x, y-1, z]
O7A ••• O27B	2.870(6)	[x, y-1, z]
O7A ••• O25B	3.26(2)	[x, y-1, z]
O12A ••• O3A	2.750(5)	[-x+2, y+1/2, -z+1]
O3B ••• O12B	2.817(4)	[-x, y-1/2, -z]
O7B ••• O3B	2.632(5)	[-x, y-1/2, -z]
O12B ••• O27A	2.804(5)	[x, y+1, z]
O12B ••• O24A	2.679(2)	[x, y+1, z]
O12B ••• O25A	3.38(3)	[x, y+1, z]
2		
O7B ••• O3B	2.663(2)	[-x+2, y-1/2, -z]
O12B ••• O25A	2.767(2)	[x, y+1, z]
O3B ••• O12B	2.800(2)	[-x+2, y-1/2, -z]
O24A ••• O7B	2.606(2)	
O12A ••• O31	2.886(2)	
O3A ••• O25B	2.752(2)	[-x+1, y-1/2, -z+1]
O30••• O7A	2.738(2)	[x, y+1, z]
O31••• O3A	2.974(2)	[-x+1, y+1/2, -z+1]
O32••• O3A	2.753(2)	[-x+1, y-1/2, -z+1]
O30••• O32	2.847(2)	[-x+1, y+3/2, -z+1]
O32••• O12A	2.782(2)	[x, y-1, z]
O24B ••• O30	2.571(2)	
3		
O7A ••• O3B	2.666(2)	[x-1, y, z]
O24A ••• O7B	2.626(2)	[x, y-1, z-1]
O12A ••• O25B	2.873(2)	[x-1, y-1, z-1]
O3A ••• O12B	2.784(2)	[x-1, y, z]
O24B ••• O7A	2.664(2)	[x+1, y+1, z+1]
O12B ••• O25A	2.760(2)	[x+1, y+1, z+1]
O7B ••• O3A	2.637(2)	
O3B ••• O12A	2.777(2)	
4		
O24A-••• O7B	2.636(7)	
O3B ••• O12B	2.804(7)	[-x+1, y+1/2, -z+1]
O24B ••• O12A	2.651(8)	

Table 2S: Geometrical data of the hydrogen bonds of DCA crystal structures.

Compound	D•••A/Å	Symmetry operation
5		
O24••• O12	2.656(3)	[-x, y+1/2, -z-1/2]
O12••• O3	2.679(3)	[-x-1, y+1/2, -z-1/2]
O3••• O25	2.724(3)	[x, y-1, z]
6		
O24••• O12	2.648(3)	[-x+1, y+1/2, -z+1/2]
O12••• O3	2.672(3)	[-x, y+1/2, -z+1/2]
O3-••• O25	2.720(3)	[x, y-1, z]
7		
O3••• O25	2.702(3)	[-x+1, y+1/2, -z+1/2]
O12••• O3	2.666(3)	[x, y-1, z]
O24••• O12	2.634(3)	[-x, y+1/2, -z+1/2]

1.2S Packing diagram

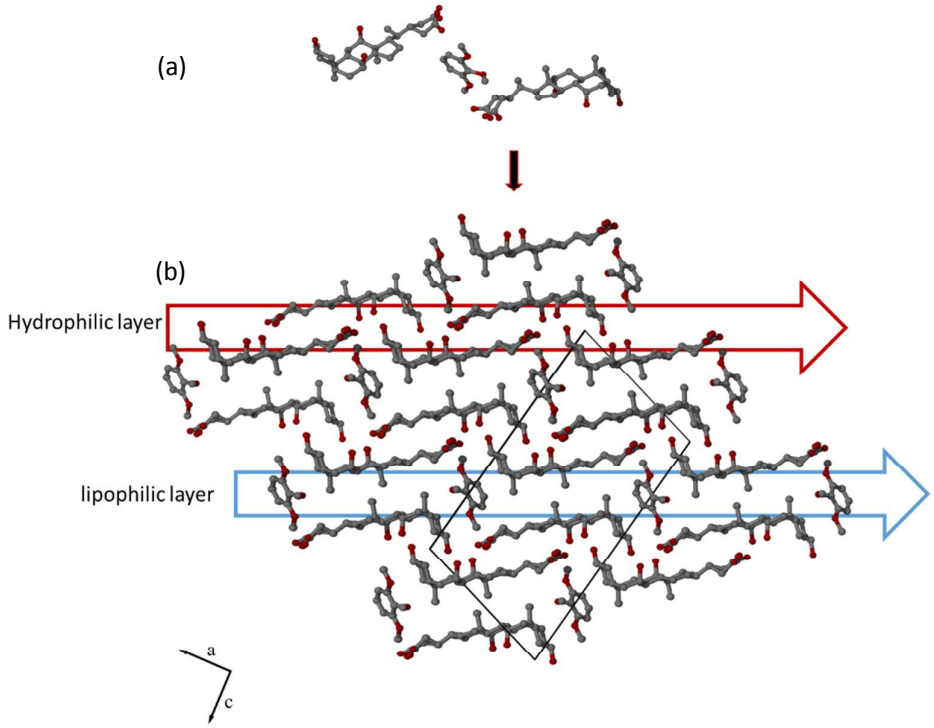

Figure 1S: CA•TMB123 a) asymmetric unit and b) packing diagram along [010].

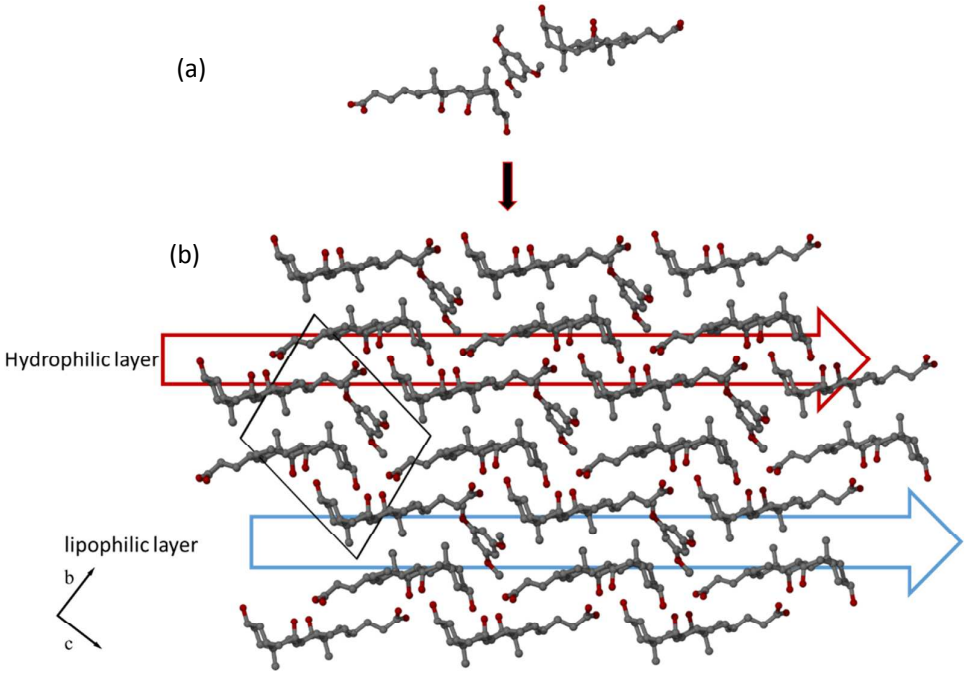

Figure 2S: CA•TMB135 a) asymmetric unit and b) packing diagram along [010].

Chapter 4.

Separation of Lutidine Isomers by Selective Enclathration

4.1 Summary

The separation of isomers had long been used particularly for enantiomer compounds. In this context, the “Dutch Resolution” method, which is the process whereby a mixture of host compounds is used to separate racemic mixture, has been applied. In this process, the addition of closely related host compound was found to increase the diastereomeric excesses of a particular enantiomer thru the formation of salts1,2. Moreover, the present technique has also been employed as an extension of Louis Pasteur's method of separation while taking into consideration the combinatorial approach used in drug discovery3,4,5. In this framework, the separation of lutidine isomer was carried out and an attempt to improve selectivity was completed with two additional diol host compounds.

Lutidine (LUT) isomers were separated by their selective enclathration of host 3,3′-bis(9hydroxy-9-fluorenyl)-2−2′-binaphthyl (H1). The separation was done by analysing crystalline materials made from the mixture of host H1 with pairwise isomers by 1H NMR. The final trend obtained from the fifteen combinations was as follow: 3,4-LUT > 2,6-LUT > 2,5-LUT > 2,3-LUT > 2,4-LUT ≈ 3,5-LUT. Low selectivity was observed in some combinations which then lead to four structures with mixed guest molecules. The compounds were H1·2(2,3-LUT/2,6LUT), H1·1(2,4-LUT)/·1.5(2,5-LUT), H1·2(2,4-LUT/3,5-LUT) and H1·2(2,6-LUT/3,4- LUT).

To analyse the selectivity patterns, each guest was then crystallized with H1 which then led to H1·2(2,3-LUT); H1·(2,4-LUT); H1·2(2,6-LUT); H1·2(3,4-LUT); H1·(3,5-LUT). It was found that the structure of H1 with 2,5-lutidine could not be elucidated due to the low solubility of H1 in this guest. However, from the five structures formed, a packing coefficient analysis describing the efficiency of packing between host and guest was derived. The packing coefficient values confirmed the trend found from the competition experiment analysis by the 1H NMR.

An attempt in simulating the “Dutch resolution” method directed the research into the selection of two hosts with similar properties as H1. In this segment, no specification on the bulkiness of the extra branches governing the host was considered. Instead, the hosts were selected due to their closeness in the eventual bonding system that may be formed from their combination with the guest molecules. The mixed host experiments were partly successful. When a mixture of host 1 and host 3 were exposed to the equimolar mixture of 2,4-LUT/3,5LUT, the resulting

structure was H1·(3,5-LUT). In the case of the combined H1+ H2 dissolved in the equimolar 2,3-LUT/2,6-LUT, only H2 was found in the crystal structure with an improved proportion of 2,3-LUT (1H NMR and crystal structure of 75%). However, there was no case where the two host compounds were retained in the resulting crystal structures. Thermal analysis of the different crystalline compounds was also reported in this paper along with an attempt of vapor competition experiments. Unfortunately, this latter did not yield to significant changes toward the selectivity of one isomer.

4.2 References:

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Separation of Lutidine Isomers by Selective Enclathration

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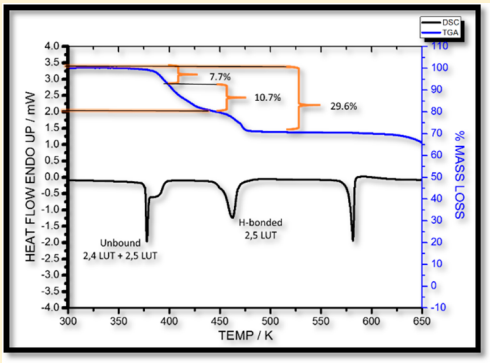
Supporting Information

ABSTRACT: The host compound 3,3′-bis(9-hydroxy-9-fluorenyl)-2−2′-binaphthyl, **H1**, has been employed to separate the six isomers of lutidine. Competition experiments showed that the preference for enclathration is in the sequence 3,4-LUT > 2,6-LUT > 2,3-LUT > 2,5-LUT > 2,4-LUT ≈ 3,5-LUT. The structures yielded results that agree with the ^{1}H NMR analyses and with the thermal analysis. The effects of mixed hosts and vapor-phase competitions were briefly explored with two extra hosts, namely, 2,2′-bis(1-hydroxy-4,5-dihydro-2:3,6:7-dibenzocycloheptadien-1-yl)biphenyl (**H2**) or 3,3′-bis(di-*p*-tolylhydroxymethyl)-1,1′-binaphthyl (**H3**).



INTRODUCTION

The separation of a particular component from a mixture may be carried out by exploiting the physico-chemical properties of the compounds in that mixture. The most common techniques, viz. distillation, crystallization, liquid−liquid extraction, and various forms of chromatography, rely on differences in solubility and vapor pressure of the components. In the case of molecular isomers, however, their macro-properties are often similar, rendering the traditional separation techniques inefficient. For example, considering the isomers of dimethylbenzene, ortho-, meta-, and para-xylene, their normal boiling points range from 136.2 to 144.4 °C rendering distillation difficult. In such cases, host−guest chemistry, which depends on the process of complexation by inclusion, is an effective technique. The process relies on a host compound H being exposed to a mixture of guest molecules A, B, C... resulting in a host−guest complex:

$$H + n_1A + n_2B + n_3C... \rightarrow H{\cdot}Am$$

In the above equation, the host H is usually a solid, and the various guests A, B, C... may be solid, liquid or gases in proportions given by n_1, n_2, n_3..., yielding a product H·Am, an inclusion compound with guest/host (G:H) ratio of *m*. The above represents an ideal situation in which a single component A is selectively enclathrated. This seldom occurs in practice. In order to examine such a process, most studies have restricted themselves to two guests, and less often to three guests, being exposed to the host H simultaneously:

$$H(s, \alpha) + n_1A(l) + n_2B(l) \leftrightarrow H{\cdot}Am_1{\cdot}Bm_2(s, \beta)$$

The solid host H, in its nonporous α-phase (the apohost), is dissolved in a known mixture of the two guests A and B, and upon recrystallization from the inclusion compound, yields the enclathrating β-phase. The stoichiometry of the compound is determined by a suitable analytical technique such as NMR, thermal gravimetry, or gas chromatography. This process has been reviewed, and its applications to the separation of isomers have been described.[1] Several groups of isomers have been separated by enclathration. The host 1,1,6,6-tetraphenylhexa-2,4-diyne-1,6-diol was employed in the resolution of a mixture of *o*-, *m*-, and *p*-methylbenzaldehydes.[2] 1,1′-Bi-2-naphthol has been used to separate alcohols from aqueous solution.[3] The host 1,1-bis(4-hydroxyphenyl) cyclohexane was applied in the separation of phenylenediamines[4] and benzenediols.[5]

In this work we present the results of the separation of lutidines by the host 3,3′-bis(9-hydroxy-9-fluorenyl)-2-2′-binaphthyl, **H1**.[6] The initial procedure was carried out by dissolving **H1** in binary equimolar mixtures of the six lutidine isomers, harvesting the resultant crystals and determining the relative quantities of the two guests by ^{1}H NMR. This was followed by the determination of the resultant crystal structures, and, where appropriate, relevant thermal analysis. Following the idea of the Dutch resolution method,[7] we briefly explored the effects of the addition of a second, similar host 2,2′-bis(1-hydroxy-4,5-dihydro-2:3,6:7-dibenzocycloheptadien-1-yl)biphenyl (**H2**)[8] or 2,2′-bis(di-*p*-tolylhydroxymethyl)-1,1′-binaphthyl (**H3**)[9] to a lutidine mixture and analyzed the results.

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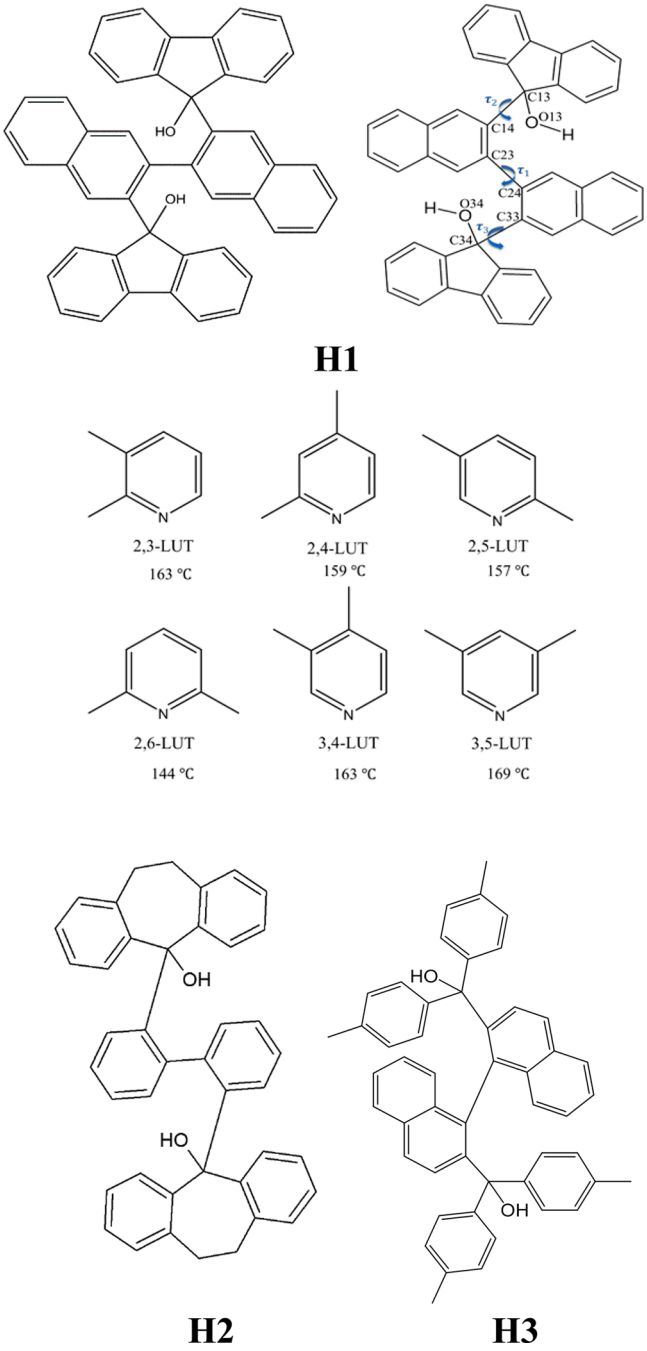
The study was unsuccessfully extended to three component liquid mixtures, and in addition the separation of the lutidine pairs as vapors was examined. The structural formulas of **H1**, **H2**, and **H3** along with the six lutidines are drawn in Scheme 1.

Scheme 1. Structural Formulae of Host and Guest Molecules Used



EXPERIMENTAL SECTION

Materials. The host compounds, **H1**, **H2**, and **H3** were synthesized by Weber[6,8,10] and were used without further purification. The lutidine guest compounds were all purchased from Sigma-Aldrich and used as received. Single crystals of the inclusion compounds were obtained by dissolving the particular host or mixture of hosts in an excess of the relevant guest or binary guest mixtures. The resulting solutions were allowed to crystallize by slow evaporation at room temperature. Some solutions were filtered when necessary.

X-ray Crystallography. Single crystal X-ray diffraction data were collected on a Bruker DUO APEX II diffractometer for all structures using Mo Kα (λ = 0.71073 Å) at a temperature of 153 K.[11] The intensity data were collected using the phi scan and omega scan techniques, scaled, and reduced with SAINT-Plus.[12] The correction of the collected intensities for absorption was done using the SADABS program.[13]

The structures were solved by direct methods using SHELX-97 and refined using full-matrix least-squares methods in SHELXL.[14] The graphical interface used was the program X-SEED.[15] Some diagrams were generated using MERCURY (3.5).[16]

Thermal Analysis. Thermogravimetric analysis (TGA) was performed using a TA-Q500 thermogravimetric analyzer. Results were analyzed using Universal Analysis 2000 software. The samples were crushed and blotted dry (2−4 mg) and weighed directly into open aluminum oxide TGA crucibles. Differential scanning calorimetry (DSC) was performed using a Surface Solutions GmbH DSC XP-10. Crushed and dried samples (1−3 mg) were weighed directly into vented aluminum pans on an analytical balance.

^{1}H Nuclear Magnetic Resonance (^{1}H NMR) Spectroscopy. ^{1}H NMR spectra were recorded on a Bruker 300 MHz with $CDCl_3$ as internal standard. Samples were blotted dry, crushed, and dissolved in deuterated chloroform. The appropriate signals were integrated to determine the relative proportions of the guests.

Vapor Experiment. The vapor absorption experiments were carried out by placing 10 mg of **H1** in a vial and a selected equimolar mixture of the lutidines in a second vial, and placing both in a closed jar in an oven at a fixed temperature. The powders were then analyzed by ^{1}H NMR after 24 h.

RESULTS AND DISCUSSION

^{1}H NMR Analysis. The initial analysis was carried out on the crystals harvested from the mother liquors of the equimolar lutidine binary mixtures. These crystals were blotted dry on absorbing paper but were not washed with any solvent for fear of guest exchange with the entrapped lutidines. This gave rise to some inaccuracies of the ^{1}H NMR results from surface lutidines which were not found in the crystal structures.

For example, in the 2,3-LUT/2,4-LUT competition experiment, the ^{1}H NMR result was 88% 2,3-LUT/12% 2,4-LUT as shown in Table 1. However, in the crystal structure only the 2,3-LUT guest molecule was located. The six lutidines give rise to 15 equimolar mixtures, the results of which are given in Table 1. From these, seven single crystal structures containing **H1** were elucidated. The other mixtures either yielded the same single lutidine guest or gave rise to a powdered product which was unsuitable for single crystal diffraction.

The ^{1}H NMR results are shown in Table 1 which displays the percentage of each lutidine guest as well as its appearance in the corresponding crystal structure. Similar tables (Tables S1 and S2) for **H2** and **H3**, in which only the mixture which gave very poor separation with **H1** are shown. These have been deposited as Supporting Information (SI). The crystal data and final refinement parameters are given in Tables 2 and 3. The results of the ^{1}H NMR analyses shown in Table 1 can be summarized as yielding the preference of enclathration by **H1** as 3,4-LUT > 2,6-LUT > 2,3-LUT > 2,5-LUT > 2,4-LUT ≈ 3,5-LUT. This is different from that found by three similar diol hosts, namely, 9,10-bis[2-(9-hydroxy-9-fluorenyl) ethynyl)] anthracene, 9,10-bis[2-(2,7-di-*tert*-butyl-9-hydroxy-9-fluorenyl)-ethyl] anthracene and 1,4-bis[2-(9-hydroxy-9-fluorenyl)-ethynyl]benzene which yielded the sequence 3,5-LUT > 2,3-LUT ≈ 3,4-LUT > 2,5-LUT > 2,4-LUT.[17]

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Table 1. Results of the ^{1}H NMR Analyses and Concomitant Structures

LUT	2,3	2,4	2,5	2,6	3,4	3,5
2,3						
2,4	^{1}H NMR 2,3-88% 2,4-12% STRUCT. 2,3					
2,5	^{1}H NMR 2,3-45% 2,5-55% STRUCT. No suitable crystals	^{1}H NMR 2,4-40% 2,5-60% STRUCT. 2,4/2,5				
2,6	^{1}H NMR 2,3-44% 2,6-56% STRUCT. 2,3/2,6	^{1}H NMR 2,4-22% 2,6-78% STRUCT. 2,6	^{1}H NMR 2,5-7% 2,6-93% STRUCT. 2,6			
3,4	^{1}H NMR 2,3-14% 3,4-86% STRUCT. 3,4	^{1}H NMR 2,4-11% 3,4-89% STRUCT. 3,4	^{1}H NMR 2,5-9% 3,4-91% STRUCT. 3,4	^{1}H NMR 2,6-45% 3,4-55% STRUCT. 2,6/3,4		
3,5	^{1}H NMR Not recorded STRUCT. 2,3	^{1}H NMR 2,4-53% 3,5-47% STRUCT. 2,4/3,5	^{1}H NMR Not recorded STRUCT. No suitable crystals	^{1}H NMR 2,6-88% 3,5-12% STRUCT. 2,6	^{1}H NMR 3,4-81% 3,5-19% STRUCT. 3,4	

Table 2. Crystallographic Data Parameters of the Host-Guest Complexes

structures	**H1**·2(2,3-LUT)	**H1**·(2,4-LUT)	**H1**·2(2,6-LUT)	**H1**·2(3,4-LUT)	**H1**·(3,5-LUT)
empirical formula	$C_{60}H_{48}N_2O_2$	$C_{53}H_{39}NO_2$	$C_{60}H_{48}N_2O_2$	$C_{60}H_{48}N_2O_2$	$C_{53}H_{39}NO_2$
M [g mol^{-1}]	829.00	721.90	829.00	829.00	721.90
data collection temp T [K]	153(2)	153(2)	153(2)	152(2)	173(2)
crystal system	monoclinic	monoclinic	monoclinic	triclinic	monoclinic
space group	Pn	$P2_1/c$	$P2_1/n$	$P\bar{1}$	$C2/c$
a [Å]	11.5086(12)	14.654(2)	17.8543(9)	11.7133(3)	25.641(6)
b [Å]	11.6112(12)	11.8621(19)	11.3796(5)	11.8756(3)	11.641(3)
c [Å]	16.8095(18)	22.188(4)	22.7167(11)	17.4899(5)	25.497(5)
α [°]	90	90	90	77.8280(10)	90
β [°]	99.206(2)	94.221(3)	108.1850(10)	76.1330(10)	94.260(4)
γ [°]	90	90	90	73.0240(10)	90
volume [Å^3]	2217.3(4)	3846.5(10)	4384.9(4)	2232.92(10)	7589.23
Z	2	4	4	2	8
D_c, calc. density [g cm^{-3}]	1.242	1.246	1.256	1.233	1.2634
absorption coefficient [mm^{-1}]	0.074	0.075	0.075	0.074	0.076
$F(000)$	876	1520	1752	876	3040
θ range	1.75−28.39	1.39−25.75	1.27−28.34	1.21−28.29	1.59−25.01
reflections collected	37684	21804	66324	31260	23848
no. data $I > 2\sigma(I)$	8358	4056	7872	8714	3850
final R indices	R = 0.0563	R = 0.0532	R = 0.0582	R = 0.0453	R = 0.0572
$[I > 2\sigma(I)]$	wR = 0.1327	wR = 0.1066	wR = 0.1413	wR = 0.1119	wR = 0.1314
R indices (all data)	R_1 = 0.0777	R_1 = 0.1215	R_1 = 0.0859	R_1 = 0.0609	R_1 = 0.1174
	wR_2 = 0.1460	wR_2 = 0.1318	wR_2 = 0.1613	wR_2 = 0.1217	wR_2 = 0.1603

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Table 3. Crystallographic Data Parameters of the Host-Guest Complexes

structure	**H1**·2(2,3-LUT/2,6-LUT)	**H1**·1(2,4-LUT)/·1.5(2,5-LUT)	**H1**·2(2,4-LUT/3,5-LUT)	**H1**·2(2,6-LUT/3,4-LUT)	**H2**·2(2,3-LUT/2,6-LUT)
empirical formula	$C_{60}H_{48}N_2O_2$	$C_{63.50}H_{52.50}N_{2.50}O_2$	$C_{60}H_{48}N2O_2$	$C_{60}H_{48}N_2O_2$	$C_{56}H_{52}N_2O_2$
M [g mol^{-1}]	829.00	882.58	829.00	829.00	785.00
data collection temp T [K]	153(2)	153(2)	153(2)	153(2)	173(2)
crystal system	monoclinic	triclinic	monoclinic	monoclinic	triclinic
space group	$P2_1/n$	$P\bar{1}$	$P2_1/n$	$P2_1/n$	$P\bar{1}$
a [Å]	17.8638(10)	11.0654(10)	18.3112(12)	17.8799(12)	8.5771(13)
b [Å]	11.3753(6)	16.9517(18)	11.7303(7)	11.3535(7)	11.0887(17)
c [Å]	22.7575(11)	26.305(3)	21.3292(12)	22.7763(15)	23.475(3)
α [°]	90	78.421(2)	90	90	93.701(3)
β [°]	108.5870(10)	89.912(2)	109.8870(10)	109.0200(10)	90.898(3)
γ [°]	90	86.062(2)	90	90	108.002(3)
volume [Å^3]	4383.3(4)	4822.0(8)	4308.2(5)	4371.2(5)	2117.5(5)
Z	4	4	4	4	2
D_c, calc density [g cm^{-3}]	1.256	1.2156	1.266	1.260	1.231
absorption coefficient [mm^{-1}]	0.075	0.075	0.074	0.075	0.074
$F(000)$	1752	1868	1735	1752	836
θ range	1.27−27.95	1.23−27.92	1.80−27.49	1.76- 25.37	1.94−27.20
reflections collected	42499	60020	31046	25448	20861
no. data $I > 2\sigma(I)$	7101	14150	6359	5338	4732
final R indices	R = 0.0856	R = 0.0581	R = 0.1404	R = 0.0544	R = 0.0618
$[I > 2\sigma(I)]$	wR = 0.2344	wR = 0.1288	wR = 0.4113	wR = 0.1358	wR = 0.1248
R indices (all data)	R_1 = 0.1223	R_1 = 0.1102	R_1 = 0.1807	R_1 = 0.0940	R_1 = 0.1472
	wR_2 = 0.2677	wR_2 = 0.1519	wR_2 = 0.4438	wR_2 = 0.1579	wR_2 = 0.1567

Vapor Competition Analysis. The vapor competition experiments were carried out at 60 and 80 °C. The pairs of lutidines chosen were 2,6-LUT/3,4-LUT and 2,3-LUT/2,6-LUT which had yielded poor discrimination in the liquid mixtures. The results did not yield significant changes in selectivity and are given in Supporting Information as Table S3. The 2,6-LUT/3,4-LUT increased marginally from the liquid experiment from 45%/55% to 58%/42% at 60 °C and 54%/46% at 80 °C. The 2,3-LUT/2,6-LUT pair similarly increased from 56%/44% to 59%/41% at 60 °C and 60%/40% at 80 °C. The results were not significantly different at different temperatures.

Crystal Structure Analysis. Crystals of **H1**·2(2,3-LUT), were obtained from different mother liquors, namely, the equimolar mixtures of 2,3/2,4 and 2,3/3,5 lutidines. The crystals yielded very similar cell parameters and were isomorphous. We report the structure derived from the 2,3-LUT/3,5-LUT equimolar mixture. **H1**·2(2,3-LUT) crystallizes in the space group Pn with Z = 2. Pn was chosen in preference to $P2/n$ from E-statistics and was vindicated by the successful refinement of the structure. There are two **H1** and four 2,3-LUT guest molecules in the unit cell.

The conformation of the host molecule is characterized by the intramolecular hydrogen bond O34−H34···O13, a constant feature of all these structures governing the torsion angle τ_1 and which dictates the conformation of the host molecule in this and other structures. Figure 1 displays the intermolecular H-bond and the (host)O13−H13···N51(2,3-LUT) interaction. The second 2,3-LUT guest molecule is not hydrogen bonded. The packing is characterized by the two guests located in common cavities.

The **H1**·2(2,4-LUT) structure, derived by dissolving **H1** in pure 2,4-LUT, crystallizes in $P2_1/c$ with Z = 4. The asymmetric unit comprises one host and one guest and again displays the intramolecular O34−H34···O13(H) and the host to guest

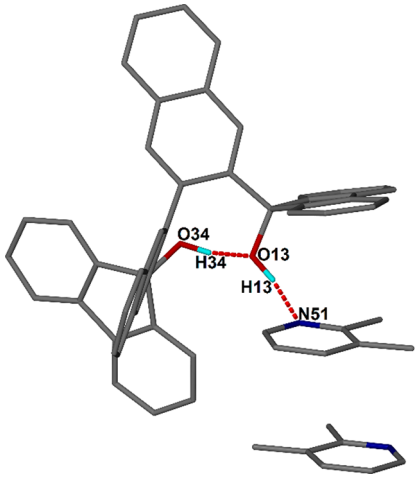

Figure 1. Asymmetric unit of **H1**·2(2,3-LUT) showing the intramolecular (host)O−H···O(H)(host) bond and the (host)O−H···N(guest) hydrogen bonding (some hydrogen atoms were omitted for clarity).

interaction (host) O13−H13···N51(2,4-LUT) as in the previous structure. The packing is characterized by highly restricted channels running along [001] which accommodate the 2,4-guest as shown in Figure 2.

The **H1**·2(2,6-LUT) structure, grown from the equimolar mixture 2,6-LUT/3,5-LUT, crystallizes in $P2_1/n$ with Z = 4. The asymmetric unit has the same motif as the **H1**·2(2,3-LUT) structure, but the packing is characterized by the guests lying in oscillating channels running in the [010] direction shown in Figure 3.

H1·2(3,4-LUT) structure, obtained from the 2,5-LUT/3,4-LUT mixture crystallizes in $P\bar{1}$ with Z = 2. The packing displays restricted channels running in the [100] direction. It is

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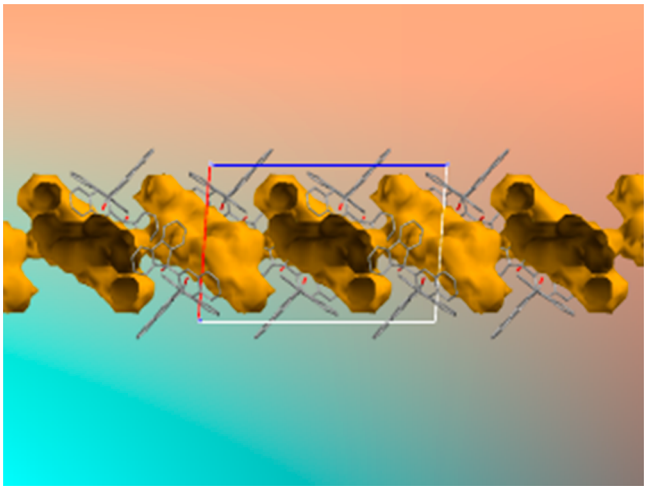

Figure 2. Channels along [010] which house the 2,4-LUT.

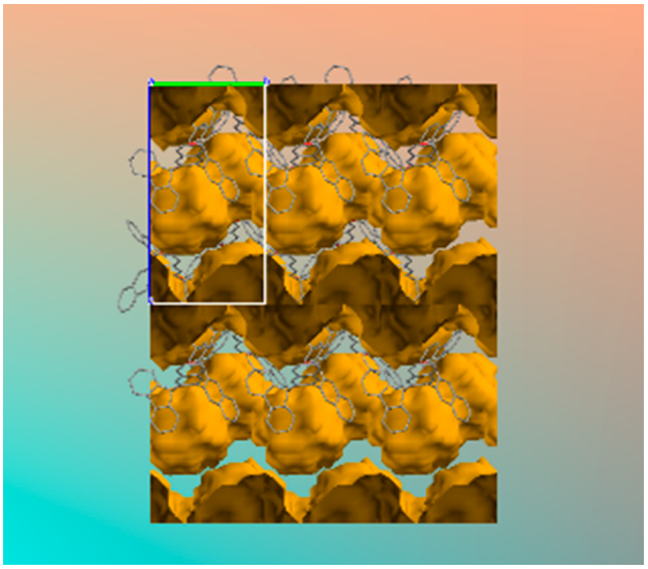

Figure 3. Oscillating channels running in the [010] direction.

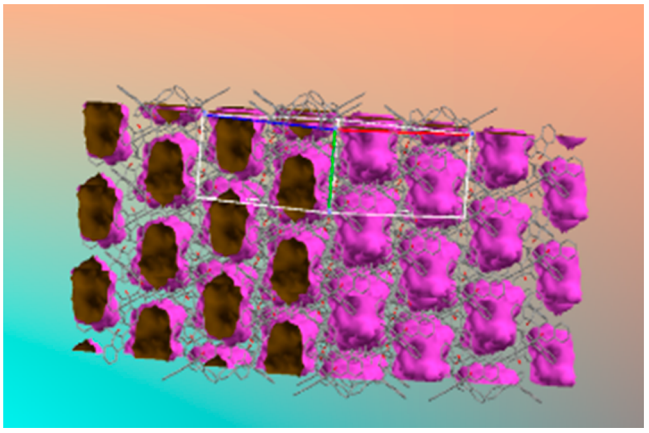

Figure 4. Packing of the **H1**·(3,5-LUT) structure showing the cavities which house the single 3,5-guest.

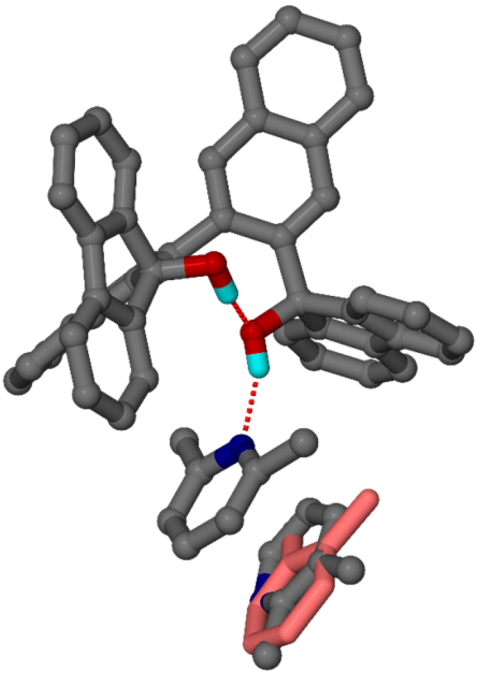

Figure 5. Asymmetric unit of **H1**·2(2,3-LUT/2,6-LUT), showing the 2,6-LUT H-bonded and the disordered 2,3-LUT (some hydrogen atoms were omitted for clarity).

interesting to note that the cell parameters of this and the **H1**·2(2,3-LUT) structures show strong similarities in their cell parameters (Table 2). Their packings, however, are dissimilar by virtue of their different space groups and are recorded in the Supporting Information as Figure S1.

The structure of **H1**·(3,5-LUT) was derived from an equimolar host mixture of **H1** and **H3** which were dissolved in a mixture of 2,4-LUT/3,5-LUT but yielded only the host **H1** and the guest 3,5-LUT in a 1:1 ratio. This structure crystallizes in $C2/c$ with $Z = 8$. The 3,5-LUT guest lies in discrete cavities as shown in Figure 4.

The **H1**·2(2,3-LUT/2,6-LUT) structure crystallizes in $P2_1/n$ with $Z = 4$. The ^{1}H NMR results yielded 56% 2,6-LUT and 44% 2,3-LUT. The structure clearly shows the 2,6-LUT molecule to be H-bonded to the host, while the 2,3-LUT exhibits 2-fold disorder (s.o.f. % 71/29) as shown in Figure 5. The guest molecules reside in channels running along [010]. The disordered 2,3-LUT could not be perfectly modeled, and only the C and N atoms were placed.

The structure of **H1**·1(2,4-LUT)/·1.5(2,5-LUT) crystallizes in $P\bar{1}$. In the asymmetric unit, there are two hosts and five guest molecules. The latter comprises two (2,4-LUT) and three (2,5-LUT) molecules. Two molecules of the 2,5-LUT guest are disordered and are located in the centers of inversion at Wykoff positions b and d. These were given site occupancies of 0.5. The ordered 2,5-LUT molecule is H-bonded to the **H1** hosts. This is shown in Figure 6.

The ^{1}H NMR results for this structure, given in Table 1, yielded 60% 2,5-LUT and 40% 2,4-LUT. The TGA curve is shown in Figure 7. The total mass loss of 29.6% corresponds to the calculated value of 30.4%. On the basis of the experimental value of 29.6% as the total guest loss, we interpreted the TGA desorption profile as having three steps (Figure 7). The one disordered 2,5-LUT molecule corresponds to the first decomposition step (measured/calculated % 7.7/6.1). The two ordered 2,4-LUT (10.7/12.1%) and the two H-bonded 2,5-LUT (11.3/12.1%) correspond to the second and third decomposition steps. These and other TGA results are summarized in Table S6 in the Supporting Information. The

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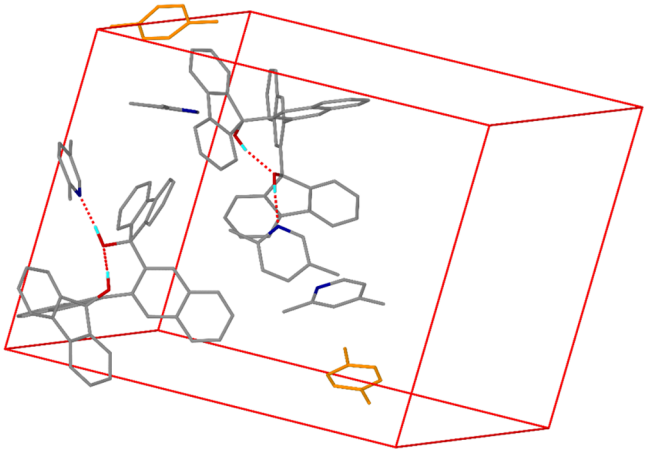

Figure 6. Asymmetric unit of **H1**·1(2,4-LUT)/·1.5(2,5-LUT), showing the disordered 2,5-LUT molecules (orange) on the centers of inversion (some hydrogen atoms were omitted for clarity).

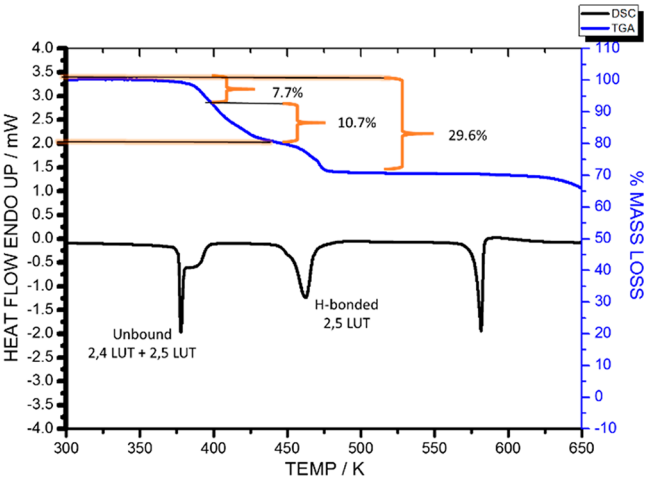

Figure 7. DSC and TGA profiles for **H1**·1(2,4-LUT)/·1.5(2,5-LUT).

corresponding DSC curve is shown in Figure 7, which exhibits the two endotherms for the unbound and bound lutidines.

The **H1**·2(2,4-LUT/3,5-LUT) structure crystallizes in $P2_1/n$ with Z = 4. In this structure the 3,5-LUT is H-bonded to the host, but the 2,4-LUT was severely disordered and could not be modeled. We therefore applied the program SQUEEZE from the PLATON[18] suite of subroutines to complete the refinement. The ^{1}H NMR result of 53% 2,4-LUT and 47% 3,5-LUT is in agreement with the TGA result, which shows two approximately equal steps of desorption for a total loss of 25.7% (calculated value been 25.9%). The figure of the asymmetric unit and the TGA profile have been deposited in the Supporting Information as Figure S2.

The structure of **H1**·2(2,6-LUT/3,4-LUT) crystallizes in $P2_1/n$ with $Z = 4$. The 2,6-LUT is H-bonded to the host **H1**, while the 3,4-LUT is disordered on a general position, with occupancies of 53/47%. The 3,4-LUT guests are located in channels running along [010]. The TGA shown in Figure 8 shows an initial loss of 4.1% attributed to the surface guest, followed by a two steps loss of the 3,4-LUT followed by the H-bonded 2,6-LUT (11.8%, 12.6% respectively). The DSC profile in Figure 8. shows the corresponding double endotherm for the lutidines desorption.

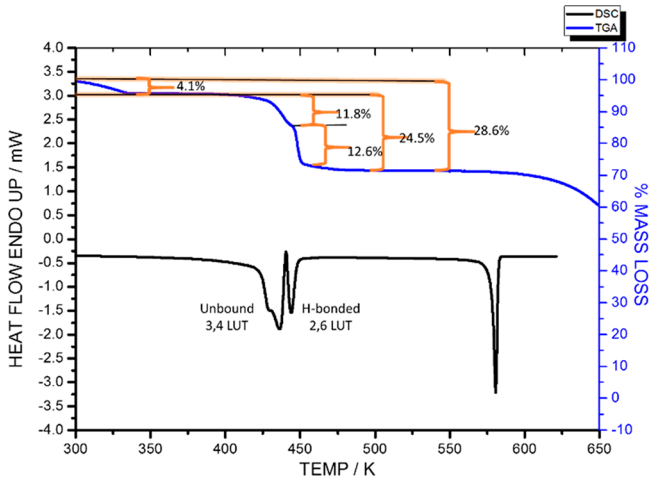

Figure 8. DSC and TGA profiles for **H1**·2(2,6-LUT/3,4-LUT).

The sequence for the preference of enclathration as derived from equimolar competition experiments was 3,4-LUT > 2,6-LUT > 2,3-LUT > 2,5-LUT > 2,4-LUT ≈ 3,5-LUT. In order to understand the structural reason for the result, we selected the structures which yielded a single guest, as shown in Table 2, and calculated the volume of the single guest divided by the volume of the cavity. The latter was obtained by employing a probe sphere of radius 1.2 Å with the program MERCURY (3.5).[16] This packing coefficient (PC) is a measure of the efficiency of packing between host and guest. The result is given below:

3,4-LUT > 2,6-LUT > 2,3-LUT > 2,5-LUT > 2,4-LUT ≈ 3,5-LUT

PC (%)	67.9	Disorder	67.2	No structure	65.1	61.6

There is no result for the isomer 2,5-LUT structure because no crystal was obtained with this guest alone. The value which resulted from the 2,6-LUT structure was neglected because one of the 2,6-LUT guest molecules displayed disorder rendering the result invalid. The PC of crystalline organic molecules range from 0.65 to 0.77 according to Kitaigorodskii,[19] and it is gratifying that for the four structures with a single guest and no disorder, the packing coefficient matches the sequence of the preference of enclathraton.

The **H2**·2(2,3-LUT/2,6-LUT) structure was derived from an equimolar mixture of **H1** and **H2** dissolved in an excess of equimolar (2,3-LUT + 2,6-LUT) guests. The product contained only **H2** and the two lutidine guests as crystals in space group $P\bar{1}$ with $Z = 2$. The host **H2** has strong similarities to **H1** in that the fluorenyl moiety of **H1** is replaced by the 1-hydroxy-4,5-dihydro-2:3,6:7-dibenzocycloheptane moiety, while the 2,2-biphenyl replaces the 2,2′-binaphthyl link. The conformation about the 1,1′-binaphthyl bond is again governed by the intramolecular O−H···O(H) bond as occurs in **H1**. In this structure, which may be contrasted directly with **H1**·2(2,3-LUT/2,6-LUT) because the 2,3-LUT is H-bonded to the host, while the 2,6-LUT/2,3-LUT are disordered and occupy the same site occupancies of 51/49% respectively. The asymmetric unit is shown in Figure 9 yielding an overall result of 75% 2,3-LUT and 25% 2,6-LUT.

The ^{1}H NMR results of 77% 2,3-LUT and 23% of 2,6-LUT are in agreement with the stoichiometry of the crystal structure and with the TGA profile. The latter shows a two-step decomposition with a total loss of 26.8% (27.3% calculated), shown in Figure 10. The DSC reflects the two-step

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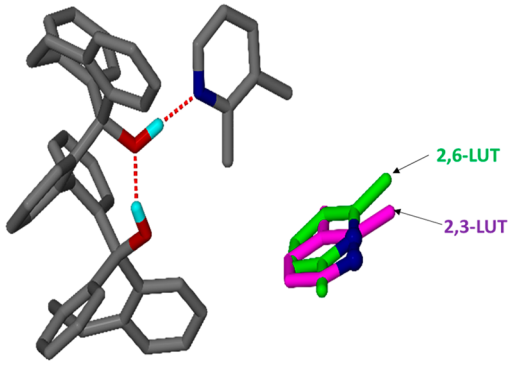

Figure 9. Asymmetric unit of **H2**·2(2,3-LUT/2,6-LUT) (some hydrogen atoms were omitted for clarity).

decomposition by yielding the corresponding two endotherms followed by the melt of the host.

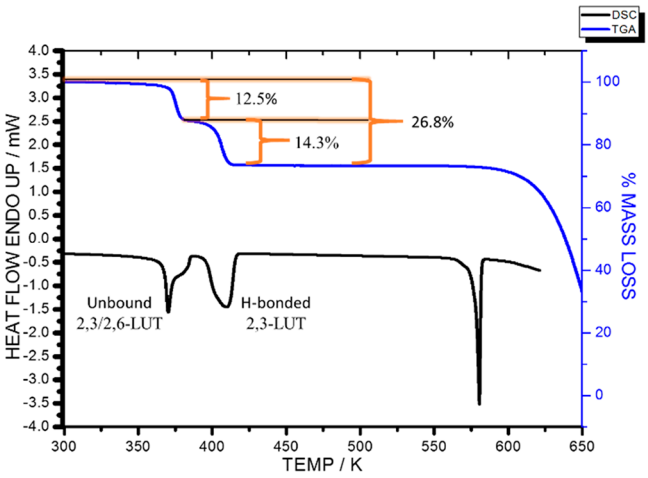

Figure 10. DSC and TGA profiles of **H2**·2(2,3-LUT/2,6-LUT).

Torsion Angles Analysis. The conformation of the host molecule **H1**, is defined by the three torsion angles:

τ_1 = C14-C23-C24-C33

τ_2 = O13-C13-C14-C23

τ_3 = O34-C34-C33-C24

They are summarized in Table S4 in the Supporting Information. The three torsion angles are remarkably constant, with τ_1 varying from 82.5° to 96.0° τ_2 from 21.1° to 31.4° and τ_3 21.3° to 30.4°. τ_1 is generated by the intramolecular hydrogen bond O−H···O(H) whose O···O distances are given in Tables S5 and S6 in the Supporting Information. These vary in the narrow range of 2.67−2.75 Å while the host···guest H-bond distances O···N vary from 2.70 to 2.75 Å.

CONCLUSION

The six isomers of lutidine form inclusion compounds with the host **H1**, and competition experiments with equimolar pairs of lutidines show the preference for enclathration in the sequence 3,4-LUT > 2,6-LUT > 2,3-LUT > 2,5-LUT > 2,4-LUT ≈ 3,5-LUT.

The crystal structures yield stoichiometries which are in fair agreement with the ^{1}H NMR competition results, and these have been confirmed by the profiles of the TGA and DSC experiments. It is interesting that for any pair of lutidines in the competition experiments, the lutidine that is hydrogen bonded to the host is the one that is higher on the enclathration preference sequence given above.

The mixed host experiments were partly successful in that the combined **H1** + **H3** when exposed to the equimolar mixture of 2,4-LUT/3,5-LUT did result in **H1**·(3,5-LUT). In the case of the combined **H1** + **H2** dissolved in the equimolar 2,3-LUT/2,6-LUT, only **H2** was found in the crystal structure with an improved proportion of 2,3-LUT (^{1}H NMR and crystal structure of 75%). However, in neither case were both host compounds retained in the resulting crystal structures.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.cgd.8b00251.

Tables of hydrogen bonding, selectivity profiles of **H1** and **H2**, torsion angle and thermal analysis data. Figures of packing diagram and TGA/DSC profile (PDF)

Accession Codes

CCDC 1821311−1821320 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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SUPPLEMENTARY INFORMATION

Separation of lutidine isomers by selective enclathration

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1. Tables

Table S1: ^{1}H NMR results of the vapour competition experiment for pairs of lutidines.

	Liquid 25℃	Vapour 60℃	Vapour 80℃
2,6-LUT/3,4-LUT	2,6-45% 3,4-55%	2,6-58% 3,4-42%	2,6-54% 3,4-46%
2,3-LUT/2,6-LUT	2,3-44% 2,6-56%	2,3-41% 2,6-59%	2,3-40% 2,6-60%

Comparison of results of liquid pairs at 25℃ versus vapour pairs at 60℃ and 80℃.

Table S2: ^{1}H NMR results for host H2 selectivity on selected pairs of lutidines.

	2,3	2,4	2,6
2,3			
2,5	2,5		
2,6	2,3-77% 2,6-23%		
3,4			2,6-10% 3,4-90%
3,5		2,4-52% 3,5-48%	

Table S3: ^{1}H NMR results for host H3 selectivity on selected pairs of lutidines.

	2,3	2,4	2,6
2,3			
2,5			
2,6	2,3-74% 2,6-26%		
3,4			2,6-7% 3,4-93%
3,5		2,4-9.3%/ 3,5-90.7%/	

Table S4: Geometrical data of the hydrogen bonds.

	D•••H/Å	H•••A/Å	D•••A/Å	<(DHA)/°
H1•2(2,3-LUT)				
O13-H13...N51	0.96	1.78	2.722(3)	166
O34-H34...O13	0.92	1.81	2.671(3)	156
H1•(2,4-LUT)				
O13-H13...N51	1.11	1.65	2.754(3)	177.3
O34-H34...O13	1.02	1.73	2.713(2)	160.8
H1•2(2,6-LUT)				
O13-H13...N51	0.90	1.86	2.700(2)	155.6
O34-H34...O13	0.98	1.75	2.6872(17)	158.5
H1•2(3,4-LUT)				
O13-H13...N51	0.90	1.84	2.747(14)	174.3
O34-H34...O13	0.89	1.84	2.6963(12)	160.0
H1•(3,5-LUT)				
O13-H13...N51	1.01	1.7	2.708(3)	172.7
O34-H34...O13	1.01	1.83	2.755(3)	150.6

Table S5: Geometrical data of the hydrogen bonds.

	D•••H/Å	H•••A/Å	D•••A/Å	<(DHA)/°
H1•2(2,3-LUT/2,6-LUT)				
O13-H13...N51	0.82	1.92	2.697(10)	157
O34-H34...O13	0.88	1.86	2.684(9)	157
H1•2.5(2,4-LUT/2,5-LUT)				
O34AH34A...O13A	0.87	1.86	2.711(2)	164.9
O13AH13A...N51	0.95	1.79	2.734(3)	171.7
O34BH34B...O13B	0.94	1.80	2.715(2)	162.4
O13BH13B...N61	1.03	1.72	2.742(3)	176.4
H1•2(2,6-LUT/3,4-LUT)				
O13-H13...N51	0.88	1.87	2.701(2)	157
O34-H34...O13	0.97	1.79	2.676(2)	150
H2•2(2,3-LUT/2,6-LUT)				
O15-H15... N51	0.88	1.80	2.633(3)	156
O28-H28...O15	1.01	1.753	2.753(4)	167

Table S6: Thermal analysis data of selected pairs of lutidines complexes with host H1 and H2

	H1•1(2,4-LUT)/•1.5(2,5-LUT)	H1•2(2,4-LUT/3,5-LUT)	H1•2(2,6-LUT/3,4-LUT)	H2•2(2,3-LUT/2,6-LUT)
TGA calculated %mass loss	32.8	25.9	25.9	27.3
TGA experimental %mass loss	29.6	25.7	24.5	26.8
DSC exotherm (solvent 1) (T_{on}/K)	371.1	369.7	422.6	367.5
DSC exotherm (solvent 2) (T_{on}/K)	463.9	477.1	441.1	395.7

Table S7: Torsion angles.

	τ_1/°	τ_2/°	τ_3/°
H1•2(2,3-LUT)	-87.2	28.1	27.9
H1•2(2,4-LUT)	-96.0	23.4	21.3
H1•2(2,6-LUT)	91.7	-21.1	-30.4
H1•2(3,4-LUT)	-92.8	22.7	22.8
H1•(3,5-LUT)	82.5	-29.2	-24.8
H1•2(2,3-LUT/2,6-LUT)	90.8	-22.9	-30.4
H1•2.5(2,4-LUT/2,5-LUT)	A/-92.2 B/-91.5	A/28.7 B/29.6	A/21.1 B/24.0
H1•2(2,4-LUT/3,5-LUT)	-89.4	24.6	29.7
H1•2(2,6-LUT/3,4-LUT)	93.3	-67.9	-77.2

2. Figures

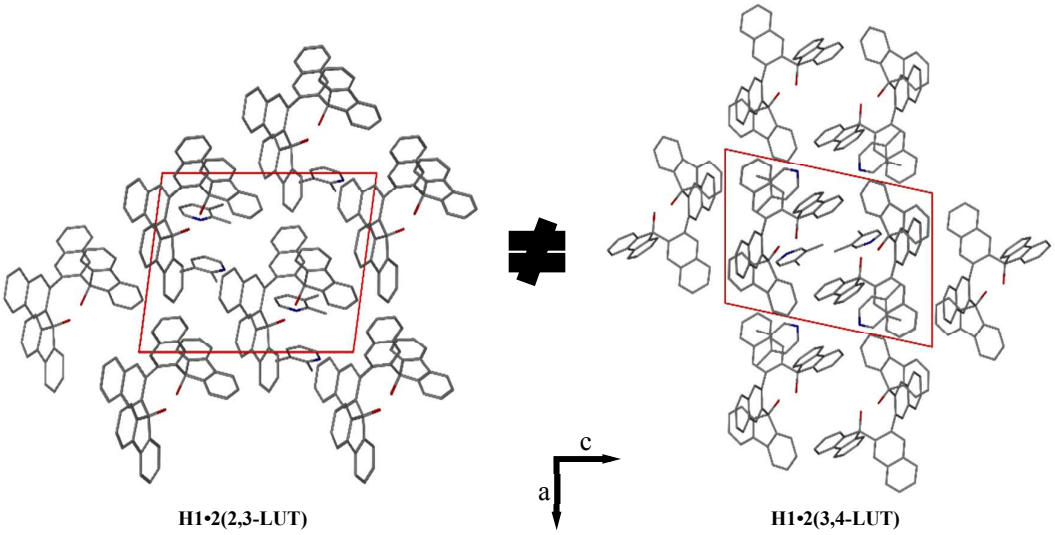

Figure S1: Packing diagram of H1•2(2,3-LUT) and H1•2(3,4-LUT).

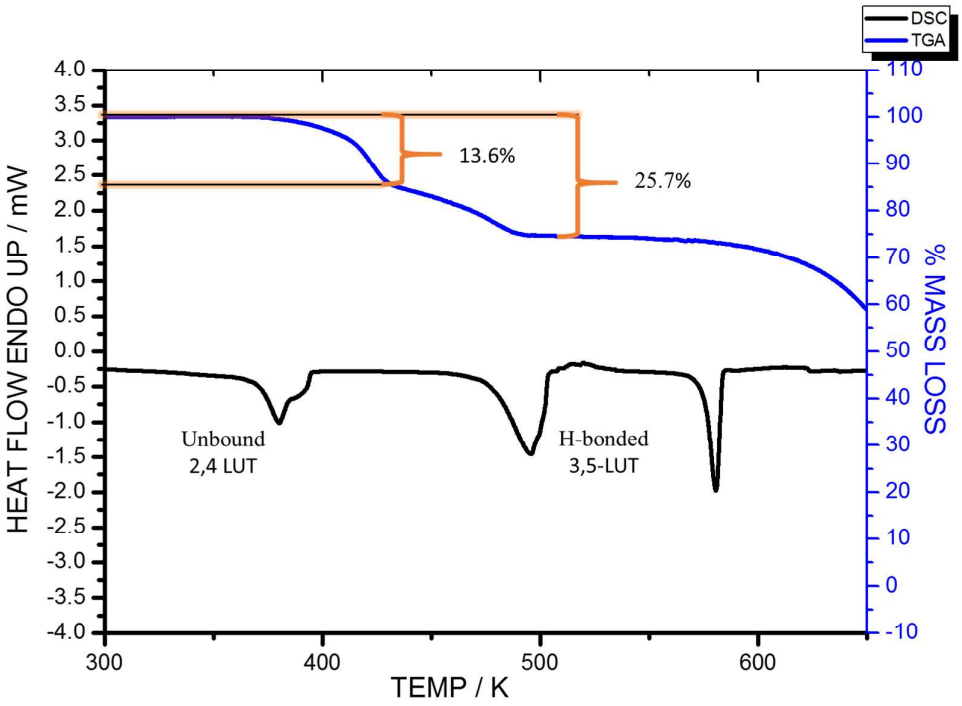

Figure S2: DSC and TGA profiles for H1•2(2,4-LUT/3,5-LUT).

Chapter 5.

Preferential enclathration of lutidine isomers by diol-hosts

5.1 Summary

Paper 3 continues the subject of lutidine separation. The difference is that the new hosts are built round biphenyl moieties. The five hosts all have different groups attached and this leads to surprisingly different results in the resulting separation outcomes. The choice and synthesis of hosts compound has a very important place in crystal engineering because it governs the outcome of crystallization. Crystallographers tend to look at characteristics as synthon that will be formed after interaction of the host and guest molecules. The rigidity of the host and its flexibility also direct its ability to bond with a series of guest compounds[1,2]. Additionally, the crowdedness of the host may also be an important character for its selection. The more crowded is a host compound, the more difficult it may be found to dissolve as well as give structures with no disordered molecules. In other terms, the structure would be quite difficult to solve which is a barrier in practical crystallography to get the best information possible on the molecular level.

A difficult procedure of the family resolution method is the choice of a host to improve the separation process. In this chapter, a focus is done over the hosts applied for separation and how to extend the backbone and still improve the selectivity. Therefore, the structure of the hosts varied from the addition of a methyl group, an electron-rich atom, by fixing the rigidity of the backbone or removing some component so it may move freely. These were the different aspects of crystal engineering that were dealt with in this chapter.

Chapter 3 is a continuation of chapter 1 focusing on the host compounds used for mimicking the "Dutch Resolution" method. A survey of the selectivity of host H1 was done over the series of pairs of lutidine isomers. During this survey, a competition experiment was carried out using ^{1}H NMR. The present analysis provided the selection of a pair of lutidine isomers where the H1 host did not present a high preference towards one guest. From this competition experiment, H1 was found to selectively enclathrate lutidine isomers as 3,4-LUT>2,4-LUT≈3,5-LUT>2,5-LUT>2,3-LUT>2,6-LUT. Thermal analysis of the single guest compounds with H1 resulted in the Tpeak-Tbp. This was used to confirm that the selectivity preference of the host depended strength of the interaction between guest and host.

After the competition experiment, four pairwise mixtures of the isomers were selected to further explore selectivity. To these pairs, a screening of host compounds was done to see eventually which of the host would also show a lower selectivity. H2 host presented a low

selectivity toward 2,4-LUT/3,5-LUT, and was taken for further analysis. During this step, the percentage of H1: H2 was then evaluated to see if by increasing or decreasing one of the hosts, a better selectivity would be found toward one of the guests. Eventually, the selectivity was in the advantage of host H2. To understand better the characteristics of the host compounds which showed a particular selectivity toward one guest, each of the different hosts was crystallized with either 2,4-lutidine or 3,5-lutidine. It was found that 2,4-lutidine was preferentially selected by H3 and H4 while 3,5-lutidine was preferred by H2 and H5. H3 and H4 presented lower flexibility compare to H2 and H5 since these hosts presented a much higher $\boldsymbol{\tau}1$ and $\boldsymbol{\tau}3$. Additionally, the preference toward 2,4-lutidine and 3,5-lutidine by a given host was then attributed to the different groups bonded to the central biphenyl moiety.

5.2 References:

(1) Weber, E. Molecular Inclusion and Molecular Recognition - Clathrates I; Springer-Verlag: Berlin-Heidelberg, 1987.

(2) Bishop, R. Designing New Lattice Inclusion Hosts. *Chem. Soc. Rev.* **1996**, *25* (5), 311-319.

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Preferential enclathration of lutidine isomers by diol-hosts

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ABSTRACT

The Host compound 2,2′ bis(1-hydroxy-4,5-dihydro-2,3:6,7-dibenzocycloheptatrien-1-yl)-biphenyl, H1, has been employed to discriminate between all the pairs of lutidine isomers. The preference for guest enclathration follows the sequence 3,4-LUT>2,4-LUT ≈ 3,5-LUT>2,5-LUT>2,3-LUT>2,6-LUT. This has been confirmed by guest-release endotherms measured by DSC. Four other diol host compounds, H2–H5, were tested on pairs of lutidine isomers which were poorly separated by H1.

1. Introduction

The separation of a given component from a mixture depends on the physico-chemico properties of its individual compounds. The various common techniques exploit the different properties in the single compounds, such as vapor pressure, solubility, density, dipole moment, boiling point and melting point. Common techniques of separation include fractional distillation, crystallization, liquid-liquid extraction and various form of chromatography.

In the case of liquid isomers, however, their macro-properties are often similar, rendering these techniques generally inefficient. In such cases the process of enclathration by a suitable host compound is a useful technique. This method of separation has been employed to differentiate a wide selection of mixtures, one of the most challenging being the C8 hydrocarbons: ortho-, meta- and para-xylenes and ethyl benzenes whose boiling points vary from 136.2 to 144.4 °C. This process has been reviewed, and focusses on metal-organic frameworks, organic diol-host molecules [1–3] and various Werner clathrate hosts [4,5]. Enclathration has also been employed to separate a variety of gases, such as ethylene from other hydrocarbons by employing hydroquinone [6], and entrapping the greenhouse gas CHF_3 by the formation of gas hydrates [7].

Recently, substituted piperidines have been separated using fluorenol host molecules, the crystal packing analyzed and confirmed by thermal results [8]. The question of co-operative Host-Guest recognition and the resulting structural implications have been studied by employing guanidinium and biphenylsulfonate, which enclathrate a variety of substituted benzene guests [9]. In this work, we present the results of the separation of lutidine isomers by different diol host compounds and report the results of the selectivity of the enclathration results with the lutidine isomers exposed as equimolar pairs to the host compounds. We also used known mixtures of similar host compounds in order to test changes in selectivity. This is in analogy with the Dutch method of chiral resolution of racemic modifications, in which a family of similar resolving agents has been shown to improve the separation of enantiomers. This is particularly useful in the pharmaceutical industry, where only one particular enantiomer of an Active Pharmaceutical Ingredient (API) may be required [10].

Selectivity in host-guest chemistry is dependent on the phenomenon of molecular recognition, that relies on the sum of secondary interactions occurring between the molecules in the crystal structure. There are a number of methods which may be employed to analyze the interactions which impinge on the host-guest assembly. These include competition experiments, packing coefficients, thermal methods, Hirshfield surface analysis, lattice energies and solubility measurements. These have been used in this work to understand the preferential sequence for the individual isomers by a given host compound. The structural formulae of the host and guests are given in Scheme 1.

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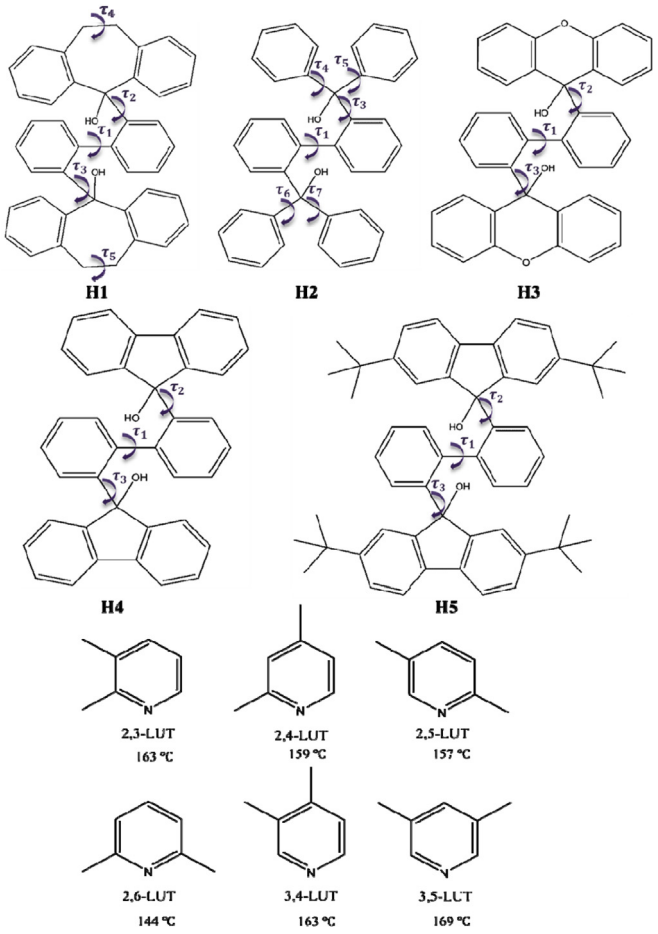

Scheme 1. The structural formulae of host and guest molecules employed.

2. Experimental

2.1. Competition experiments

The competition experiments were carried out by exposing an equimolar mixture of a pair of lutidine guests (800 mg) to 50 mg of host compound, adding 400 mg of chloroform as cosolvent, dissolving by gentle warming and allowing crystallization by slow evaporation. The resulting crystals were recovered, blotted dry and subjected to NMR, PXRD (Cu Kα radiation, λ = 1.542 Å) and thermal analysis. The results are presented in Table 1. When the proportion of the majority guest was >80%, it was regarded as 'highly selected' and their crystal structures were not elucidated.

2.2. Materials

The host compounds, H1 [11], H2 [12], H3 [11], H4 [13] and H5 [14] were synthesized by Weber and were used without further purification.

H1. 2,2′-bis(5-hydroxydibenzosuberan-5-yl)biphenyl

H2. 2,2'-bis(diphenylhydroxymethyl)biphenyl

H3. 2,2'-bis(9-hydroxy-9*H*-xanthen-9-yl)biphenyl

H4. 2,2'-bis(9-hydroxyfluoren-9-yl)biphenyl

H5. 2,2'-bis(2,7-di-*tert*-butyl-9-hydroxyfluren-9-yl)biphenyl

The lutidine guest compounds were all purchased from Sigma Aldrich and used as received. Single crystals of the inclusion compounds were obtained by dissolving the particular host or mixture of hosts in an excess of the relevant guest or binary guest mixture. The resulting solutions were allowed to crystallize by slow evaporation at room temperature. Some solutions were filtered when necessary.

2.3. X-ray crystallography

Single crystals were selected using optical microscopy under plane polarized light and the intensity data were recorded on a Bruker DUO APEX II diffractometer for all structures using Mo Kα (λ = 0.71073 Å) at a temperature of 153 K [15]. The intensity data were collected using the phi scan and omega scan techniques, scaled and reduced with SAINT-Plus [16]. The correction of the collected intensities for absorption was done using the SADABS program [17].

The structures were solved by direct methods using SHELX-97 [17] and refined using full-matrix least squares methods in SHELXL [17]. The graphical interface used was the program X-SEED [18]. Diagrams were generated using MERCURY (3.5) [19].

2.4. Thermal analysis

Thermogravimetric analysis (TGA) was performed using a TA-Q500 thermogravimetric analyzer. Results were analyzed using Universal Analysis 2000 software. The samples were crushed and blotted dry (3–6 mg) and weighed directly into open aluminum oxide TGA crucibles. Differential scanning calorimetry (DSC) was performed using a TA Instruments DSC-Q200. Crushed and dried samples (1–3 mg) were weighed directly into vented aluminum pans on an analytical balance.

2.5. Nuclear magnetic resonance (NMR) spectroscopy

Approximately 5 mg of representative samples of crystals were blotted dry, crushed and dissolved in 600 μL of $CDCl_3$ and introduced into a 5 mm NMR tube for data acquisition. 1D ^1H and 2D HSQC NMR spectra were recorded on a Bruker 300 or 400 MHz spectrometer at 303 K and processed using standard Bruker software (Topspin 3.5). The HSQC experiment was optimized for $J = 145$ Hz (for directly attached ^1H-^{13}C correlations). The spectra were referenced relative to the solvent signal at 7.26 ppm (for ^1H) and 77.16 ppm (for ^{13}C); appropriate signals were integrated to determine the relative proportions of the guests.

The analysis was carried out on the crystals harvested from the mother liquors of the equimolar lutidine binary mixtures. These crystals were dried using blotting paper but were not washed with any solvent to avoid any exchange of guests. In some cases this gave small inaccuracies in the ^1H NMR results arising from residual lutidine present at the crystal surface which were not found in the crystal structures.

Integration of the peaks of the methyl substituents of the isomers were used to determine their relative proportions of guests in the different samples. Fig. 1 shows an overlay of the expansion of the methyl region of the ^1H NMR spectra of the guests (2,4-LUT and 3,5-LUT) and the host and guests. Fig. 1a has CH_3-2 at 2.53 ppm and CH_3-4 at 2.32 ppm for 2,4 LUT and Fig. 1b has CH_3-3 and CH_3-5 at 2.30 ppm. These diagnostic peaks were used to determine the relative ratio of 52/48% for the 2,4-LUT/3,5-LUT guests in the host-guests mixture (Fig. 1c). The same procedure was applied to all

Table 1
Results of the competition experiment with equimolar pairs of lutidine guests. Experiment number [ ], NMR and structures.

LUT	2,3	2,4	2,5	2,6	3,4	3,5
2,4	[1] NMR 2,4 STRUCT. No suitable crystals					
2,5	[2] NMR 2,5 STRUCT. No suitable crystals	[3] NMR 2,4–66% 2,5–34% STRUCT. No suitable crystals				
2,6	[4] NMR 2,3–77% 2,6–23% STRUCT. 2,3/2,6	[5] NMR 2,4–74% 2,6–26% STRUCT. 2,6	[6] NMR 2,5–79% 2,6–21% STRUCT. No suitable crystals			
3,4	[7] NMR 2,3–27% 3,4–73% STRUCT. 2,3/3,4	[8] NMR 2,4-4% 3,4–93% STRUCT. No suitable crystals	[9] NMR 2,5–12% 3,4–88% STRUCT. 3,4	[10] NMR 2,6–8% 3,4–92% STRUCT. 3,4		
3,5	[11] NMR 2,3–10% 3,5–90% STRUCT. 3,5	[12] NMR 2,4–52% 3,5–48% STRUCT. 2,4/3,5	[13] NMR 2,5–29% 3,5–71% STRUCT. 2,5/3,5	[14] NMR 3,5 STRUCT. 3,5	[15] NMR 3,4–91% 3,5–9% STRUCT. 3,4	

other mixtures and gave the results shown in Table 1. When two isomers had overlapping methyl peaks in the ^{1}H spectrum, but the ^{13}C NMR signals were resolved, then quantification was performed by integration of the relevant HSQC cross peaks. Thus NMR analysis elucidated the relative ratio of the guests, whereas the percentage host-host and host-guest was also obtained when mixed hosts method was used.

3. Results

3.1. Competition experiments of pairs of lutidine with H1

The competition experiments with equimolar pairs of lutidine guests are summarized in Table 1.

No crystals were obtained for Expt. 1–3 and 8, however, for Expt. 4, the NMR result yielded 2,3-LUT (77%) and 2,6-LUT (23%). The

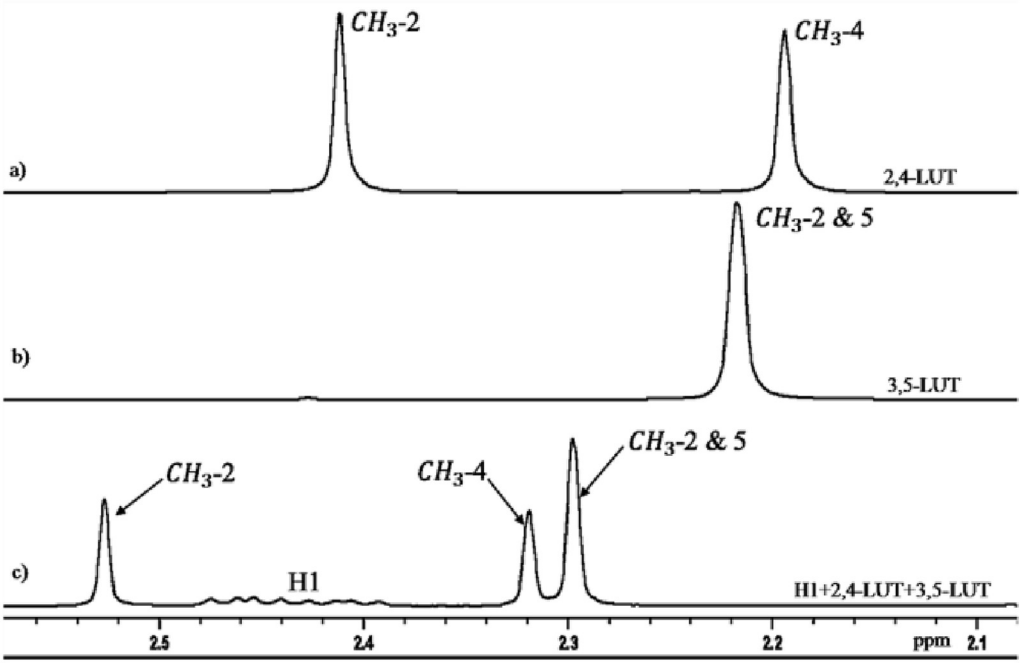

Fig. 1. Overlay of the expansion of the ^{1}H NMR methyl region of H1+2,4-LUT+3,5-LUT.

structure of the compound as well as its thermal analysis has been previously reported [20].

The structure analysis for Expt. 5 showed the presence of 2,4-LUT, although NMR gave 2,4-LUT (74%) and 2,6-LUT (26%). Solubility analysis measurements were carried out with H1 in both 2,4-LUT and with 2,6-LUT. These showed that H1 was 14 times more soluble in 2,6-LUT compound than in 2,4-LUT. We surmise that the H1•2,4-LUT compound was the first to crystallize in the mother liquor and a crystal of this was used for data collection.

For Expt. 7, NMR gave 3,4-LUT (73%) and 2,3-LUT (27%). The structure crystallizes in $P2_1/c$ with Z = 4. The asymmetric unit is shown in Fig. 2 which displays the host H1 intra-molecular O-H···O(H) and the (H1)O-H···N (3,4-LUT) hydrogen bonds. The other lutidine guest is disordered and was located on a center of inversion at Wyckoff position d. The two N atoms were assigned position site occupancies of 0.405 and 0.0905, this agrees with the NMR and the TG results.

The thermal analysis result is presented in Fig. 3. The TG shows that the two guests are lost in a single step measured as 22.1% mass loss (calc. 22.0%), and the DSC displays a broad endotherm peaking at 184.3 °C, with a sharp endotherm peaking at 308.2 °C due to the melting of the apohost.

Expt. 12: the NMR yielded 2,4-LUT (52%) and 3,5-LUT (48%), therefore H1 had practically no discrimination.

Expt. 13: the NMR afforded 2,5-LUT (29%) and 3,5-LUT (71%), which were employed as the site occupancies of the two guests in the structure. The space group is $P2_1/c$, with Z = 4, with the disordered guests lying on the same site. Both N atoms were found to act as acceptors of the (Host)O15-H···N15 (lutidine) hydrogen bond. The TG shows that the two lutidines are desorbed in a single step (experimental mass loss 15.9%, calc. 15.8%). The DSC displays a broad endotherm, T_{peak} = 168.3 °C and the host melting endotherm has T_{peak} = 307.8 °C. These data have been deposited in the supplementary data.

3.2. Single guest inclusion compounds

The structures with a single guest were obtained either from the competition experiments or by crystallization of H1 from the solution of the appropriate guest with chloroform. These were employed for the calculation of packing coefficients (PCs) and thermal analysis. The H1•1 (3,5-LUT) structure was obtained from the equimolar mixture of 2,6-LUT and 3,5-LUT in Expt. 14. This compound crystallizes in $P2_1/c$ with Z = 4 and the asymmetric unit displays the usual host intramolecular O-H···O(H) hydrogen bond and the (Host)O-H···N (3,5-LUT) interaction.

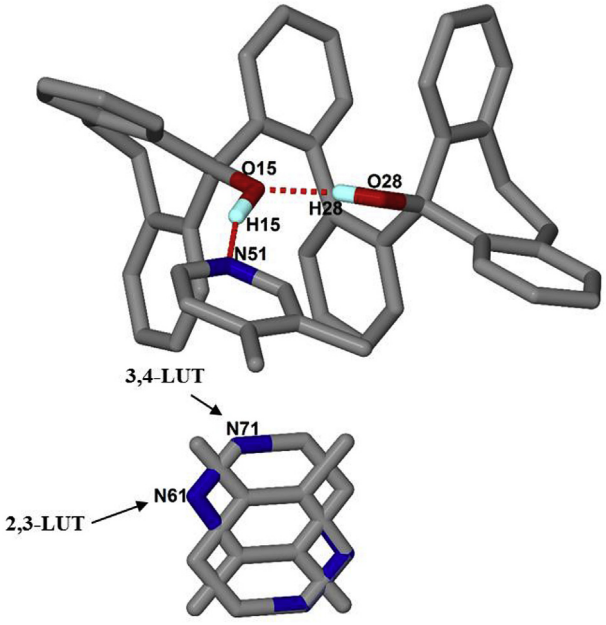

Fig. 2. Asymmetric unit of H1•1,5(2,3-LUT/3,4-LUT).

The H1•1.5 (3,4-LUT) structure, crystallizes in $P2_1/c$ with Z = 4, was obtained from Expt. 15, exhibits the expected intramolecular O-H···O(H) and the (Host)O-H···N (3,4-LUT) hydrogen bond but in addition contains a disordered 3,4-LUT guest, located on a center of inversion at Wykoff position a. This is shown in Fig. 4.

The H1•2 (2,3-LUT), obtained by dissolution of H1 in the pure guest, crystallizes in *P*-1, Z = 2. The Host:Guest ratio is 1:2 and only one 2,3-LUT molecule is hydrogen-bonded to the host.

The H1•2 (2,6-LUT) structure, obtained by direct crystallization of H1 in 2,6-LUT and crystallizes in *P*-1 with Z = 2, has a H:G ratio of 1:2. The asymmetric unit shows one 2,6-LUT molecule to be H-bonded to H1, while the second 2,6-LUT molecule is disordered over two different centers of inversion at Wykoff positions b and h. This is shown in Fig. S1 of the supplementary data. No structure comprising only 2,5-LUT as guest was elucidated as no suitable crystals could be grown under the same conditions as the ones that were reported in this paper.

Analysis of the competition experiment, given in Table 1, yields the following guest preference for enclathration by H1:

3,4-LUT>2,4-LUT ≈ 3,5-LUT>2,5-LUT>2,3-LUT>2,6-LUT

The DSC results of H1 with each of the six single guests were obtained and are given in Table 2. The guest release reactions yielded broad endotherms and the T_{peak} temperatures were recorded in preference to the T_{on} (onset) temperatures. When the Host:Guest ratio was 1:2, this corresponded to a first endotherm associated with the lutidine which was not H-bonded to the host, and the second endotherm which was bonded via the (Host) —O—H•••N (LUT) H-bond. The latter endotherm T_{peak} (endo2) were compared for each guest, and their T_{peak}-T_{bp} were recorded. These varied from +27 °C to −25 °C and follow the same preference sequence given by the competition experiments, a satisfying result.

In addition to competition experiment and thermal analyses (DSC), we also explored the Packing Coefficient (PC) of various structures as a measure of the degree of efficiency of packing. The packing coefficient, as defined by Kitaigoroskii [21], is the ratio of the volume of the atoms/volume of the unit cell. This was computed using the program Platon [22], which does not allow any disorder in the structure. We applied this to three structures with a single guest, viz H1•2,4-LUT (PC = 69.2%), H1•3,5-LUT (PC = 68.0%) and H1•2,3-LUT (PC = 68.5%), these results were too close to be useful for predicting selectivity.

No attempt was made to compute lattice energies, because these are strongly dependent on the position of the H atoms, and on the advice of Professor Sally price [23] we were advised that H positions from laboratory diffractometers data were insufficiently accurate for such calculations.

3.3. Screening of hosts H2, H3, H4, H5 for selectivity of various lutidine pairs

In order to improve the selectivity of 2,4-LUT/3,5LUT in which the NMR results in Expt. 12 were equimolar, we used pairs of host compounds. This approach is by analogy with the Dutch resolution method in which two or more resolving agents are exposed simultaneously to a target racemate in order to improve its

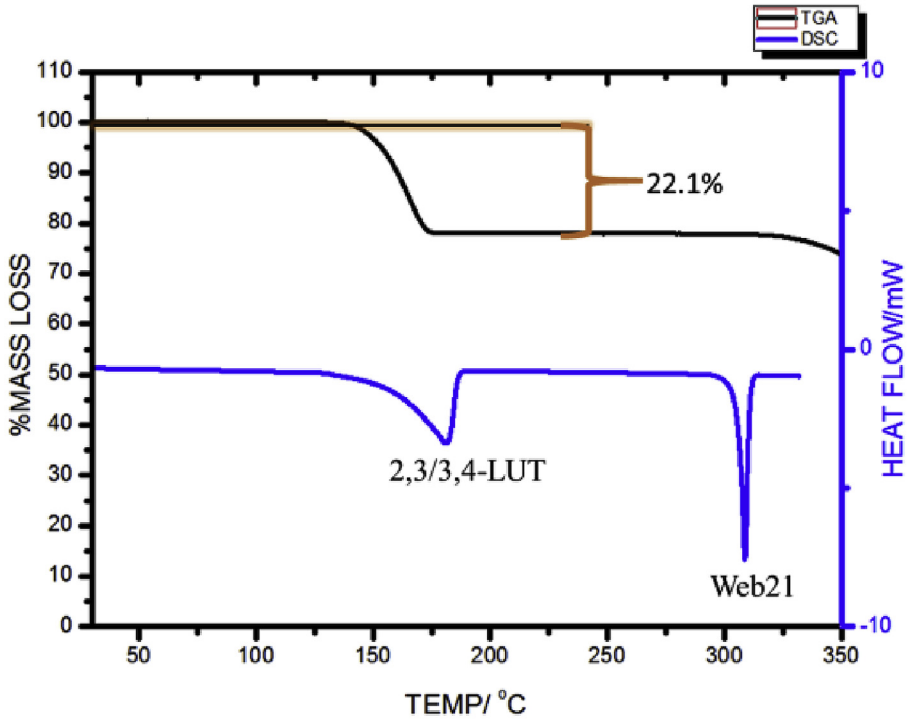

Fig. 3. DSC and TGA profiles for H1•1.5(2,3-LUT/3,4-LUT).

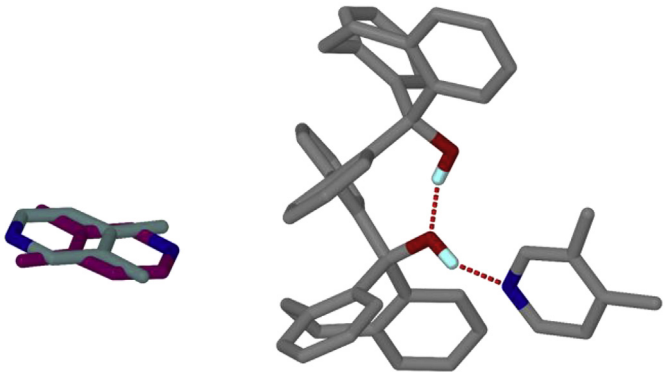

Fig. 4. Asymmetric unit of H1•1,5(3,4-LUT) with a disordered 3,4-LUT on the center of inversion at Wykoff position a.

resolution to individual enantiomers. This method has shown that the separation achieved is better than that achieved with individual compounds [10].

The second host compound, H2 was chosen after screening the host compounds H2, H3, H4 and H5 with pairs of lutidine guests 2,3-LUT/2,6-LUT; 2,3-LUT/3,4-LUT; 2,4-LUT/2,6-LUT; 2,4-LUT/3,5-LUT. These guest pairs were chosen because they yielded low selectivity with H1. The results, given in Table 3, proved disappointing in that they either yielded no crystals or showed that H3, H4 and H5 to be highly selective.

The only useful host for the Dutch method was H2 which afforded 2,4-LUT (25%)/3,5-LUT (75%). The pair of hosts H1+H2, were then exposed in varying proportions to the equimolar mixtures of 2,4-LUT and 3,5-LUT. The results are given in Table 4.

This result was unsatisfactory, in that no significant change in selectivity was observed for the H1/H2 mixtures.

However, it is noteworthy that for the host mixtures H1(25%)/H2 (75%) two kinds of crystals were observed in the mother liquor (needles and blocks). Samples of these were separated under the microscope and both structures were elucidated. The H1•2,4-LUT•3,5-LUT compound crystallizes in *P*-1 with Z = 2 and H:G ratio of 1:2. The asymmetric unit is shown in Fig. 5 which displays the intramolecular (Host)—O—H•••O(H) and the (H1)O-H···N (2,4-LUT).

The second set of crystals from this batch, H2•1 (2,4-LUT) crystallized in $P2_1/n$ with Z = 4 and a H:G ratio of 1:1. Fig. 6 shows its asymmetric unit.

3.4. Selectivity preference of hosts H2 to H5 towards 2,4-LUT and 3,5-LUT

The crystal structures of the inclusion compounds derived from H2, H3, H4 and H5 with either 2,4-LUT or 3,5-LUT were elucidated

Table 2
DSC results showing the T_{peak} values of the guest-release endotherms and the T_{peak}-T_{bp} results.

	H1•1,5(3,4-LUT)	H1•1(2,4-LUT)	H1•1(3,5-LUT)	H1•(2,5-LUT)	H1•2(2,3-LUT)	H1•2(2,6-LUT)
H:G	1:1.5	1:1	1:1	No suitable crystals	1:2	1:2
$T_{peak/endo1}$/°C	broad peak	–	-	–	105.4	72.8
$T_{peak/endo2}$/°C	189.92	169.94	170.18	157.5	143.86	118.47
T_{peak}-T_{bp}/°C	+27	+11	+1	0	−19	−25
T_{melt}/°C	308.2	306.6	309.4	295.9	302.8	309.1

Table 3
Screening of hosts H2 to H5 for selectivity of chosen lutidine pairs' NMR content.

Composition	H1	H2	H3	H4	H5
2.3 + 2.6	[4]	[16]	[20]	[24]	*[28]*
	2,3-LUT-77%	2,3-LUT-0%	2,3-LUT-15%	2,3-LUT-89%	2,3-LUT-95%
	2,6-LUT- 23%	2,6-LUT-100%	2,6-LUT- 85%	2,6-LUT-11%	2,6-LUT-5%
2.3 + 3.4	[7]	[17]	[21]	*[25]*	*[29]*
	2,3-LUT-27%	2,3-LUT-10%	2,3-LUT-15%	2,3-LUT-82%	2,3-LUT-%
	3,4-LUT-73%	3,4-LUT-90%	3,4-LUT-85%	3,4-LUT-18%	3,4-LUT-%
2.4 + 2.6	[5]	[18]	[22]	*[26]*	*[30]*
	2,4-LUT-74%	2,4-LUT-98%	2,4-LUT-12%	2,4-LUT-96%	2,4-LUT-%
	2,6-LUT-26%	2,6-LUT-2%	2,6-LUT-88%	2,6-LUT-4%	2,6-LUT-%
2.4 + 3.5	[12]	[19]	[23]	*[27]*	*[31]*
	2,4-LUT-52%	2,4-LUT-25%	2,4-LUT-91%	2,4-LUT-91%	2,4-LUT-16%
	3,5-LUT-48%	3,5-LUT-75%	3,5-LUT-9%	3,5-LUT-9%	3,5-LUT-84%

Table 4
Selectivity towards 2,4-LUT/3,5-LUT in a mixture of hosts H1 and H2.

H1%	H2%	%Host content NMR	%Guest content NMR 2,4-LUT/3,5-LUT
100	0	H1 only	52/48
75	25	H1 only	45/55
50	50	H1 only	55/45
25	75	H1+H2 (50/50)	55/45
0	100	H2 only	25/75

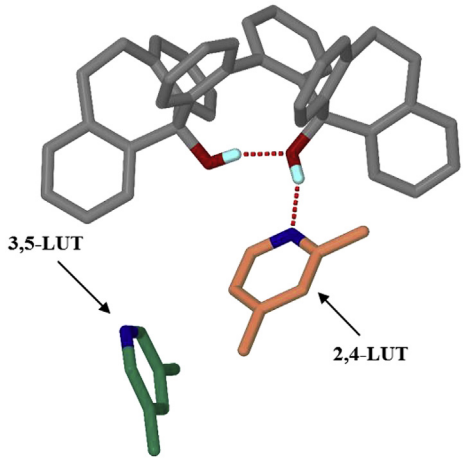

Fig. 5. Asymmetric unit of H1C1(2,4-LUT)1(3,5-LUT).

in order to understand the selectivity obtained from the NMR results. The H2•1 (2,4-LUT) structure was described above and the H2•2 (3,5-LUT) crystallizes in *P*-1 with Z = 2 and the H:G ratio of 1:2. The DSC traces of these two compounds gave T_{peak}-T_{bp} of −13 °C and −18 °C, showing that these guests were weakly enclathrated.

Expt. 23 afforded H3•1 (2,4-LUT) which crystallized in $P2_1/n$ with Z = 4. This structure is isomorphous with H3•1 (3,5-LUT) the cell metrics of which are from Table 5. The projection of these two structures, viewed along [100], from which the lutidine have been omitted, is shown in Fig. 7.

The packing coefficient (PC) for the H3•1 (2,4-LUT) structure is 68.7%, while for the H3•1 (3,5-LUT) it is 68.6%. These are not significantly different. However the DSC results yielded T_{peak}-T_{bp} as +15 °C for H3•1 (2,4-LUT) and −32 °C for the H3•1 (3,5-LUT) structures, confirming the result (Table 3) of the competition experiment.

Expt. 23 (Table 3) shows that H3 prefers 2,4-LUT (91%) over 3,5-LUT (9%). The solubility of H3 in these two guests is similar (15 mg per gram of 2,4-LUT/16 mg/g of 3,5-LUT).

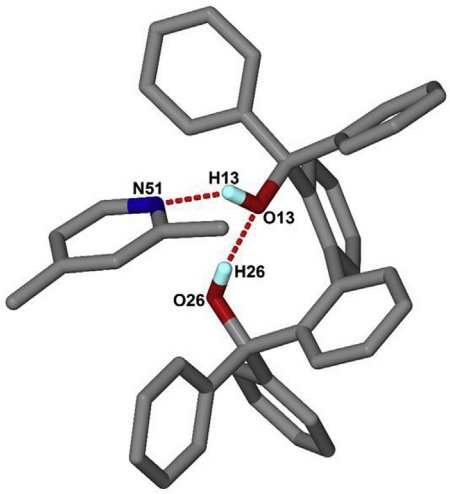

Fig. 6. Asymmetric unit of H2•1(2,4-LUT).

Expt. 27 showed that H4 preferred 2,4-LUT (91%)/3,5-LUT (9%). The structure H4•1 (2,4-LUT) crystallizes in $P2_1/n$ with Z = 4. The asymmetric unit follows the usual motif with the intramolecular (Host)—O—H•••O(H) hydrogen band and the (H1)O-H···N (2,4-LUT) hydrogen bond. H4•1 (3,5-LUT) structure follows the same pattern. The PC is 68.1 for the 2,4-LUT structure and 66.4 for the 3,5-LUT structure. The DSC result gave T_{peak}-T_{bp} of +32 °C for 2,4-LUT compared to +25 °C for the 3,5-LUT structure, in agreement with the competition experiment.

Expt. 31 shows that H5 prefers 3,5-LUT (84%) over 2,4-LUT (16%). The structure of H5•1.5 (3,5-LUT) crystallizes in $P2_1/c$ with Z = 8. The asymmetric unit comprises two hosts molecules and three 3,5-LUT guest, one of which is disordered over two positions. In the host molecules, some of the tertiary butyl moieties are disordered and were treated accordingly.

The H5•1.25 (3,5-LUT) structure crystallizes in *P*-1. The asymmetric unit comprises two host molecules. One 2,4-LUT is ordered, a second one is disordered with the 2-methyl moieties disordered and a third lutidine located near a center of inversion and thus disordered. The overall H:G ratio is therefore 1:1.25. The asymmetric unit is shown in Fig. 8.

3.5. Conformation of the host compounds

In Scheme 1, each host shows the torsion angles that were measured and the intramolecular hydrogen bond that is the major factor that locks the hosts in similar conformations. These have

Table 5a
Crystallographic data parameters of the Host-Guest complexes of single guest inclusion compounds of H1.

Structures	H1•2 (2,3-LUT)	H1•1 (2,4-LUT)	H1•2 (2,6-LUT)	H1•1.5 (3,4-LUT)	H1•1 (3,5-LUT)
H:G_{tot} Ratio	1:2	1:1	1:2	1:1.5	1:1
Empirical formula	$C_{56}H_{52}N_2O_2$	$C_{49}H_{43}NO_2$	$C_{56}H_{52}N_2O_2$	$C_{52.50}H_{47.50}N_{1.50}O_2$	$C_{49}H_{43}NO_2$
M [g mol^{-1}]	785.00	677.84	785.00	731.42	677.84
Data collection temp T [K]	173 (2)	133 (2)	173 (2)	173 (2)	173 (2)
Crystal system	triclinic	triclinic	triclinic	monoclinic	triclinic
Space group	*P*-1	*P*-1	*P*-1	$P2_1/c$	*P*-1
a [Å]	8.5827 (6),	8.554 (4)	8.722 (3)	15.5310 (10)	21.1016 (18)
b [Å]	10.9895 (9)	10.671 (4)	10.752 (3)	14.4810 (9)	8.9161 (8)
c [Å]	23.5374 (19)	20.818 (9)	24.035 (8)	17.5807 (12)	20.8181 (19)
α [°]	85.696 (2)	77.071 (8)	79.794 (6)	90.00	90.00
β [°]	89.987 (2)	86.601 (9)	83.073 (5)	96.715 (2)	112.433 (2)
γ [°]	72.489 (2)	73.861 (8)	75.024 (5)	90.00	90.00
Volume [Å^3]	2110.6 (3)	1779.2 (13)	2136.3 (12)	3926.9 (4)	3620.4 (6)
Z	2	2	2	4	4
D_c, Calc. density [g cm^{-3}]	1.235	1.265	1.206	1.237	1.244
Absorption coefficient [mm^{-1}]	0.074	0.076	0.073	0.074	0.075
F(000)	836	720	818	1556	1440
***θ* range**	1.74–27.93	2.01–25.15	1.73–25.07	1.320–28.305	1.04–28.74
Reflections collected	23866	10992	11486	53109	56337
No. data I > 2sigma (I)	7126	2765	2980	6890	11301
Final R indices [I > 2sigma (I)]	$R_1 = 0.0537$ w$R_2 = 0.1251$	$R_1 = 0.0696$ w$R_2 = 0.1236$	$R_1 = 0.0882$ w$R_2 = 0.1942$	$R_1 = 0.0486$ w$R_2 = 0.1103$	$R_1 = 0.0523$ w$R_2 = 0.1095$
***R* indices (all data)**	$R_1 = 0.0818$ w$R_2 = 0.1408$	$R_1 = 0.1856$ w$R_2 = 0.1658$	$R_1 = 0.2281$ w$R_2 = 0.2618$	$R_1 = 0.0769$ w$R_2 = 0.1276$	$R_1 = 0.0909$ w$R_2 = 0.1289$

Table 5b
Crystallographic data parameters of the Host-Guest complexes of mixed-guest inclusion compounds of H1.

Structure	H1 • 1 (2,5-LUT/3,5-LUT)	H1•1(2,4-LUT)•1(3,5-LUT)	H1•1.5 (2,3-LUT/3,4-LUT)
H:G_{tot} Ratio	1:1	1:2	1:1.5
Empirical formula	$C_{49}H_{43}NO_2$	$C_{56}H_{52}N_2O_2$	$C_{53.5}H_{47.5}N_{1.5}O_2$
M [g mol^{-1}]	677.84	785.00	743.98
Data collection temp T [K]	173 (2)	173 (2)	173 (2)
Crystal system	monoclinic	triclinic	monoclinic
Space group	$P2_1/c$	*P*-1	$P2_1/c$
a [Å]	20.7725 (11)	8.5894 (10)	15.5415 (14)
b [Å]	8.8467 (5)	10.7839 (12)	14.3769 (12)
c [Å]	21.1937 (11)	23.947 (3)	17.6006 (16)
α [°]	90	84.484 (2)	90
β [°]	111.9450 (10)	88.416 (3)	96.529 (2)
γ [°]	90	72.484 (2)	90
Volume [Å^3]	3612.5 (3)	2105.5 (4)	3907.1 (6)
Z	4	2	4
D_c, Calc. density [g cm^{-3}]	1.246	1.238	1.265
Absorption coefficient [mm^{-1}]	0.075	0.074	0.076
F(000)	1440	836	1582
θ range		1.99–28.35	1.319–28.366
Reflections collected	28871	25657	49574
No. data I > 2sigma (I)	5692	6942	6628
Final R indices [I > 2sigma (I)]	$R_1 = 0.0497$ w$R_2 = 0.1365$	$R_1 = 0.0548$ w$R_2 = 0.1188$	$R_1 = 0.0639$ w$R_2 = 0.1704$
***R* indices (all data)**	$R_1 = 0.0847$ w$R_2 = 0.1632$	$R_1 = 0.0924$ w$R_2 = 0.1371$	$R_1 = 0.0965$ w$R_2 = 0.1950$

been deposited as Table S3 in the supplementary data.

This table shows that the intramolecular H-bond measured as the O···O distance, is remarkably consistent, ranging from 2.63 Å to 2.81 Å, this locks all the host molecules into a similar conformation as shown by the central biphenyl bond torsion angle, which varies from +88.2° to +102.0°. The preference for 2,4-LUT or 3,5-LUT by a given host may be attributed to the different groups bonded to the central biphenyl moiety. These different conformations are reflected in the values of the torsion angles τ_2 and τ_3. For H1 these range from +67.2° to +78.8°. These high values arise from the $-CH_2-CH_2-$ bridge joining the phenyl groups.

The conformational flexibility of phenyl groups is a factor governing the selectivity of guest compounds. This has been demonstrated in the selective properties of Werner clathrates, where a central transition-metal atom is bonded to four substituted pyridines [24].

2,4-LUT is preferentially selected by H3 and H4 the hosts with the least flexibility which display lower values of τ_1 and τ_3 (average ≈ 17°), while 3,5-LUT is preferred by H2 and H5. H2 is characterized by unbridged phenyl moieties while H5 has bulky *tert*-butyl groups which change the range of host … guest non-bonded contacts.

4. Conclusion

The six isomers of lutidine were selectively enclathrated by the

Table 5c
Crystallographic data parameters of the Host-Guest complexes of single-guest inclusion compounds for Hosts H2, H3, H4 and H5.

Structure	H2 • 1 (2,4-LUT)	H2•2 (3,5-LUT)	H3•1 (2,4-LUT)	H3•1 (3,5-LUT)	H4 • 1 (2,4-LUT)	H4•1 (3,5-LUT)	H5•1.25 (2,4-LUT)	H5• 1.5 (3,5-LUT)
$H:G_{tot}$ Ratio	1:1	1:2	1:1	1:1	1:1	1:1	1:1.25	1:1.5
Empirical formula	$C_{45}H_{39}NO_2$	$C_{52}H_{48}N_2O_2$	$C_{45}H_{35}N_1O_4$	$C_{45}H_{35}N_1O_4$	$C_{45}H_{35}NO_2$	$C_{45}H_{35}NO_2$	$C_{62.75}H_{69.25}N_{1.25}O_2$	$C_{64.50}H_{71.50}N_{1.50}O_2$
M [g mol^{-1}]	625.77	732.92	653.78	653.78	621.74	621.74	871.75	899.73
Data collection temp T [K]	173 (2)	173 (2)K	173 (2)	173 (2)	173 (2)	173 (2)	173 (2)	173 (2)
Crystal system	monoclinic	triclinic	monoclinic	monoclinic	monoclinic	monoclinic	triclinic	monoclinic
Space group	$P2_1/n$	P-1	$P2_1/n$	$P2_1/n$	$P2_1/n$	$P2_1/c$	P-1	$P2_1/c$
a [Å]	15.4528 (13)	10.5935 (12)	9.4823 (7)	9.6955 (7)	11.0106 (9)	15.8194 (15)	15.6267 (14)	17.5978 (14)
b [Å]	10.5392 (9)	12.8156 (14)	21.3355 (15)	21.2035 (16)	21.8194 (17)	15.7216 (16)	17.2808 (14)	42.019 (3)
c [Å]	21.1810 (16)	16.0880 (16)	16.5628 (10)	16.2828 (12)	13.8711 (11)	13.5542 (14)	20.3324 (18)	15.5539 (11)
α [°]	90.00	70.374 (2)	90.00	90.00	90.00	90.0	105.137 (2)	90
β [°]	98.313 (2)	89.460 (2)	94.963 (2)	93.4520 (10)	100.099 (2)	94.291 (2)	98.198 (2)	108.265 (2)
γ [°]	90.00	89.168 (2)	90.00	90.00	90.00	90.0	94.551 (2)	90
Volume [Å^3]	3413.3 (5)	2057.0 (4)	3338.3 (4)	3341.3 (4)	3280.8 (5)	3361.6 (6)	5206.7 (8)	10921.8 (15)
Z	4	2	4	4	4	4	4	8
D_c, Calc. density [g cm^{-3}]	1.218	1.183	1.381	1.347	1.259	1.229	1.1137	1.093
Absorption coefficient [mm^{-1}]	0.073	0.071	0.085	0.081	0.076	0.074	0.066	0.065
F(000)	1328	780	1472	1440	1312	1312	1882	3880
***θ* range**	1.53–28.31	1.34–27.19	1.56–27.88	1.58–28.39	1.76–28.36	1.83–27.16	1.38–27.96	1.56–27.20
Reflections collected	40012	26812	49121	47718	54493	26299	72501	146112
No. data I > 2sigma (I)	5688	6736	5508	6324	6111	5089	13246	13846
Final R indices [I > 2sigma (I)]	$R_1 = 0.0525$ $wR_2 = 0.1149$	$R_1 = 0.0454$ $wR_2 = 0.1035$	$R_1 = 0.0469$ $wR_2 = 0.0999$	$R_1 = 0.0425$ $wR_2 = 0.1037$	$R_1 = 0.0470$ $wR_2 = 0.1053$	$R_1 = 0.0454$ $wR_2 = 0.0971$	$R_1 = 0.0886$ $wR_2 = 0.2405$	$R_1 = 0.0747$ $wR_2 = 0.1908$
R indices (all data)	$R_1 = 0.0864$ $wR_2 = 0.1320$	$R_1 = 0.0681$ $wR_2 = 0.1156$	$R_1 = 0.0788$ $wR_2 = 0.1163$	$R_1 = 0.0617$ $wR_2 = 0.1150$	$R_1 = 0.0679$ $wR_2 = 0.1162$	$R_1 = 0.0784$ $wR_2 = 0.1109$	$R_1 = 0.1566$ $wR_2 = 0.2915$	$R_1 = 0.1326$ $wR_2 = 0.2282$

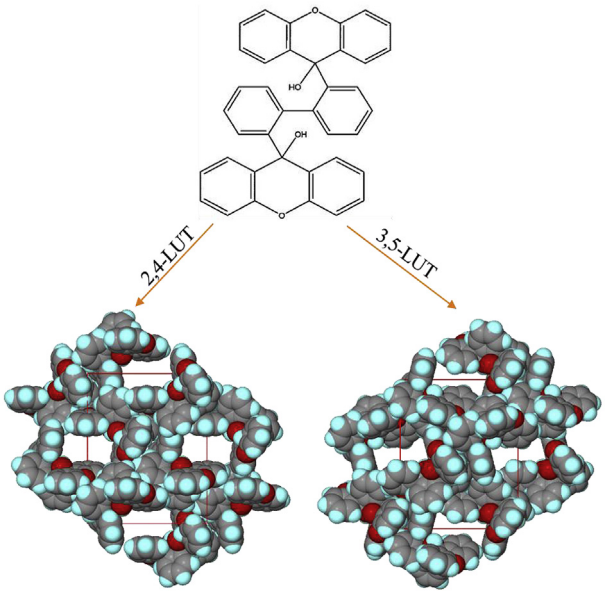

Fig. 7. Van der Waals representation of H3•1 (2,4-LUT) and H3•1 (3,5-LUT) with the guests omitted.

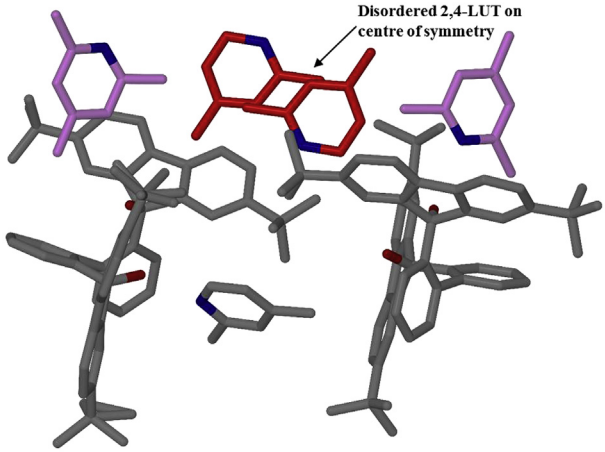

Fig. 8. Asymmetric unit of H5•1.25 (2,4-LUT) showing the disordered 2,4-LUT on the center of symmetry.

diol-host H1 = 2,2′-bis(5-hydroxydibenzosuberan-5-yl)biphenyl. The result of the pair-wise competition experiments yielded the selectivity preference as 3,4-LUT>2,4-LUT≈3,5-LUT>2,5-LUT>2,3-LUT>2,6-LUT and were confirmed by thermal measurements by DSC which yielded the same sequence of preferential inclusion. Four similar diol host compounds were tested similarly, and one of them, H2 was combined in various known proportions with H1 by analogy with the Dutch method for improving the resolution of racemic modifications. This yielded two different crystalline products, one of which contained both H1 and H2.

Declaration of interest

None.

Associated content

Supplementary Data contains tables of thermal analysis data, O···O distances in single guest structure with H1 and also torsion

angles with figures of packing diagram showing the disordered 2,6-LUT. CCDC 1867484 and CCDC 1867566–1867580 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.molstruc.2018.12.084.

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SUPPLEMENTARY DATA

Preferential enclathration of lutidine isomers by diol-hosts

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1.1S Tables

Table S1: Thermal analysis data of selected pairs of lutidines complexes with host H1

	H1•1(2,5-LUT)•(3,5-LUT)	**H1•1.5(2,3-LUT/3,4-LUT)**
TGA calc % mass loss	15.8	22.0
Exp% mass loss	15.9	22.1
DSC exotherm (guests) (T_{peak}/℃)	168.3	184.3
DSC exotherm (host) (T_{peak}/℃)	307.8	308.2

Table S2: O•••O distances in single guest structure with H1

	Internal H-bond O•••O/Å	External H-bond O•••N/Å
H1•2(2,3-LUT)	2.64	2.76
H1•1(2,4-LUT)	2.63	2.73
H1•2(2,6-LUT)	2.66	2.94
H1•1,5(3,4-LUT)	2.59	2.69
H1•1(3,5-LUT)	2.63	2.67

Table S3: Torsion angles

	Internal H-bond O•••O/Å	τ_1/°	τ_2/°	τ_3/°	τ_4/°	τ_5/°	τ_5/°	τ_6/°
H1•1(2,4-LUT)	2.63	96.0	67.2	75.1	58.2	48.3	-	-
H1•1(3,5-LUT)	2.63	95.7	66.3	78.8	55.1	40.5	-	-
H2•1(2,4-LUT)	2.80	102.0	39.6	48.7	-19.4	-52.6	-19.0	-52.6
H2•2(3,5-LUT)	2.67	98.4	45.5	43.3	+18.8	+54.7	+50.5	+26.8
H3•1(2,4-LUT)	2.72	99.0	8.5	12.7	-	-	-	-
H3•1(3,5-LUT)	2.74	100.5	24.2	3.9	-	-	-	-
H4•1(2,4-LUT)	2.75	88.3	22.3	21.7	-	-	-	-
H4•1(3,5-LUT)	2.72	93.7	20.1	20.1	-	-	-	-
H5•1.25(2,4-LUT)	A/2.81 B/2.68	A/88.2 B/92.2	A/30.9 B/31.0	A/21.2 B/23.6	-	-	-	-
H5•1.5(3,5-LUT)	A/2.70 B/2.74	A/85.7 B/92.4	A/29.1 B/33.4	A/31.7 B/27.0	-	-	-	-

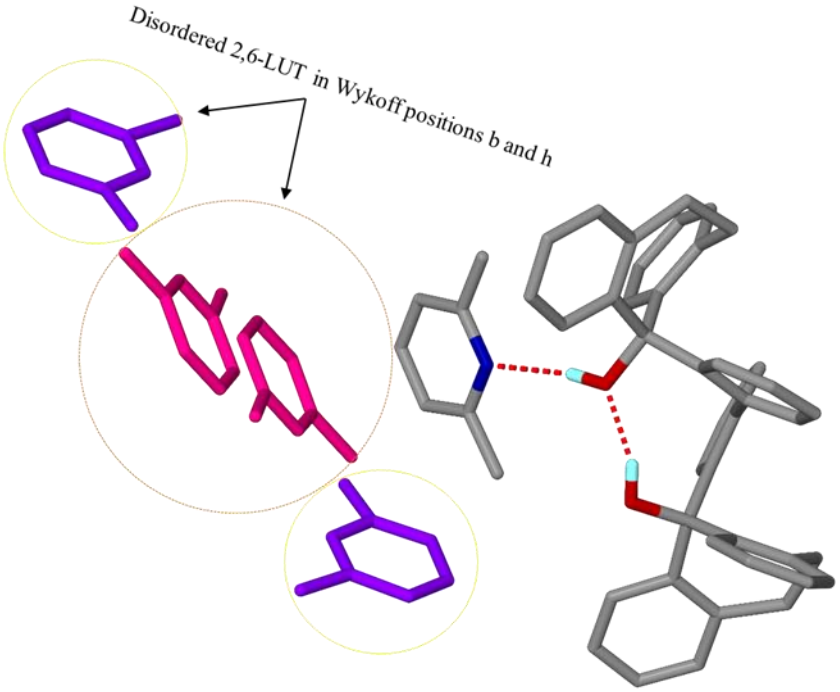

Figure S1: Packing diagram showing the disordered 2,6 on the Wykoff position b and h

Chapter 6.

Separation and resolution of methylcyclohexanones by enclathration with deoxycholic acid

6.1 Summary

Enantiomeric resolution remains important due to the unique position that enantiomers occupy in the drug industry. An enantiomer may have toxic effect caused by its undesired presence in the human body. In some cases, even when a R or S-enantiomer is administered, the isomer could change its configuration within the metabolism of the patient. Therefore, scientists have been looking for several methods to select the correct enantiomer while keeping its efficiency. The present situation can be addressed by the formation of complexes with the enantiomer strongly attached to one host compound and which upon administration may just act as its needed form. The formation of adequate compounds is significant in crystal engineering as well as drug discovery. Deoxycholic acid is widely used because it forms complexes with various types of guest compounds[1]. It has been employed for the separation of enantiomers as well as the separation of structural isomers. Since it is a chiral compound, its use in the enantiomeric resolution has been registered. Therefore, in this chapter, the enantiomeric resolution and the separation of methylcyclohexanone (MCH) isomers was explored from which the 2-methylcyclohexanone (2MCH) and 3-methylcyclohexanone (3-MCH) are racemic mixtures.

In this study, complexes of each methylcyclohexanone with deoxycholic acid were formed. This resulted in an enantiomeric resolution of the 2MCH and the formation of complexes with the 3MCH and 4-MCH. DCA was found to form a compound with the S-enantiomer of 2-MCH while 3-MCH was not resolved. The resolution was followed by several competition experiments. The aforementioned experiments gave rise to the selectivity of DCA to be 2MCH > 3MCH > 4MCH. One of the most interesting finding of this study was observed in the competition experiment of the 2MCH with 3MCH. During the resolution experiments, 3MCH isomer was still found as a R/S mixture in the complex that it formed with DCA. When It was set in competition with 2MCH, the resulting complex showed that the 3MCH was captured as the S-enantiomer along with the 2MCH S-enantiomer. Tests were then carried to confirm this observation. It was found that the 2-MCH enantiomer had a templating effect over the DCA selectivity toward the S-enantiomer of 3MCH. The resolution of (S)-2MCH over (R)-2MCH is very high and could contain up to 15% (R)-2MCH, corresponding to an e.e. of 70%

Thermal analysis and kinetics experiments were used to confirm the selectivity preference of DCA. The differential scanning calorimetry (DSC) results provided the same trend as the one observed with ^{1}H NMR. The activation energies of desorption reactions were also estimated by carrying out the host-guest decompositions at various heating rates using the method of Flynn and Wall[2]. Although the values were similar for the different complexes, they were still found to follow the same trend as the results obtained by ^{1}H NMR and DSC analysis of the onset of the different complexes.

6.2 References

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Separation and Resolution of Methylcyclohexanones by Enclathration with Deoxycholic Acid

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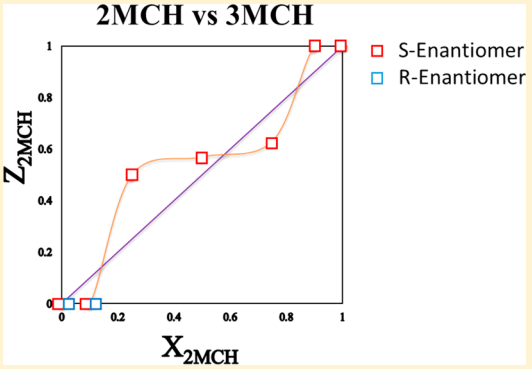
Supporting Information

ABSTRACT: Deoxycholic acid (DCA) includes all the isomers of methylcyclohexanones (MCH). Competition experiments showed that the preference is 2MCH > 3MCH > 4MCH confirmed by crystal structure analysis, NMR, and thermal analysis. DCA resolves 2MCH, enclathrating the S-conformer, whereas 3MCH remains unresolved. However, in competition experiments of rac-2MCH/rac-3MCH, both guests are resolved yielding S-conformers, suggesting that 2MCH has a templating effect on the final structures. The activation energies of desolvation of the clathrates with 2MCH and 3MCH are similar (~74 kJ/mol) but significantly lower for 4MCH (~48 kJ/mol).



INTRODUCTION

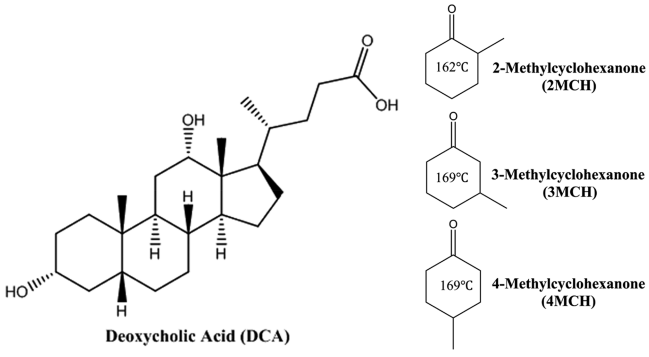
Methylcyclohexanones and their enantiomeric derivatives are important starting materials in organic synthesis.[1] However, they are difficult to purify because their isomers have similar boiling points and some are racemates. Their purification by enclathration with a suitable host compound is thus a suitable method of separation.[2] The resolution of methylcyclohexanones (MCH) by enclathration has been studied using a variety of chiral hosts. The host (2*S*)-(9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboximido)1,1-diphenylpropan-1-ol and its racemic (2RS) analogue yielded similar structures, and the resolution by the (2*S*)-host was only partially successful.[3] The host 2,2′-(benzene-1,4-diyl-diethynylene) diborneol[4] resolved 2-methylcyclohexanone (2MCH e.e. 72% S) and 3-methylcyclohexanone (3MCH e.e. 57% S). The host TETROL, (+)-(2*R*,3*R*)-1,1,4,4-tetraphenylbutane-1,2,3,4-tetrol, has been successfully used to include the three isomers of methylcyclohexanone, and, unusually, 3MCH and 4MCH were included with their methyl moieties in their axial conformations.[5,6] Weber also synthesized optically active clathrate-forming hosts derived from lactic acid,[7] which were employed to resolve the racemic modification of ketones, alcohols and sulfoxides which included 3-methylcyclohexanone.

Following the concept of the Dutch resolution method, which employs a family of similar resolving agents,[8] 3-methycyclohexanone resolved completely to the R-enantiomer using the host (*R*,*R*)-(−)-1,6-bis(*o*-chlorophenyl)-1,6-diphenylhexa-2,4-diyn-1,6-diol, which was combined with a similar achiral host.[9]

In this work, we present the separation of the three methylcyclohexanone isomers by deoxycholic acid (DCA) as well as the resolution of 2MCH and 3MCH. We also discuss the structures of the host and single-isomer compounds as well as those resulting from binary guest competition. The stability of these clathrates was monitored by thermal methods.

DCA is a well-known host that enclathrates a large variety of guests and whose structural chemistry has been reviewed extensively.[10−12] The structural formulas of DCA as well as those of the three MCH are given in Scheme 1.

Scheme 1. Structural Formulas of the Host and Guests Together with the Boiling Points of the Guests



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EXPERIMENTAL SECTION

Materials. The compounds were obtained from Sigma-Aldrich, and they were used without further purification. 2MCH and 3MCH were always used as racemates. Single crystals of the inclusion compounds were obtained by dissolving the host in an excess of the relevant guest or guest mixture and by adding 2 mL of methanol as cosolvent. The resulting solutions were then allowed to crystallize by slow evaporation at room temperature.

Competition Experiments. The competition experiments were carried out by exposing an equimolar mixture of a pair of guests (4 mL) to 200 mg of host compound, adding 2 mL of methanol as cosolvent, dissolving by gentle warming and allowing crystallization by slow evaporation. The resulting crystals were recovered, blotted dry, and subjected to NMR and thermal analysis.

X-ray Crystallography. Single crystal X-ray diffraction data were collected on a Bruker DUO APEX II diffractometer for all structures using Mo Kα radiation (λ = 0.71073 Å) at a temperature of 173 K.[13] The intensity data were collected using the phi scan and omega scan techniques, scaled, and reduced with SAINT-Plus.[14] The correction of the collected intensities for absorption was done using the SADABS program.[15]

The structures were solved by direct methods using SHELX-97[16] and refined using full-matrix least-squares methods in SHELXL.[16] The graphical interface used was the program X-SEED.[17] All C−H hydrogen atoms were placed geometrically and with a riding model for their isotropic temperature factors.

Thermal Analysis. Thermogravimetric analysis (TGA) was performed using a TA-Q500 thermogravimetric analyzer. Results were analyzed using Universal Analysis 2000 software. The samples were crushed and blotted dry (3−6 mg) and weighed directly into open aluminum oxide TGA crucibles. Differential scanning calorimetry (DSC) was performed using a TA Instruments DSC-Q200. Crushed and dried samples (1−3 mg) were weighed directly into vented aluminum pans on an analytical balance.

NMR Spectroscopy. Approximately 5 mg of representative crystals were blotted dry, crushed, and dissolved in 600 μL of DMSO-d_6 and introduced into a 5 mm NMR tube for data acquisition. One-dimensional (1D) ^{1}H and two-dimensional (2D) ^{1}H−^{13}C HSQC NMR spectra were recorded on a Bruker 300 or 400 MHz spectrometer at 30 °C and processed using standard Bruker software (Topspin 3.5). The HSQC experiment was optimized for J = 145 Hz (for directly attached ^{1}H−^{13}C correlations). The spectra were referenced relative to the solvent signal at 7.26 ppm (for ^{1}H) and 77.16 ppm (for ^{13}C); appropriate signals were integrated to determine the relative proportions of the guests.

The analysis was carried out on the crystals harvested from the mother liquors of the equimolar methylcyclohexanone binary mixtures. These crystals were dried using blotting paper but were not washed with any solvent to avoid any exchange of guests.

RESULTS

Single Guest Structures. Table 1 gives the crystallographic and refinement parameters of the structures obtained by crystallization of DCA with the single isomers of methylcyclohexanones.

The crystal structure of (DCA)$_2$·(2MCH) crystallizes in the space group $P2_12_12_1$ with Z = 4. In the asymmetric unit, there are two crystallographically independent DCA host molecules and one methylcylohexanone guest molecule. The packing is shown in Figure 1, viewed along [010].

The 2MCH guests are located in channels running parallel to the b axis. This packing is typical of many DCA·guest structures.[10] The projection shows the two crystallographically independent DCA molecules, which are almost superimposed in this view.

The packing mode is clarified by taking one column of the pairs of DCA molecules viewed along [001]. The independent molecules are colored alternatively green and blue, as shown in Figure 2. The guest 2-methylcyclohexanone is shown in Figure 3 and adopts the S conformation.

The conformation analysis of the rings in the two independent DCA molecules was carried out by the method described by Duax and Norton.[18] The A and B ring are cis-fused, while rings B, C and D are trans-fused. Measurements of the endocyclic torsion angles for rings A, B, C, and D allow the calculation of the asymmetry parameters in each ring and are given for both molecule I and II in Table 2.

The (DCA)$_2$·(3MCH) structure is isostructural with (DCA)$_2$·(2MCH) with respect to the host positions and the host conformation. The guest 3-methylcyclohexanone, how-

Table 1. Crystallographic and Refinement Parameters of Single Guest Structures

structures	(DCA)$_2$·(2MCH)	(DCA)$_2$·(3MCH)	(DCA)$_2$·(4MCH)
empirical formula	$C_{55}H_{92}O_9$	$C_{55}H_{92}O_9$	$C_{55}H_{92}O_9$
M [g mol^{-1}]	897.29	897.29	897.29
data collection temp T [K]	173(2)	173(2)	173(2)
crystal system	orthorhombic	orthorhombic	orthorhombic
space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
a [Å]	13.3926(14)	13.451(2)	13.4213(17)
b [Å]	14.0354(14)	14.0401(19)	14.0480(18)
c [Å]	26.865(3)	26.865(4)	26.847(3)
α [°]	90	90	90
β [°]	90	90	90
γ [°]	90	90	90
volume [Å^3]	5049.9(9)	5073.4(13)	5061.8(11)
Z	4	4	4
D_c, calc density [g cm^{-3}]	1.180	1.175	1.177
absorption coefficient [mm^{-1}]	0.078	0.077	0.078
F(000)	1976	1976	1976
θ range	1.52−27.10	1.64−28.28	1.52−25.07
reflections collected	49088	47618	24133
no. data $I > 2\sigma(I)$	8139	9881	6462
final R indices	R_1 = 0.0619	R_1 = 0.0625	R_1 = 0.0513
$[I > 2\sigma(I)]$	wR_2 = 0.1440	wR_2 = 0.1257	wR_2 = 0.1081
R indices (all data)	R_1 = 0.0923	R_1 = 0.1187	R_1 = 0.0854
	wR_2 = 0.1638	wR_2 = 0.1518	wR_2 = 0.1222

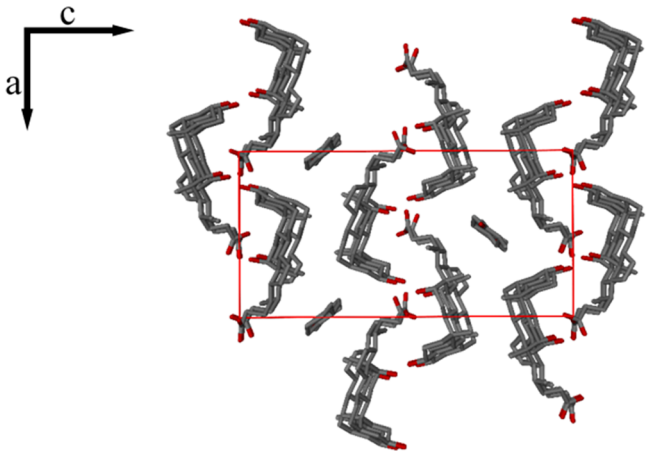

Figure 1. Packing of (DCA)$_2$·(2MCH) viewed along [010].

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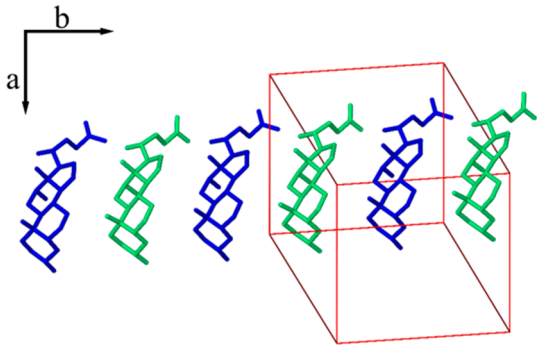

Figure 2. Packing of DCA viewed along [001].

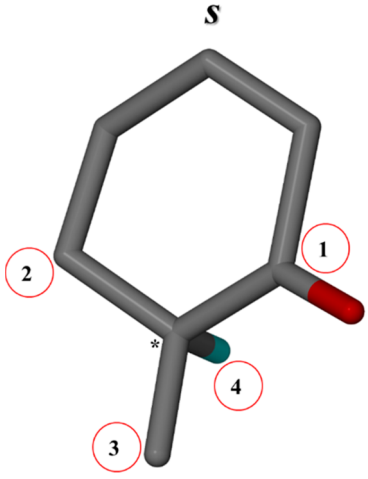

Figure 3. Guest 2-methylcyclohexanone adopting the S conformation.

ever, was not resolved, yielding 49% (S) and 51% (R) Figure 4).

The $(DCA)_2$·(4MCH) is similarly isostructural with $(DCA)_2$·(2MCH), and the methyl group of the guest is in the equatorial position. The structures display similar hydrogen bonding, which is shown in Table 3. This is exclusively of the type O−H···O(H), and we report the donor···acceptor distances.

Competition Experiments. Competition experiments were carried out by dissolving the DCA host in equimolar mixtures of 2MCH/3MCH, 2MCH/4MCH, and 3MCH/4MCH. The total guest/host molar ratio was always in excess of 70. The mother liquors were allowed to evaporate at room temperature, and the resulting crystallites were blotted dry and analyzed by NMR.

The structure of $(DCA)_2$·(2MCH/3MCH) and other structures obtained from the binary guest competitions are isostructural with $(DCA)_2$·(2MCH) and the crystal and refinement parameters are given in Table 4.

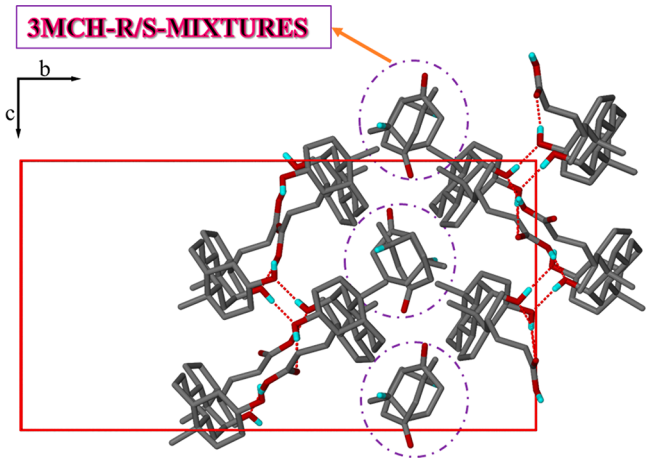

Figure 4. $(DCA)_2$·(3MCH) along [100] showing the disordered 3MCH(R/S).

Table 3. Hydrogen Bonding Displayed by the Single Guest Structures

	D···A/Å	symmetry operation
$(DCA)_2$·(2MCH)		
O3−H3··· O25	2.731	[*x*+1, *y*, *z*]
O12−H12··· O33	2.719	[*x*−1, *y*, *z*]
O24−H24··· O12	2.661	[*x*−1/2, −*y*+1/2, −*z*+1]
O33−H33··· O55	2.822	[*x*+1, *y*, *z*]
O42−H42···O3	2.671	
O54−H54··· O42	2.648	[*x*−1/2, −*y*+3/2, −*z*+1]
$(DCA)_2$·(3MCH)		
O3−H3··· O25	2.828	[*x*−1, *y*, *z*]
O12−H12··· O33	2.672	
O24−H24··· O12	2.655	[*x*+1/2, −*y*+3/2, −*z*+1]
O33−H33··· O55	2.728	[*x*−1, *y*, *z*]
O42−H42···O3	2.721	[*x*+1, *y*, *z*]
O54−H54··· O42	2.666	[*x*+1/2, −*y*+1/2, -*z*+1]
$(DCA)_2$·(4MCH)		
O3−H3··· O25	2.794	[*x*+1, *y*, *z*]
O12−H12··· O33	2.657	
O24−H24··· O12	2.655	[*x*-1/2, −*y*+1, −*z*+1]
O33−H33··· O55	2.727	[*x*+1, *y*, *z*]
O42−H42···O3	2.715	[*x*−1, *y*, *z*]
O54−H54··· O42	2.659	[*x*−1/2,−*y*+3/2, −*z*+1]

The two guest molecules are located in the hydrophobic channel and share the same site. The relative proportion of the isomers in the crystalline products was measured by NMR and yielded the following values: 66%(*S*)-2MCH/34%(*S*)-3MCH; 74%(*S*)-2MCH/26%4MCH; 59%(*R*,*S*)-3MCH/41%4MCH. The crystal structures obtained from these binary guest competitions display severe disorder of the guests, and the site occupancies do not compare well with those obtained from

Table 2. Asymmetric Parameters Angles for Rings A, B, C, and D of Each Structure

	$(DCA)_2$·(2MCH)		$(DCA)_2$·(3MCH)		$(DCA)_2$·(4MCH)	
	Molecule 1	Molecule 2	Molecule 1	Molecule 2	Molecule 1	Molecule 2
Ring A (deg)	C_S (2) = 2.2	C_S (2) = 1.6	C_S (2) = 1.5	C_S (2) = 2.2	C_S (2) = 1.7	C_S (2) = 2.1
Ring B (deg)	C_S (2) = 1.8	C_S (2) =1.2	C_S (2) = 0.83	C_S (2) =1.4	C_S (2) = 0.57	C_S (2) =1.5
Ring C (deg)	C_S (2) = 2.0	C_S (2) = 0.35	C_S (2) = 0.63	C_S (2) = 3.9	C_S (2) = 0.34	C_S (2) = 2.2
Ring D (deg)	C_2(13−14) = 8.3	C_2(43−44) = 9.7	C_2(13−14) = 2.0	C_2(43−44) = 8.0	C_2(13−14) = 1.1	C_2(43−44) = 7.5

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Table 4. Crystal and Refinement Parameters of Binary Guests' Structures

structures	$(DCA)_2$·(2MCH/3MCH)	$(DCA)_2$·(2MCH/4MCH)	$(DCA)_2$·(3MCH/4MCH)
empirical formula	$C_{55}H_{92}O_9$	$C_{55}H_{92}O_9$	$C_{55}H_{92}O_9$
M [g mol^{-1}]	897.29	897.29	897.29
data collection temp T [K]	173(2)	173(2)	173(2)
crystal system	orthorhombic	orthorhombic	orthorhombic
space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
a [Å]	13.4135(8)	13.3790(17)	13.4273(6)
b [Å]	14.0171(8)	13.9931(18)	14.0273(6)
c [Å]	26.8324(17)	26.823(4)	26.8218(12)
α [°]	90	90	90
β [°]	90	90	90
γ [°]	90	90	90
volume [Å^3]	5045.0(5)	5021.5(11)	5051.9(4)
Z	4	4	4
D_c, calc. density [g cm^{-3}]	1.181	1.187	1.180
absorption coefficient [mm^{-1}]	0.078	0.078	0.078
$F(000)$	1976	1976	1976
θ range	1.52−28.31	2.15−28.57	1.64−28.29
reflections collected	52853	7993	55830
no. data $I > 2\sigma(I)$	8495	5884	10480
final R indices	R_1 = 0.0581	R_1 = 0.0735	R_1 = 0.0503
$[I > 2\sigma(I)]$	wR_2 = 0.1188	wR_2 = 0.1750	wR_2 = 0.1270
R indices (all data)	R_1 = 0.0987	R_1 = 0.1109	R_1 = 0.0641
	wR_2 = 0.1384	wR_2 = 0.1974	wR_2 = 0.1367

the NMR. The methyl group of 4MCH was invariably equatorial.

These results show that the preferential enclathration by DCA follows the sequence 2MCH > 3MCH > 4MCH. We noted that the DCA resolved (rac)2MCH to yield $(DCA)_2$·(S)(2MCH) and that the (rac)2MCH/(rac)3MCH competition resulted in $(DCA)_2$·(0.57(*S*)2MCH·0.43(*S*)3MCH). This hinted at the possibility of (*S*)2MCH acting as a template which produced (*S*)3MCH. We tested this hypothesis by altering the relative composition of the starting proportion of the (rac)2MCH/(rac)3MCH mixtures. The fractions of (rac)2MCH were varied as follows: $X_{(rac)2MCH}$ = 0, 0.10, 0.25, 0.50, 0.75, 0.90, 1 and the corresponding crystal structures showed the corresponding values of the (*S*)2MCH. These values are shown in Table 5.

The table shows that there was no selectivity between 2MCH and 3MCH in the range of X_{2MCH} = 0.0−0.1 and 0.9−1. In both of these ranges, the host only enclathrated the majority guest. Over the range of X_{2MCH} = 0.25−0.75, the crystals had a mole fraction that varied from 0.50 to 0.63 which is shown in Figure 5. This confirms the templating effect of (*S*)-2MCH on the resulting (*S*)-3MCH.[19]

Figure 5 shows that the resulting mole fraction $Z_{(S)2MCH}$ varies narrowly from 50% to 63% over the range of 0.25−0.75 of (rac)2MCH in the mother liquor. This interesting result confirms the templating effect of (*S*)2MCH over (*S*)3MCH. The hydrogen bonding which occurs in the binary guest structures has been deposited in the Supporting Information as Table S1.

Table 5. Results of Competition Experiments for 2MCH/3MCH mixtures

mother liquor		crystals	
mol fraction of rac mixture		mol fraction of 2MCH/3MCH	
2MCH	3MCH	2MCH	3MCH
0.00	1.00	2MCH = 0.00	(rac)-3MCH = 1.00
0.10	0.90	2MCH = 0.00	(rac)-3MCH = 1.00
0.25	0.75	(*S*)-2MCH = 0.50	(*S*)-3MCH = 0.50
0.50	0.50	(*S*)-2MCH = 0.57	(*S*)-3MCH = 0.43
0.75	0.25	(*S*)-2MCH = 0.63	(*S*)-3MCH = 0.37
0.90	0.10	(*S*)-2MCH = 1.00	3MCH = 0.00
1.00	0.00	(*S*)-2MCH = 1.00	3MCH = 0.00

Thermal Analysis. The TGA and DSC results for $(DCA)_2$·(2MCH) are shown in Figure 6. It is noteworthy that the DSC displays a single endotherm that peaks at 177.0 °C. In DSC profiles of host−guest compounds which contain volatile guests and hosts with high melting points (>200 °C), one usually observes two distinct endotherms, the first due to the guest desorption and the second associated with the melting of the host. Analysis of the DSC endotherm for $(DCA)_2$·(2MCH) shows that this thermal event starts at ∼140 °C and ends at ∼191 °C. This extends over the two relevant temperatures of the boiling point of 2MCH (162 °C) and the melting point of DCA (176−178 °C). Thus, the single endotherm observed is due to the combination of guest desorption and concomitant dissolution in the liquefied host. This was confirmed by hot stage microscopy. Similar results were obtained for $(DCA)_2$·(3MCH) and $(DCA)_2$·(4MCH). Their results have been deposited in the Supporting Information as Figures S1 and S3, respectively.

The summary of the TGA and DSC results is given in Table 6. A measure of the thermal stability of a host−guest compound may be estimated by the $T_{peak} - T_{bp}$ of the DSC endotherm. In this case the following sequence of 2MCH > 3MCH > 4MCH is observed, which is the same order as that given by the competition experiments. We have analyzed the guest-channel cross sections volumes and the secondary interaction (guest···guest and host···host) and found the 2MCH structure with DCA to be tightly held. The 3MCH structure could not be compared due to the guest disorder. The results of this analysis have been placed in the additional information.

The activation energies of desorption reactions were estimated by carrying out the host−guest decompositions at various heating rates, following the method of Flynn and Wall.[20] The TGA curves were recorded at heating rates β = 8.00, 11.3, 16.0, 22.6 K/min. The semilogarithmic points of log β/β_0 versus $\frac{1000}{T}$ K were recorded for the extent of reaction α = 2%, 3%, and 4%. β_0 is the standard value of the heating rate = 1°/min. The plots for $(DCA)_2$·(2MCH) are shown in Figure 7.

The slopes of these linear plots are $\frac{-0.457E_a}{R}$, yielding activation energies in the range of 78−81 kJ/mol. The activation energies for the $(DCA)_2$·(3MCH) and $(DCA)_2$·(4MCH) were evaluated in a similar manner, their values ranging from 71 to 74 kJ/mol (3MCH) and 42 to 54 kJ/mol (4MCH), and their semilogarithmic plots have been placed in the Supporting Information as Figures S2 and S4.

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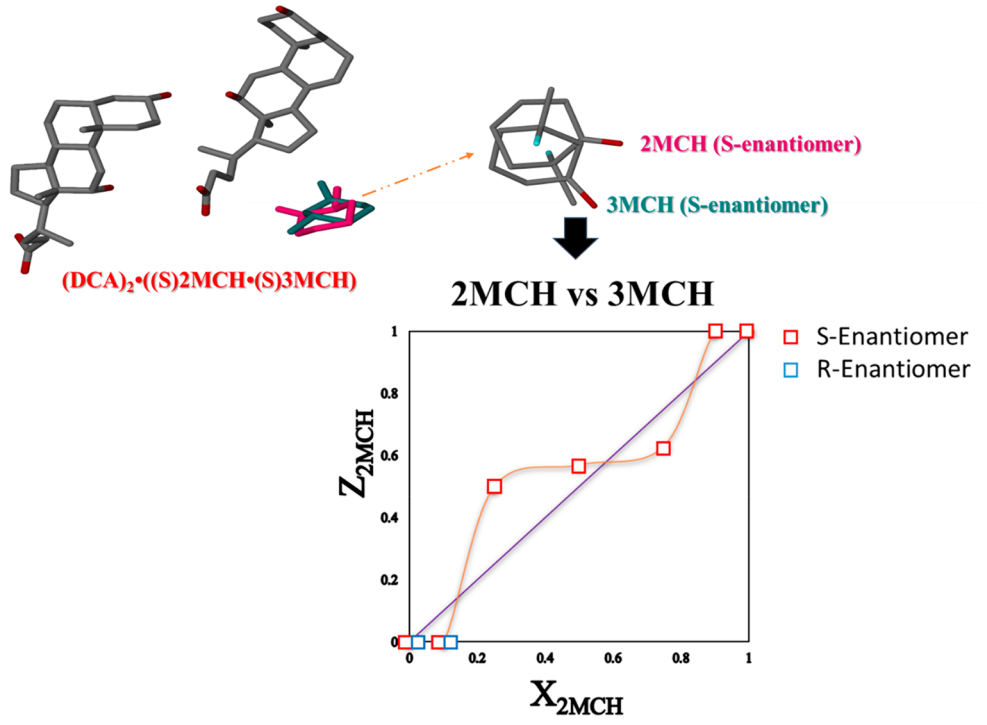

Figure 5. Competition experiment of 2MCH vs 3MCH with the S-enantiomer represented in red, while the R-enantiomer is represented in blue.

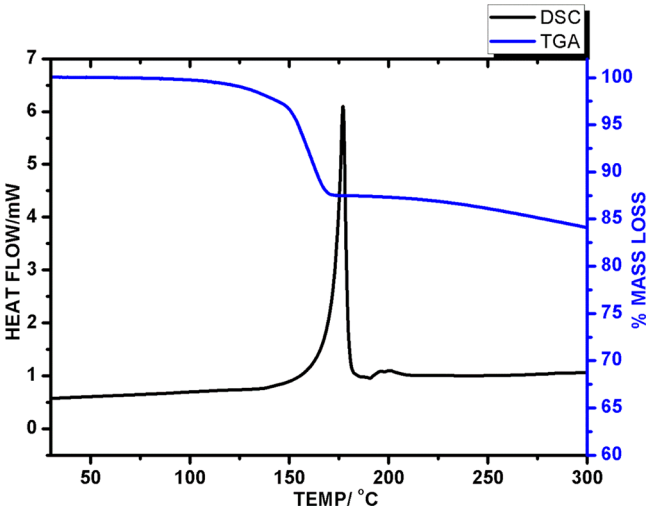

Figure 6. TGA and DSC plot of $(DCA)_2$·(2MCH).

Table 6. Summary of TG and DSC Results

	$(DCA)_2$·(2MCH)	$(DCA)_2$·(3MCH)	$(DCA)_2$·(4MCH)
H:G	2:1	2:1	2:1
% mass loss exp(calc)	13.0 (12.5)	12.4 (12.5)	12.2 (12.5)
$T_{peak/endo1}$/°C	177.0	171.8	169.6
$T_{peak} - T_{bp}$/°C	15	2.8	0.6

The kinetics of the salts formed by DCA with selected amines has been studied,[21] and the activation energies for the decomposition of the salts $(DCA)^-(BA)^+$ (BA= *sec*-butylamine) and $(DCA)^-(DBA)^+$ (DBA = di-*n*-butylamine) yielded values of ∼223 kJ/mol and ∼109 kJ/mol, respectively. The host lithocholic acid (LCA) also forms salts with *n*-propylamine (PPA) and *sec*-butylamine (BA),[22] and their activation energy of decomposition had values of ∼127 kJ/mol for $(LCA)^-(BA)^+$ respectively. These activation energies are higher than those obtained in this work and may be justified by the stronger ionic host−guest interactions that occur in the salts.

The effects of topology on the thermal stability and kinetics of decomposition of inclusion compounds have been reviewed,[23] and intercalates are generally less stable than tabulates, which are less stable than cryptates. Thus, when a guest is completely surrounded by host molecules, its activation energy of decomposition will be higher than that of a more open compound.

The activation energies of desolvation for 2MCH (∼75 kJ/mol) and 3MCH (∼73 kJ/mol) are significantly higher than that of 4MCH (∼48 kJ/mol). This may be attributed to the cross sectional area of these three guest molecules. The channels that run in the [010] direction in each of the structures crystallized with the single guest have practically identical rectangular cross sections with a diagonal distance of ∼8.3 Å. The minimum cross sectional area of 4MCH, measured perpendicularly from the mean plane of the cyclohexyl ring, is ∼6.0 Å, smaller than those of 2MCH (7.7 Å) and 3MCH (8.0 Å). This estimate is an indication of an easier passage of 4MCH through the channels, which is associated with the lowered activation energy.

■ CONCLUSION

Deoxycholic acid (DCA) enclathrates the isomers of methylcyclohexanone (MCH) yielding isomorphous structures in $P2_12_12_1$ with a host/guest ratio of 2:1. Competition experiments showed that the selectivity of enclathration was in the order of 2MCH > 3MCH > 4MCH, which was in agreement with the results obtained by DSC.

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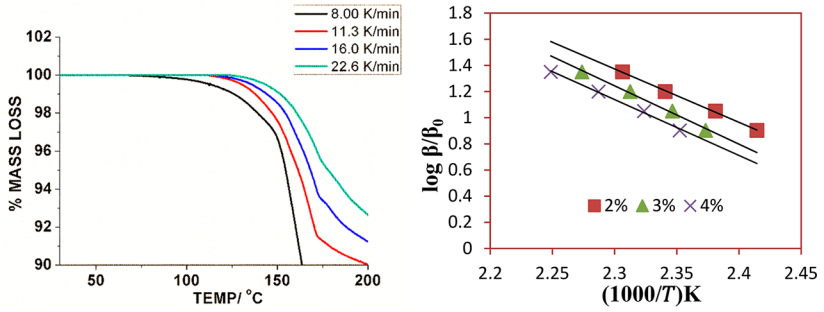

Figure 7. Non-isothermal TG curves and the associated semilogarithmic plot for $(DCA)_2 \cdot (2MCH)$.

The DCA resolved 2MCH yielding $(DCA)_2 \cdot (S)(2MCH)$ but did not resolve 3MCH. However, competition experiments by DCA exposed to racemic modification of 2MCH/3MCH in differing proportions yielded inclusion compounds in which both 2MCH and 3MCH were enclathrated in their S-configurations, showing 2MCH to have a templating effect. All structures involving 4MCH showed that the methyl groups were in the equatorial position.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.cgd.9b00369.

Thermal analysis figures (PDF)

Accession Codes

CCDC 1900469−1900474 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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Supporting Information

Separation and resolution of methylcyclohexanones by enclathration with deoxycholic acid

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INDEX

1.1S Thermal analysis

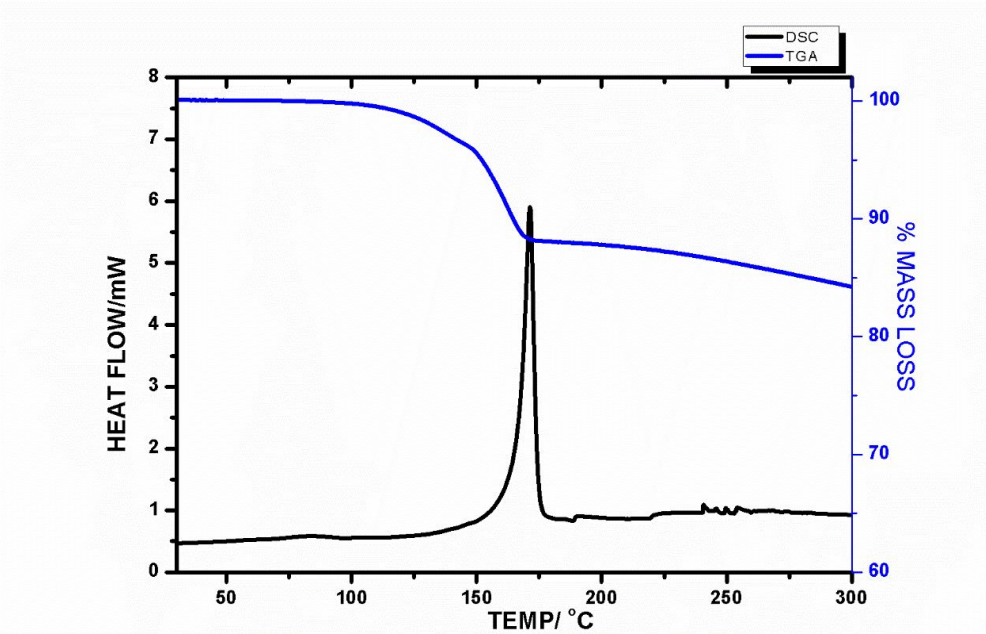

Figure S1: TG and DSC plot of $(DCA)_2$•(3MCH)

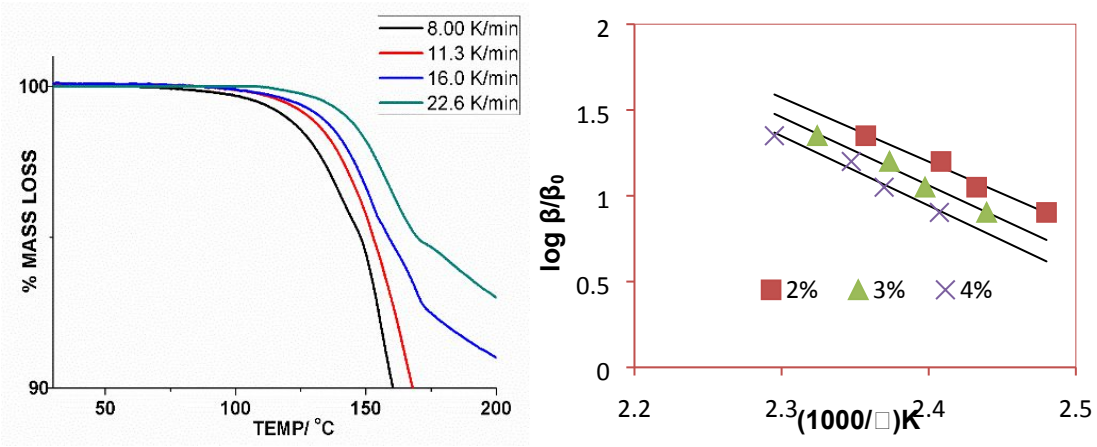

Figure S2: Non-isothermal TG curves and activation energies for $(DCA)_2$•(3MCH)

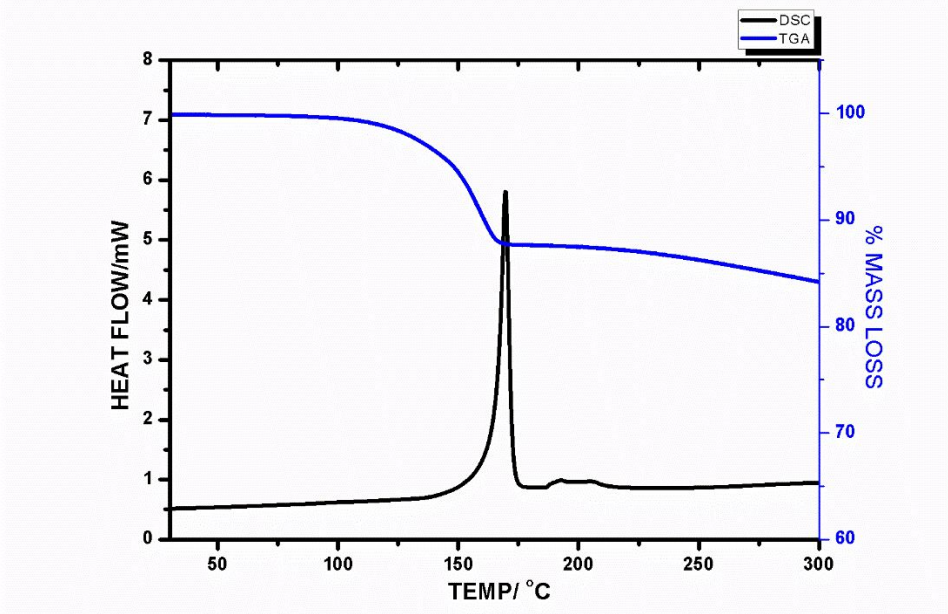

Figure S3: TG and DSC plot of $(DCA)_2$•(4MCH)

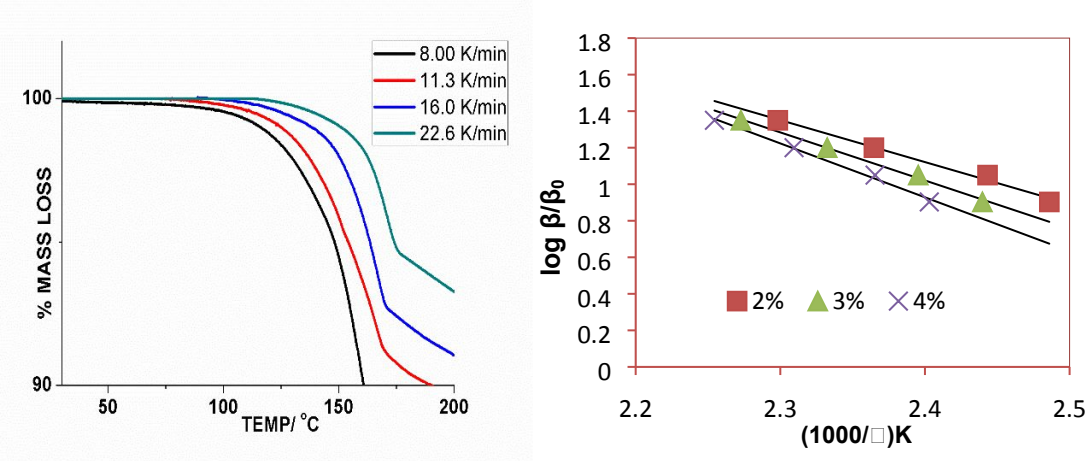

Figure S4: Non-isothermal TG curves and activation energies for $(DCA)_2$•(4MCH)

Table S1. Hydrogen bonding displayed by the binary guest structures

	D•••A/Å	Symmetry operation
$(DCA)_2$•(2MCH/3MCH)		
O3-H3•••O25	2.822	[x+1, y, z]
O12-H12••• O33	2.666	-
O24-H24••• O12	2.650	[x-1/2, -y+1/2, -z+1]
O33-H33••• O55	2.723	[x+1, y, z]
O42-H42•••O3	2.718	[x-1, y, z]
O54-H54••• O42	2.665	[x-1/2, -y+3/2, -z+1]
$(DCA)_2$•(2MCH/4MCH)		
O3-H3••• O25	2.816	[x+1, y, z]
O12-H12••• O33	2.665	[x-1/2, -y+3/2, -z+2]
O24-H24••• O12	2.655	[x-1/2, -y+3/2, -z+2]
O33-H33••• O55	2.714	[x+1, y, z]
O42-H42•••O3	2.712	[x-1/2, -y+3/2, -z+2]
O54-H54••• O42	2.655	[x-1/2, -y+3/2, -z+2]
$(DCA)_2$•(3MCH/4MCH)		
O3-H3••• O25	2.822	[x-1, y, z]
O12-H12••• O33	2.666	-
O24-H24••• O12	2.653	[x+1/2, -y+3/2, -z+1]
O33-H33••• O55	2.726	[x-1, y, z]
O42-H42•••O3	2.715	[x+1, y, z]
O54-H54••• O42	2.666	[x+1/2, -y+1/2, -z+1]

❖ **Correlation between structures and thermal properties**

We have measured the cross-sectional area of the channels (Using Mercury) as well as their volumes over one unit cell along [010] for the three structures $(DCA)_2$•(2MCH), $(DCA)_2$•(3MCH) and $(DCA)_2$•(4MCH). The channels display similar geometry, which is not surprising since the structures are isomorphous. The results were as follows:

	$(DCA)_2$•(2MCH)	$(DCA)_2$•(3MCH)	$(DCA)_2$•(4MCH)
Cross sectional area ($Å^2$)	15.87	20.60	19.78
Channel Volume per cell ($Å^3$)	820.1	839.1	828.2

We note that the 3MCH guest is disordered and contains equal proportions of the (R)- and (S)-anantiomers, therefore the largest cross section/volume is expected and cannot be compared with that of the other two guests: 2MCH (15.87 $Å^2$/820.1 $Å^3$); 4MCH (19.78 $Å^2$/828.2 $Å^3$).

We also studied any significant secondary interactions. The cyclohexanone guests are located between the hydrophobic double layers of the DCA hosts (Figure 1 in the manuscript) and the only interactions are 2MCH guest•••guest C-H•••O 2.70 Å, (R)-3MCH, three methyl C-H•••O guest•••guest 2,44; 2.54; 2.69 Å. This guest has a site occupancy of 50%. For 4-MCH, there is one host-guest interaction C-H•••O of 2.71 Å. All these interactions are regarded as weak.

Chapter 7.

Selective enclathration of xylenols: synergistic effects of mixed hosts

7.1 Summary

Enantiomeric resolution remains important due to the unique position that enantiomers occupy in the drug industry. An enantiomer may have toxic effect caused by its undesired presence in the human body. In some cases, even when a R or S-enantiomer is administered, the isomer could change its configuration within the metabolism of the patient. Therefore, scientists have been looking for several methods to select the correct enantiomer while keeping its efficiency. The present situation can be addressed by the formation of complexes with the enantiomer strongly attached to one host compound and which upon administration may just act as its needed form. The formation of adequate compounds is significant in crystal engineering as well as drug discovery. Deoxycholic acid is widely used because it forms complexes with various types of guest compounds1. It has been employed for the separation of enantiomers as well as the separation of structural isomers. Since it is a chiral compound, its use in the enantiomeric resolution has been registered. Therefore, in this chapter, the enantiomeric resolution and the separation of methylcyclohexanone (MCH) isomers was explored from which the 2-methylcyclohexanone (2MCH) and 3-methylcyclohexanone (3MCH) are racemic mixtures.

In this study, complexes of each methylcyclohexanone with deoxycholic acid were formed. This resulted in an enantiomeric resolution of the 2MCH and the formation of complexes with the 3MCH and 4-MCH. DCA was found to form a compound with the S-enantiomer of 2-MCH while 3-MCH was not resolved. The resolution was followed by several competition experiments. The aforementioned experiments gave rise to the selectivity of DCA to be 2MCH > 3MCH > 4MCH. One of the most interesting finding of this study was observed in the competition experiment of the 2MCH with 3MCH. During the resolution experiments, 3MCH isomer was still found as a R/S mixture in the complex that it formed with DCA. When It was set in competition with 2MCH, the resulting complex showed that the 3MCH was captured as the S-enantiomer along with the 2MCH S-enantiomer. Tests were then carried to confirm this observation. It was found that the 2-MCH enantiomer had a templating effect over the DCA selectivity toward the S-enantiomer of 3MCH. The resolution of (S)-2MCH over (R)-2MCH is very high and could contain up to 15% (R)-2MCH, corresponding to an e.e. of 70%

Thermal analysis and kinetics experiments were used to confirm the selectivity preference of DCA. The differential scanning calorimetry (DSC) results provided the same trend as the one observed with 1H NMR. The activation energies of desorption reactions were also estimated

by carrying out the host-guest decompositions at various heating rates using the method of Flynn and Wall2. Although the values were similar for the different complexes, they were still found to follow the same trend as the results obtained by 1H NMR and DSC analysis of the onset of the different complexes.

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Selective enclathration of xylenols: synergistic effects of mixed hosts†

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The six xylenol (XYL) isomers can be separated by selective enclathration with the host 4,4-isopropylidene bisphenol, H1. Crystal structures were elucidated for the following single and mixed guest inclusion compounds with H1: H1·34XYL (I), H1·35XYL (II), H1·23XYL·26XYL (III), H1·23XYL·35XYL (IV), where the xylenol isomers are abbreviated as, for example 34XYL for 3,4-xylenol. The crystal structures of selected H1·xylenols showed that there is extensive host···host and host···guest hydrogen bonding. Competition experiments with equimolar mixtures of pairs of xylenols (XYL) showed that the preference for inclusion was in the sequence 34XYL > 35XYL > 26XYL > 23XYL > 25XYL > 24XYL. By analogy to the Dutch resolution method (in which families of resolving agents are used to achieve chiral separations), two host compounds similar to H1 were used in pairs with H1 to improve the selectivity of the xylenols. 4,4′-(9-Fluorenylidene)bisphenol, H2, and 4,4′(cyclohexylidene)bisphenol, H3, were used in pairs with H1 and were shown to enhance the selectivity of a given xylenol which had been poorly separated by H1 alone. The crystal structure was elucidated for an unusual mixed host–mixed guest inclusion compound, H1·H2 ·26XYL/35XYL (V).

Introduction

The separation of mixtures of closely related molecules is an important chemical process and separation techniques are dependent on the difference in the physico-chemical properties of the individual components, and include several types of chromatography, crystallization, distillation, and evaporation. However, if the individual components have similar properties, standard techniques may not be suitable. This is the case with many isomers, while their separation remains important as they are frequently produced as mixtures in industrial processes. The individual components are usually more valuable than the mixture, because they form the feedstock for the syntheses of novel products.[1]

Host–guest (or inclusion) chemistry has proved to be a useful methodology for the separation of closely related molecular species.[2] When a host compound, H, is exposed to a mixture of guest molecules, A, B, C… this may result in an inclusion compound

$$H + n_1A + n_2B + n_3C\ldots \rightarrow H{\cdot}A_m$$

H is usually a solid. A, B, C… can be solid, liquid or gas in the proportions given as n_1, n_2, n_3, yielding the product $H{\cdot}A_m$, an inclusion compound with guest/host ratio (G/H) of m.

The above represents an ideal case, in which A is exclusively selected. In practice this occurs seldom, and where there are many components a common strategy is to take the guests in pairs and analyse the final product by a suitable technique which yields its stoichiometry. By analysing the combination of all possible pairs of guests, it is possible to obtain the preferential affinity sequence of the host H for the complete series of guests A, B, C…

This methodology is driven by the phenomenon of molecular recognition, which is central to host–guest chemistry and crystal engineering. The special factors that lead to a suitable fit between host and guest molecules arise from the sum of multiple secondary interactions that impinge upon the molecular system. These secondary bonds are often directional, resulting in specificity and allowing a host molecule to discriminate between a given guest in a mixture of guests. This makes the host H selective, which is crucial to separation processes.

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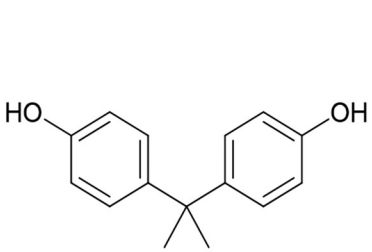
† Electronic supplementary information (ESI) available: Tables S1–S5, Fig. S1–S37. Crystallographic data for this paper have been deposited with the CCDC, accession numbers 1994170 and 1994172–1994174. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ce00510j

An important example of the separation of isomers is the petrochemical industry in which isomers of the C8 hydrocarbons (*ortho*-, *meta*-, *para*-, xylenes and ethyl benzene), the cresols and the xylenols are produced in large quantities from the catalytic reforming of crude oil. A well-known case is the separation of the isomers of xylene, which have similar normal boiling points ranging from 138.1 °C to 144.4 °C, rendering fractional distillation inefficient. This topic is the subject of a comprehensive review,[3] which discusses various materials employed in the separation techniques that include metal–organic frameworks, zeolites and organic host molecules. Other contributions describe the optimal synthesis of *p*-xylene separation[4] and the use of Werner clathrates for the separation of xylenes from in the vapour state and the concomitant kinetics of adsorption.[5]

Hydrocarbons are not the only compounds that have been separated by enclathration and there are several recent examples where mixtures of both aliphatic and aromatic compounds have been selectively included into host–guest complexes.[6–10]

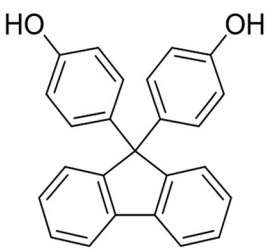
A particularly challenging problem for the separation of isomers is that of enantiomer resolution of a racemic modification. Here, the two enantiomeric components have identical physical properties such as melting point, boiling points, refractive index, density, dipole moment, and only differ in their response to polarized light. One successful strategy for separating enantiomers combines a chiral resolving agent which forms a compound preferentially with either one or the other enantiomer. This separation process is not always routine and may yield incomplete resolution. However, a significant advancement was made by the discovery by T. Vries *et al.*[11] who used a combinational approach of related "families" of resolving agents to improve the resolution of racemates. This has been summarized in the Handbook of Optical Resolutions edited by D. Kozma[12] and is known as the "Dutch Resolution Method". We were inspired by this idea to extend the usual host–guest method of separation of isomers to an analogy of the Dutch resolution method, in which we employed pairs of similar host compounds for the separation of isomers from binary mixtures, with the aim of obtaining enhanced selectivity of the guest species.

In this work, we aimed to achieve separation of the six xylenol isomers, by selective inclusion using three organic host compounds which contain the common bisphenol moiety. The structures of the host compounds are shown in Scheme 1, which also presents the six xylenol isomers with



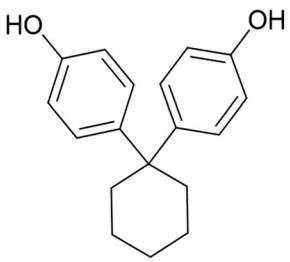
4,4'-Isopropylidene Bisphenol

H1



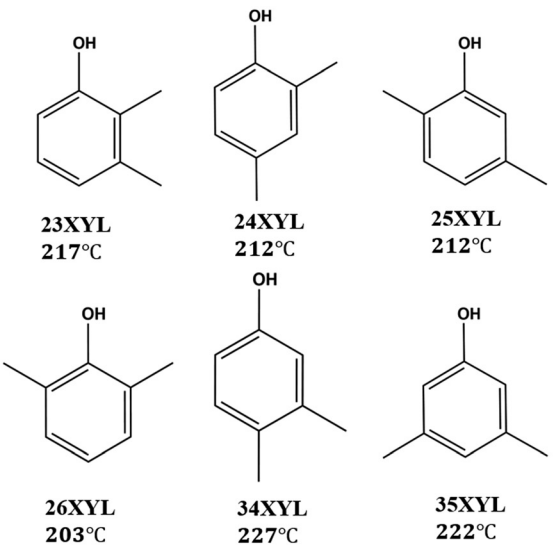
4,4'-(9-Fluorenylidene) Bisphenol

H2



4,4-(Cyclohexylidene) Bisphenol

H3



Scheme 1

their normal boiling points, as well as the abbreviations used for these compounds.

Experimental

Materials

The compounds were acquired from Sigma-Aldrich and were used without further purification.

Competition experiments

For the pairwise separation of the xylenol guests by H1, the procedure was as follows. H1 (0.82 mmol, 187 mg) was added to an equimolar mixture of the two selected xylenols (4.1 mmol, 500 mg of each) and dissolved in 0.5 ml of ethyl acetate, and the solutions stirred for 2 hours before being allowed to evaporate at room temperature (*ca.* 25 °C) until crystals formed. The total ratio of guest : host was thus 10 : 1, to ensure that an excess of both guests is always available to the host, thus eliminating an artificial selectivity developing as compounds crystallize from the solution. Ethyl acetate was chosen as the common solvent to overcome any possible solubility barriers and because it is not included by any of the host compounds, so would not be incorporated in the crystalline products. Details of the resulting crystals are given in Tables 1 and 2 in the Results section. Inclusion compounds **I** (H1·34XYL), **II** (H1·35XYL), **III** (H1·23XYL/26XYL), and **IV** (H1·23XYL/35XYL) were selected from these experiments and subjected to single crystal diffraction as detailed below.

For the competition experiments with the mixed hosts H1 + H2. Equimolar mixtures of H1 (0.41 mmol, 94 mg) and H2 (0.41 mmol, 144 mg) were added to an equimolar mixture of the two selected xylenols (an equimolar mixture of 4.1 mmol, 500 mg of each) and dissolved in 0.5 ml of ethyl acetate. The ratio of (total) guests : (total) hosts was thus 10 : 1. The solution was allowed to crystallize as before. Compound **V** (H1·H2·26XYL/35XYL) crystallized from the mixture of the two hosts with 2,6-xylenol and 3,5-xylenol, and was subjected to single crystal diffraction as described below.

For the competition experiments with the mixed hosts H1 + H3. This was carried out by changing the proportions of H1/H3 from 90/10 to 50/50 in five different experiments. A total of 0.82 mmol of the two hosts were added to a total of 8.2 mmol of the selected pair of guests (4.1 mmol of each, as described previously), and dissolved in 0.5 ml of ethyl acetate. The ratio of (total) guests : (total) hosts was again 10 : 1. The solutions were allowed to crystallize as before.

The crystals were harvested and blotted dry and subjected to NMR and single crystal X-ray diffraction analysis. The crystals were not washed with a different solvent for fear of partial dissolution and loss of the included xylenol guests.

X-ray crystallography

Single crystal X-ray diffraction data were collected on a Bruker DUO APEX II diffractometer for all structures using Mo Kα radiation (λ = 0.71073 Å) at a temperature of 173 K.[13] The intensity data were collected using the phi scan and omega scan techniques, scaled, and reduced with SAINT-Plus.[14] The correction of the collected intensities for absorption was done using the SADABS program.[15] The X-seed interface,[16] operating the SHELX suite of programs[17] was used to solve each structure by direct methods, and to carry out structure refinement using full-matrix least squares. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms bound to carbon were included in the refinement in idealized positions in a riding model with isotropic thermal parameters 1.2–1.5 times the U_{iso} values of their parent atoms. Hydrogens on the hydroxyl groups of both the hosts and guests were placed according to the formulae devised by Lusi and Barbour,[18] who analyzed the data of H-bonded system obtained from neutron diffraction. The method offers an equation based on the O(donor)···O(acceptor) distance which yields the value of the O–H bond length in H-bonded O–H···O interactions.

Table 1 ^{1}H NMR results from the competition experiments of H1 with xylenols. Experiment numbers given in square brackets. Those for which crystal structure analysis was done are indicated in bold

Xylenol (XYL)	23XYL	24XYL	25XYL	26XYL	34XYL	35XYL
24XYL	*[1]* 23XYL-90 24XYL-10					
25XYL	*[2]* 23XYL-55 25XYL-45	*[3]* Host				
26XYL	***[4]*** 23XYL-40 26XYL-60	*[5]* Host	*[6]* 25XYL-6 26XYL-94			
34XYL	*[7]* 23XYL-10 34XYL-90	*[8]* 24XYL-16 34XYL-84	*[9]* 25XYL-6 34XYL-94	*[10]* 26XYL-3 34XYL-97		
35XYL	***[11]*** 23XYL-46 35XYL-54	*[12]* 24XYL-9 35XYL-91	*[13]* 25XYL-7 35XYL-93	***[14]*** 26XYL-12 35XYL-88	***[15]*** 34XYL-94 35XYL-6	

Table 2 Crystallographic data parameters of the host–guest complexes obtained from competition experiments

Structure	I	II	III	IV
Compound	H1·34XYL	H1·35XYL	H1·23XYL/26XYL	H1·23XYL/35XYL
Formula asymm. unit	$(C_{15}H_{16}O_2)\cdot C_8H_{10}O$	$(C_{15}H_{16}O_2)\cdot C_8H_{10}O$	$2(C_{15}H_{16}O_2)\cdot 2C_8H_{10}O$	$4(C_{15}H_{16}O_2)\cdot 4C_8H_{10}O$
M [g mol^{-1}]	350.4	350.4	700.9	1402
Data collection temp T [K]	173(2)	173(2)	173(2)	173(2)
Crystal shape and size [mm]	Orange block, 0.23 × 0.28 × 0.30	Orange block, 0.05 × 0.06 × 0.10	Orange block, 0.18 × 0.25 × 0.28	Colourless needle, 0.05 × 0.09 × 0.48
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$	$C2/c$	Pn
a [Å]	6.4218(6)	11.783(3)	30.650(2)	6.3007(3)
b [Å]	14.8289(14)	11.175(2)	6.3048(5)	20.7627(11)
c [Å]	20.2173(19)	15.163(3)	39.852(3)	29.9858(14)
β [°]	96.132(2)	93.080(4)	91.359(2)	95.787(2)
Volume [Å^3]	1914.2(3)	1993.8(8)	7699(1)	3902.7(3)
Z	4	4	8	2
D_c, calc. density [g cm^{-3}]	1.216		1.209	1.193
Absorption coefficient [mm^{-1}]	0.079		0.079	0.078
F(000)	752		3008	1504
θ range	1.706–28.339		1.329–27.910	1.962–26.385
Reflections collected	30 151		101 365	69 771
No. independent reflections	4783		9208	14 770
No. reflections with $I > 2\text{sigma}(I)$	3382		8537	14 075
R_{int}	0.0654		0.0255	0.0395
Final R indices, R_1, wR_2 [$I > 2\text{sigma}(I)$]	0.0486, 0.1095		0.0387, 0.0996	0.0412, 0.1009
R indices (all data), R_1, wR_2	0.0753, 0.1226		0.0417, 0.1021	0.0440, 0.1025
Max, min residual electron density (e Å^{-3})	0.220, −0.225		0.309, −0.175	0.263, −0.188

NMR spectroscopy

Approximately 5 mg of representative crystals were blotted dry, crushed, and dissolved in 600 μL of DMSO-d6 and introduced into a 5 mm NMR tube for data acquisition. One-dimensional (1D) ^{1}H and two-dimensional (2D) ^{1}H–^{13}C HSQC NMR spectra were recorded on a Bruker 300 or 400 MHz spectrometer at 30 °C and processed using standard Bruker software (Topspin 3.5). The HSQC experiment was optimized for J = 145 Hz (for directly attached ^{1}H–^{13}C correlations). The spectra were referenced relative to the solvent signal at 7.26 ppm (for ^{1}H) and 77.16 ppm (for ^{13}C); appropriate signals were integrated to determine the relative proportions of the guests. The analysis was carried out on the crystals harvested from the mother liquors of the equimolar xylenol binary mixtures. These crystals were dried using blotting paper but were not washed with any solvent to avoid any exchange of guests.

Integration of the peaks of the methyl substituents of the isomers were used to determine their relative proportions of guests in the different samples. Fig. 1 shows an overlay of the

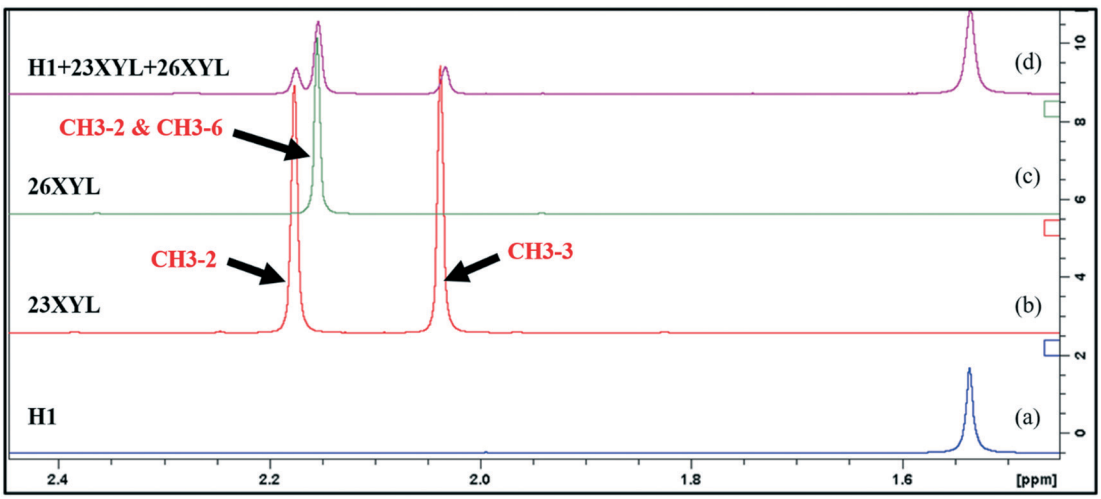


Fig. 1 Overlay of the expansion of the ^{1}H NMR methyl region for (a) H1, (b) 23XYL, (c) 26XYL, (d) complex of H1 + 23XYL + 26XYL obtained in experiment [4].

expansion of the methyl region of the ^{1}H NMR spectra of the guests (23XYL and 26XYL) and the host and guests. Fig. 1a shows the methyl groups of the host compound at 1.15 ppm. Fig. 1b has CH_3-2 at 2.03 ppm and CH_3-3 at 2.18 ppm for 23XYL and Fig. 1c has CH_3-2 and CH_3-6 at 2.15 ppm. These diagnostic peaks were used to determine the relative ratio of 60/40% for the 23XYL/26XYL guests in the host–guests mixture (Fig. 1d). The same procedure was applied to all other mixtures and gave the results shown in Table 1. Representative NMR spectra are included in the ESI.† When two isomers had overlapping methyl peaks in the ^{1}H spectrum, but the ^{13}C NMR signals were resolved, then quantification was performed by integration of the relevant HSQC cross peaks. Thus, NMR analysis elucidated the relative ratio of the guests, whereas the percentage host–host and host–guest was also obtained when mixed hosts method was used.

Results

Competition experiments: separation of xylenols by H1

To study the selectivity of the host H1 for particular isomers of xylenol, we carried out pairwise competition experiments in which H1 was dissolved with an equimolar mixture of two xylenol isomers and the resulting crystals analysed by NMR and, where possible, by single crystal structure elucidation. Table 1 shows the NMR results given as percentages of the enclathrated xylenol guests. In general, when both xylenols were enclathrated, if the major component was greater than 85%, single crystal analysis found that only the major component can be refined in the crystal structure. We have observed a similar phenomenon in the separation of lutidine isomers.[19–21] The most interesting result is obtained when the selectivity is poor because, paradoxically, more information is obtained regarding the selectivity when both isomers are entrapped in the same crystal. The resultant conformational changes in the host can thus be studied and one may be able to examine the mechanism giving rise to selectivity.

Experiments [3] and [5] resulted in the recrystallisation of the empty host structure (sometimes referred to as the apohost structure). Although experiments [1] and [6] indicated high selectivity for 23XYL and 26XYL respectively, they yielded poor quality crystals which could not be used for data collection. Experiments [7], [8], [9] [10] and [15] showed a high selectivity for 34XYL, and a crystal was selected from [15] for X-ray analysis (crystal structure **I**). 35XYL appeared to be selected in experiments [12], [13] and [14] and inclusion compound **II** was selected for crystal structure analysis from the latter. Experiments [4] and [11] resulted in the crystallization of mixed guest inclusion compounds **III** and **IV** respectively. Experiment [2] also showed evidence of a mixed-guest compound, but the crystals did not diffract adequately for single crystal analysis. In total, we elucidated four crystal structures from the competition experiments given in Table 1. Their crystal data and refinement parameters are listed in Table 2. The identity of the guests included can be unequivocally confirmed for those cases where single crystal diffraction was performed, but we note that similar confirmation is not possible for the experiments where single crystal structures were not obtained. However, we saw no evidence, on inspection under polarized light, of two or more crystalline phases being produced in any of these or subsequent experiments.

Crystal structures from competition experiments with host H1

The crystal structures exhibit networks of hydrogen bonds in which the hydroxyl moieties of the host H1 and the xylenol guests can act as both H-bond donor and acceptor.

Structure **I**, H1·34XYL, crystallizes in $P2_1/c$ with $Z = 4$. The packing is characterized by chains of H1 which are stabilized by O–H···O(H) H-bonds, and in addition, form H-bonded rings with the 34XYL guest. The packing is shown in Fig. 2, and may be described by graph-set analysis[22,23] as $C_1^1(12)$

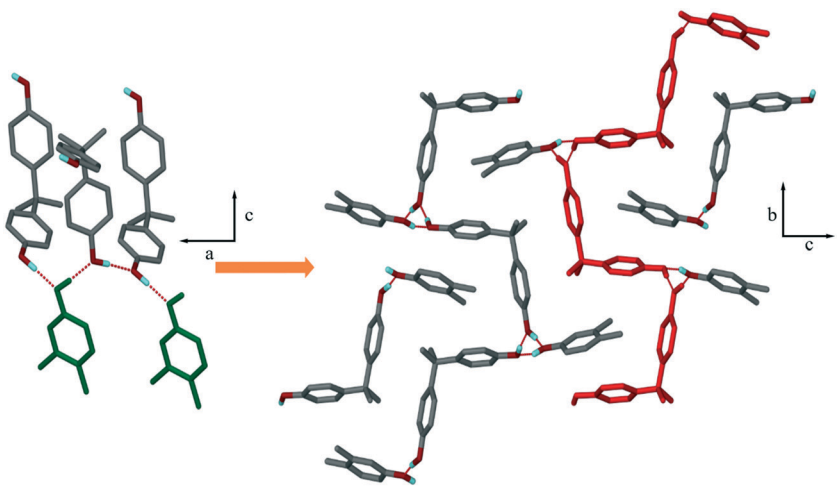


Fig. 2 Packing of compound **I** (H1·34XYL) viewed along [010] (left) and along [100] (right). Alternative host chains in red (atom colours are C: grey, O: red, H: blue) hydrogens bound to carbon are omitted for clarity.

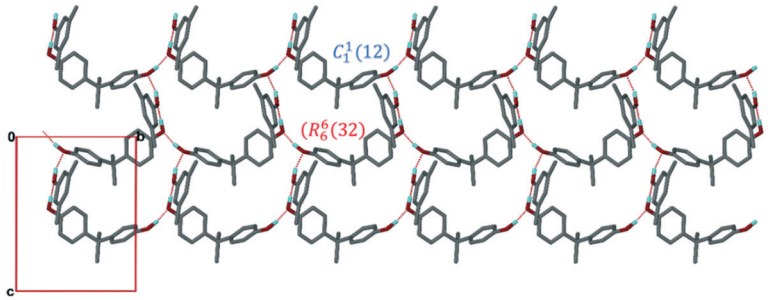


Fig. 3 Packing of compound II viewed along [100]. Colour coding as in Fig. 2.

$[R_3^3(6)]$. The H1 chains propagate in the [010] direction and the 34XYL guests are in the loops of the twisted chains.

A search of the Cambridge Structural Database[24] found 11 structures in which H1 had formed a co-crystal or solvate. One of these, refcode SIXDOS, is the co-crystal of H1 with *p*-cresol.[25] This compound is isostructural with compound **I**, having almost identical unit cell parameters and packing arrangements. Although **I** has an extra methyl group at the *meta*-position, the same hydrogen-bonding motifs can be formed in both structures, which accounts for this similarity. The CSD search revealed 20 solvate or co-crystal structures with H2 and 47 with H3, though none are similar to the structures reported here.

Structure **II**, H1·35XYL could not be refined satisfactorily and we only report the cell parameters in Table 2. However, the structure could be solved sufficiently to show that it bears certain packing similarities with **I**, in that the host forms a series of chains running along [010], with heavily disordered 35XYL guests forming hydrogen bonded bridges between chains (Fig. 3).

Structure **III** crystallizes in the space group *C*2/*c*. The asymmetric unit consists of two H1 hosts, a disordered 23XYL (86% site occupancy) and 26XYL (14% site occupancy) and one 26XYL with full site occupancy. The ratio of H1 : 23XYL : 26XYL is thus 1 : 0.43 : 0.57 which is in good agreement with the NMR data in Table 1 for experiment [4]. The packing, shown in Fig. 4 shows the H1 hosts packed in double layers running along [001]. The interior of the double layer is hydrophobic, containing the *gem*-dimethyl groups, while the outer sides of the double layer may be deemed hydrophilic in that it contains the hydroxyl moieties which hydrogen bond with the 23XYL and 26XYL guests in a series of $R_3^3(6)$ hydrogen bonded rings.

The refinement of structure **IV** (H1·23XYL/35XYL) proved difficult. Although the synthesis was repeated several times, the resultant crystals were of poor quality. The best preparation yielded crystals that did not extinguish completely under polarized light and the structure was initially solved in the space group *P*1. The resultant structure was checked for higher symmetry by the program Platon[26] which strongly suggested the space group *Pn*, duly adopted. Platon further identified twinning which was resolved by application of the appropriate twin law.

The asymmetric unit contains four H1 hosts, two 23XYL and two 35XYL guest, all crystallographically independent. The ratio of H1 : 23XYL : 35XYL is thus 1 : 0.50 : 0.50, which is in good agreement with the ratio 1 : 0.46 : 0.54 determined by NMR on the bulk sample (Table 1, experiment [11]). The packing, shown in Fig. 5, bears strong resemblances to that shown for structure **III**, in that one notes a host double layer with hydrophobic and hydrophilic surfaces. The latter features H-bonded 23XYL and 35XYL guests. The hosts and guests form chains running along [010].

The conformation of the host H1 in all the structures elucidated is reported in Table S1† which lists the torsion angles τ_1 and τ_2 are defined as $\tau_1 = (a - b - c - d)$ and $\tau_2 = (b - c - d - e)$, Scheme 2. The variations of the torsion angles τ_1 and τ_2 are relatively small, showing that the host conformation is fairly constant and is thus does not play a key role in the selectivity of xylenol isomers.

Competition experiments: separation of xylenols by mixed hosts (H1 and H2)

The Dutch resolution method[11] was first reported in 1998, and involves the use of combinations of structurally similar resolving agents ("families") to enhance the selective resolution of enantiomers. We hypothesized that the use of combinations of structurally similar host compounds might

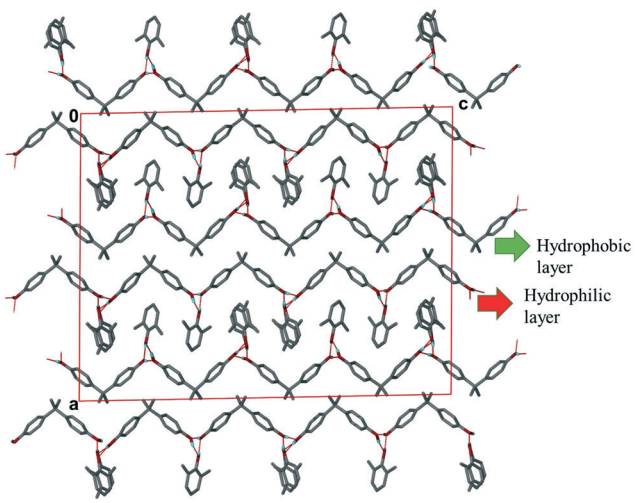


Fig. 4 Packing of **III** (H1·23XYL/26XYL) viewed along [100] showing the two layers formed within the structure.

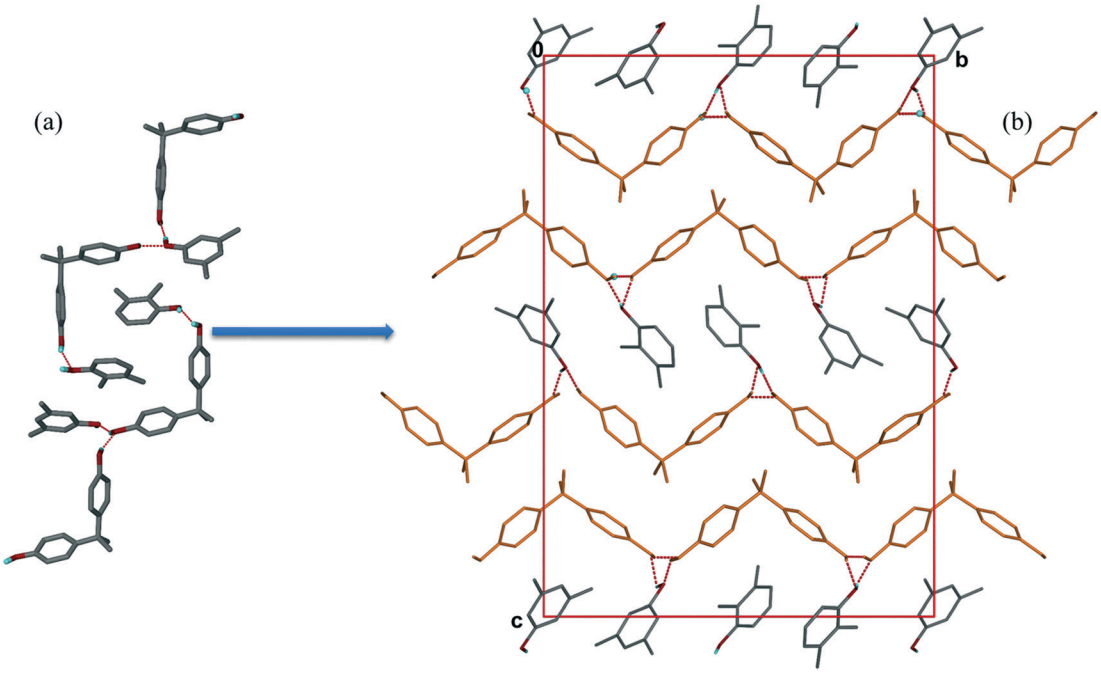
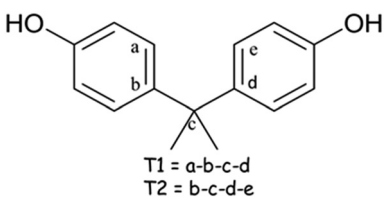


Fig. 5 Packing of **IV** showing (a) hydrogen bonding between host and host, and host and guest, (b) host forms H-bonded chains (in orange) parallel to the *b*-axis.

enhance the selectivity for isomers compared to the use of a single host compound. To that end, we carried out competition experiments using a combination of two hosts (either H1 and H2, or H1 and H3) across the pairwise combinations of xylenol isomers. As before, the competition experiments were initiated with a starting (total) guests : (total) hosts ratio of 10 : 1 to eliminate an artificial selectivity developing as compounds crystallize from the solution.

Experiments [16], [17], and [18] tested the selectivity H2 alone in competition experiments of 23XYL/26XYL, 23XYL/35XYL, and 26XYL/35XYL. These were chosen because H1 had shown poor selectivity in the first two combinations while the third combination yielded a strong preference for 35XYL (Table 1). The results testing the efficacy of H2 are reported in Table 3, and show a similar lack of selectivity for 23XYL/26XYL, a preference for 35XYL in 26XYL/35XYL and an inversion in selectivity, towards 23XYL in 23XYL/35XYL.

Experiments [19]–[21] detail the results of the mixed host/mixed guest competition experiments with H1 and H2. An interesting aspect of the Dutch resolution method is that the final crystalline product may have host–host and host–guest stoichiometries that differ from those of the starting solution. This was particularly evident in experiment [19] where an equimolar mixture of H1 and H2 resulted in crystals containing almost entirely H1, while the guest selectivity was poor in this case. Experiments [20] and [21] retained the H1 : H2 ratio and showed altered selectivity towards the xylenols compared to single host experiments. In experiment [20], the competition with 23XYL/35XYL, the selectivity changes from 54% 35XYL (with H1), or 81% 23XYL (with H2) to 88% 23XYL in the mixed host system. In experiment [21], the competition with 26XYL/35XYL, the selectivity changes from 88% 35XYL (with H1), or 72% 35XYL (with H2) to 62% 35XYL in the mixed host system. Understanding these results would be enhanced if one were able to obtain single crystals of each of these outcomes.



Scheme 2 Torsion angles of H1.

Table 3 ^{1}H NMR result for competition experiments using H2, and H1 + H2, for three selected guest pairs

Composition	H1	H2	23XYL	26XYL	35XYL
Expt [16] start	—	100	50	50	—
End	—	100	50	50	—
Expt [17] start	—	100	50	—	50
End	—	100	81	—	19
Expt [18] start	—	100	—	50	50
End	—	100	—	28	72
Expt [19] start	50	50	50	50	—
End	98	2	55	45	—
Expt [20] start	50	50	50	—	50
End	48	52	88	—	12
Expt [21] start	50	50	—	50	50
End	51	49	—	38	62

Unfortunately, this is often not possible, but we were able to obtain a crystal structure from the product of experiment [21].

Structure **V** is unusual in that it was derived from a solution containing an equimolar mixture of H1 and H2, and an equimolar mixture of 26XYL and 35XYL, and retained all four species in the crystalline product. The NMR results showed that the bulk sample contained an almost equimolar amount of H1 and H2, which had enclathrated an unequal mixture of 26XYL and 35XYL. The resulting product crystallized in $P2_1/c$ and the asymmetric unit contains two H1 molecules, two H2 molecules and a disordered 26XYL/35XYL sharing the same site in unequal proportions (26XYL : 35XYL = 0.34 : 0.66, in good agreement with NMR data). The important feature of this structure is that the disordered 26XYL/35XYL guest is surrounded by four host molecules (one pair of H1 and one pair of H2) as shown in Fig. 6. The crystallographic data parameters of **V** are given in Table 4. Mixed-host, mixed-guest crystal structures are still relatively rarely reported in the literature. One of us has previously reported a similar example, in which a family of four similar diol hosts were used singly and in pairs in an attempt to enhance the resolution of 2-butylamine.[27] Although there was no improvement in the enantiomeric resolution, a structure of two hosts with two guests was reported.

Competition experiments: separation of xylenols by mixed hosts (H1 and H3)

The selectivity of the same three pairs of isomers was studied with combinations of H1 and H3. The latter host, 4,4-cyclohexylidene bisphenol has been studied extensively and has been shown to enclathrate picolines,[28] aliphatic alcohols[29] and lutidines.[30] It has also been employed in the separation of xylenols,[31] establishing that 35XYL is preferred to 26XYL; 23XYL is preferred to 26XYL; but the competition between 35XYL and 23XYL is concentration dependent. In this work, equimolar mixtures of H1and H3 with equimolar mixtures of the xylenols gave rise to products in which both host and guest ratios had changed, with an apparent selectivity for H3 over H1 and for 23XYL over 26XYL, and 35XYL in both experiments where it was present (Tables 5 and S4 and S5†).

The observation that the relative amounts of both host and guest vary in this way led us to explore the phenomenon further by varying the starting ratio of H1 : H3 systematically for each pairwise combination of xylenol isomers. The results for the H1/H3 and the guest pair 23XYL/26XYL are reported in Table 5 and shown graphically in Fig. 7. The results for the other isomer pairs are given in the ESI† as Tables S4 and S5.

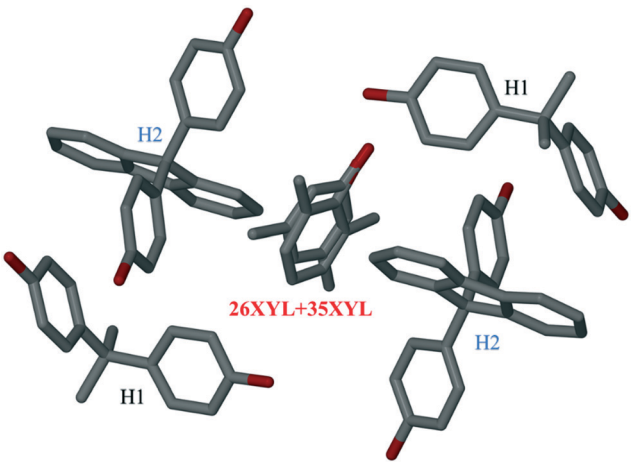


Fig. 6 Asymmetric unit of structure **V** showing 26XYL/35XYL enclathrated by a mixture of the hosts H1 and H2 (atom colours as per Fig. 2. Hydrogen atoms have been omitted for clarity).

Table 4 Crystallographic data parameters of compound **V**

	V
Compound	H1·H2·26XYL/35XYL
Formula asymm. unit	$2(C_{15}H_{16}O_2)2(C_{25}H_{18}O_2)\cdot C_8H_{10}O$
M [g mol^{-1}]	1279.5
Data collection temp T [K]	173(2)
Crystal shape and size [mm]	Orange block, 0.18 × 0.20 × 0.32
Crystal system	Monoclinic
Space group	$P2_1/c$
a [Å]	21.0580(9)
b [Å]	15.5380(6)
c [Å]	21.249(1)
β [°]	98.481(1)
Volume [Å^3]	6876.6(5)
Z	4
D_c, calc. density [g cm^{-3}]	1.236
Absorption coefficient [mm^{-1}]	0.079
$F(000)$	2712
θ range	0.978–28.370
Reflections collected	78 563
No. independent reflections	17 204
No. reflections with $I > 2\text{sigma}(I)$	11 140
R_{int}	0.0707
Final R indices, R_1, wR_2 [$I > 2\text{sigma}(I)$]	0.0500, 0.1110
R indices (all data), R_1, wR_2	0.0894, 0.1300
Max, min residual electron density (e Å^{-3})	0.239, −0.208

Table 5 Results of mixed hosts (H1 + H3) experiments for 23XYL/26XYL mixture

Composition	H1	H3	23XYL	26XYL
Expt [22] start	90	10	50	50
End	100	0	55	45
Expt [23] start	80	20	50	50
End	73	27	65	35
Expt [24] start	70	30	50	50
End	38	62	72	28
Expt [25] start	60	40	50	50
End	9	91	90	10
Expt [26] start	50	50	50	50
End	6	94	92	8

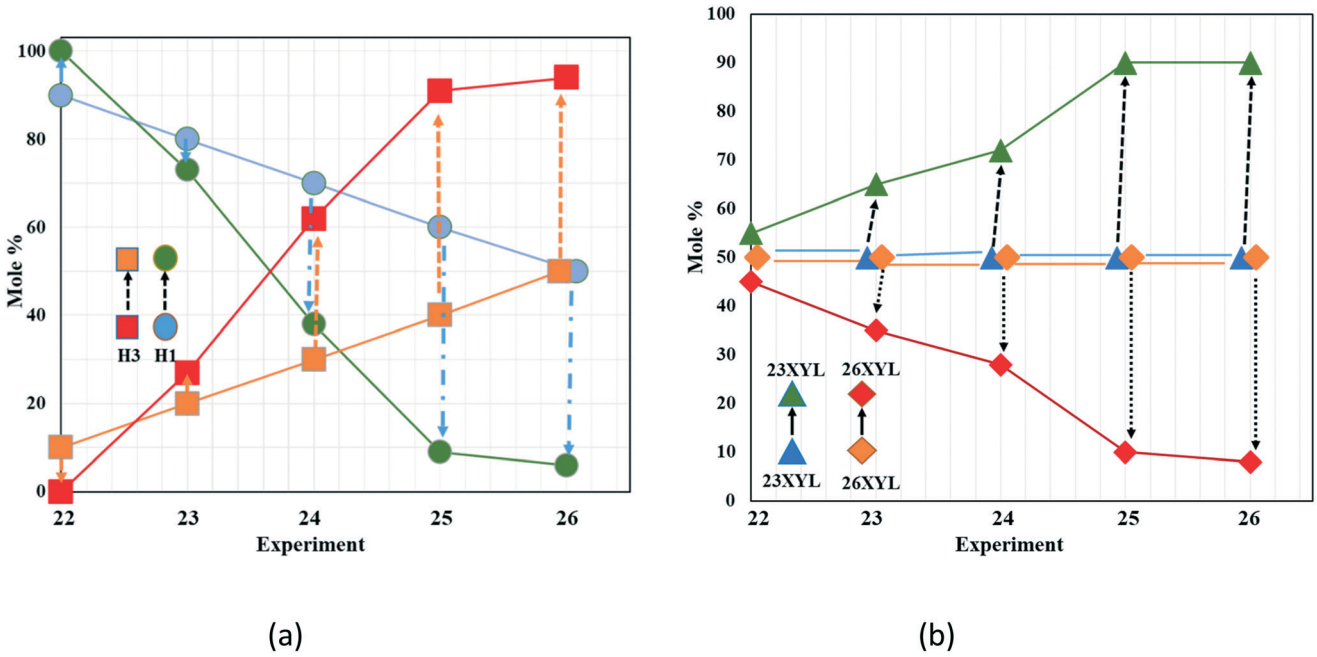


Fig. 7 Trends observed in the competition experiments varying both host and guest ratios. (a) Host H1 decreases while H3 is selected; (b) guest 23XYL is consistently selected across all compositions.

Fig. 7a shows H1 starting at 90% and decreasing linearly to 50%, while H3 starts at 10% and increases to 50%. The trend of the experiments shows H1 has decreased at the expense of H3 in the products obtained. The concomitant selectivity of the 23XYL/26XYL (Fig. 7b) shows a steady increase in 23XYL and decrease in 26XYL. There is thus a direct correlation between H1/H3 and the corresponding selectivity of 23XYL/26XYL. Similar results are obtained for H1/H3 and the guests 23XYL/35XYL (Table S4, Fig. S1†). However, Table S5† shows that changes in the H1/H3 composition had no effect in the 26XYL/35XYL selectivity, with 35XYL being exclusively enclathrated.

Conclusion

The separation of the six xylenol isomers has been carried out by enclathration employing 4,4-isopropylidene bisphenol, H1, with a selectivity preference of 34XYL > 35XYL > 26XYL > 23XYL > 25XYL > 24XYL. Crystal structure analysis of two single-guest and two mixed-guest structures showed that the host conformation remains fairly constant, thus eliminating this as the driving factor in the selectivity observed. Applying a modification of the Dutch resolution method, in which a family of similar hosts are combined, gave rise to greater guest selectivity. The combination of H1 with H2 in equimolar proportions enhances 23XYL over 35XYL, and 35XYL over 26XYL. The latter combination yielded a structure (**V**) comprising both H1 and H2, and guest refinement showed a selectivity in good agreement with that analysed in the bulk sample by NMR. The combination of H1 with H3 was carried out in different experiments which altered the proportion of H1/H3 systematically. Enclathration increased the proportion of H3 and enhanced the selectivity of 23XYL over 26XYL.

The crystal structures **I**, **II**, **III**, and **IV** obtained with H1 are all stabilized by extensive hydrogen bonded networks, linking adjacent host molecules into chains which also hydrogen bonded the captured guests. The strength of the hydrogen bonds, as estimated by the O(donor)···O(acceptor) distances vary from 2.64 Å to 2.95 Å, and may be considered to change from strong to weak.[32] These may be regarded as a constant feature throughout the structures elucidated. The synergistic selectivity effects which occur with the addition of a second host molecule may be attributed to the packing effects brought about by the different moieties (fluorenylidene in H2 and cyclohexylidene in H3). Confirmation of this effect will be sought in further work aiming to isolate crystals of these mixed-host, mixed-guest compounds.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank Dr. Clive Oliver (University of Cape Town) for useful discussions regarding the crystal structures.

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Selective enclathration of xylenols: Synergistic effects of mixed hosts

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Electronic Supplementary Information

Table S1: Torsion angles of the host molecules.

	τ_1	τ_2
Structure I	60	73
Structure II	41	79
Structure IIIa	58	60
IIIb	53	58
Structure IVa	59	59
IVb	56	60
IVc	55	59
IVd	60	66
Structure VH1a	42	70
VH1b	58	65
VH2a	42	46
VH2b	42	45

Table S2: Hydrogen bonding details for the structures obtained from the competition experiments

Compounds		
H1•34XYL		
O1-H1••• O61	2.681	
O61-H61•••O13	2.705	[-x+1, y-1/2, -z+1/2]
O13-H13•••O1	2.705	[-x+2, y+1/2, -z+1/2]
H1•23XYL/26XYL		
O1-H1•••**O21**	2.657	[x, y+1, z]
O13-H13•••O33	2.711	[x, -y+2, z+1/2]
O21-H21•••O61	2.653	
O33-H33•••O71	2.729	
O61-H61•••O1	2.686	
O71-H71•••O13	2.727	[x, -y+1, z-1/2]
H1•23XYL/35XYL		
O1-H1•••O28	2.676	[x+1, y+1, z]
O16-H16•••O70	2.664	
O91-H91•••O1	2.67	[x, y-1, z]
O31-H31•••O81	2.643	
O81-O81•••O59	2.674	[x, y-1, z]
O47-H47•••O43	2.642	
O70-H70•••O13	2.673	[x-1, y, z]
O43-H43•••O62	2.667	
O28-H28•••O91	2.651	
O59-H59•••O31	2.630	[x-1, y+1, z]
O13-H13•••O16	2.647	
O62-H62•••O47	2.680	[x+1, y, z]

Table S3: Hydrogen bonding details for structure **V** containing mixed hosts

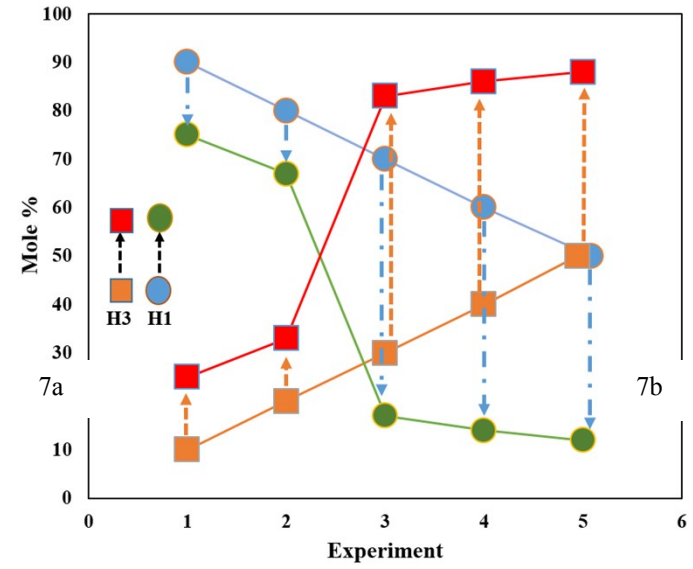
Compounds		
H1•H2•26XYL/35XYL		
O1-H1••• O16	2.809	
O53-H53•••O56	2.713	[x, y-1, z]
O41-H41•••O81_a	3.002	
O41-H41•••O91_b	2.573	
O81_a-H91••• O1	2.912	
O91_b-H91••• O1	2.587	
O13-H13••• O53	2.762	[x, y+1, z]
O22-H22•••**O**13	2.693	[x, -y+3/2, z+1/2]
O16-H16•••O22	2.787	[x, -y+1/2, z-1/2]
O62-H62••• O41	2.649	[x, -y+3/2, z-1/2]
O56-H56•••**O**62	2.701	[x, -y+3/2, z+1/2]

Table S4: Results of competition experiments with mixed hosts (H1+H3) for mixtures of 23XYL/35XYL

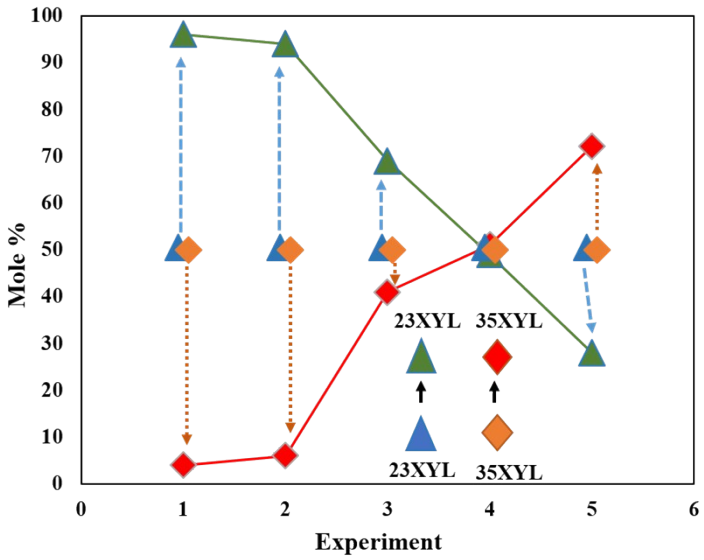
Composition	H1	H3	2.3	3.5
Expt 1 Start	90	10	50	50
End	75	25	96	04
Expt 2 Start	80	20	50	50
End	67	33	94	06
Expt 3 Start	70	30	50	50
End	17	83	69	41
Expt 4 Start	60	40	50	50
End	14	86	49	51
Expt 5 Start	50	50	50	50
End	12	88	28	72

Table S5: Results of competition experiments with mixed hosts (H1+H3) for mixtures of 26XYL/35XYL

Composition	H1	H3	2.6	3.5
Expt 1 Start	90	10	50	50
End	100	0	0	100
Expt 2 Start	80	20	50	50
End	25	75	0	100
Expt 3 Start	70	30	50	50
End	16	84	0	100
Expt 4 Start	60	40	50	50
End	11	89	0	100
Expt 5 Start	50	50	50	50
End	13	87	0	100



7a



7b

Figure S1: Trend followed by the hosts H1 and H3 (7a) and the guest 23XYL/35XYL (7b)

^{1}H NMR spectra for the different studies

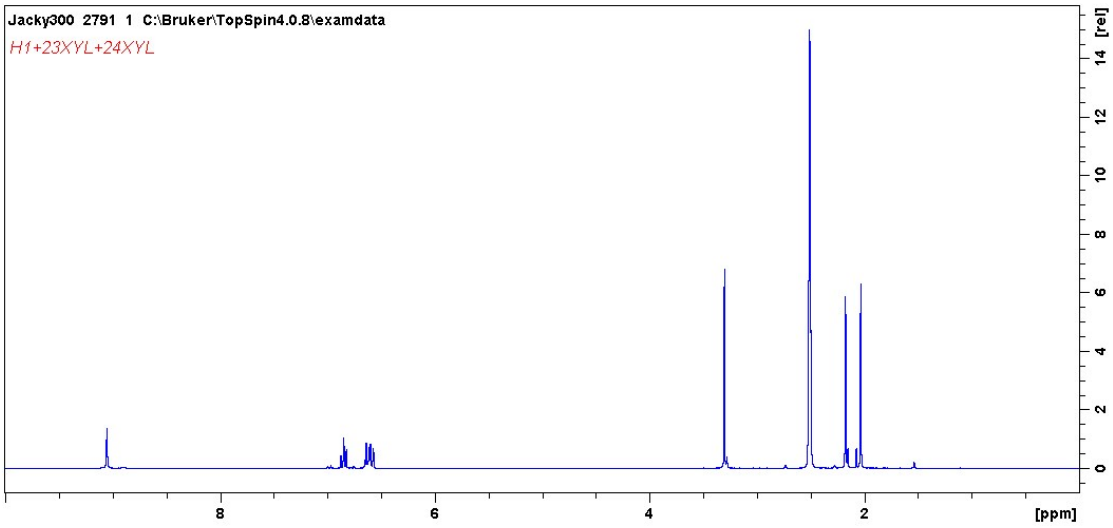


Figure S2: ^{1}H NMR spectrum for H1+ 23XYL+24XYL

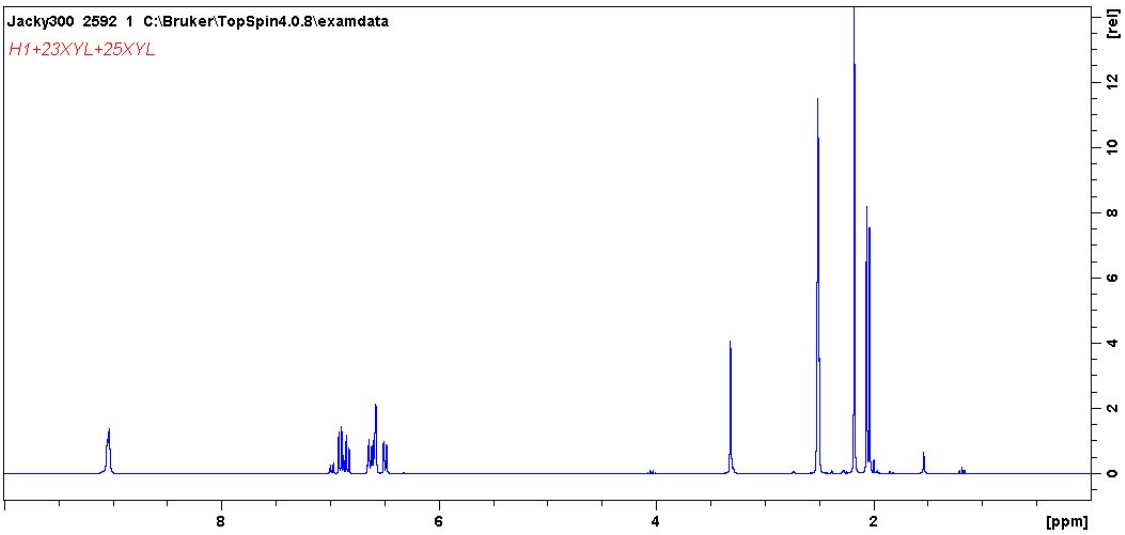


Figure S3: ^{1}H NMR spectrum for H1+ 23XYL+25XYL

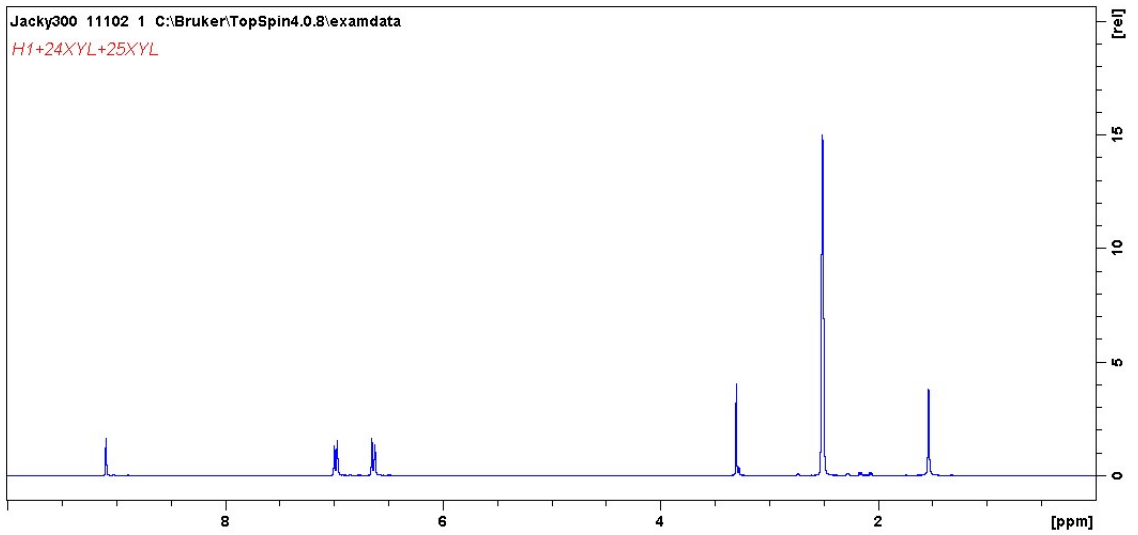


Figure S4: ^{1}H NMR spectrum for H1+ 24XYL+25XYL

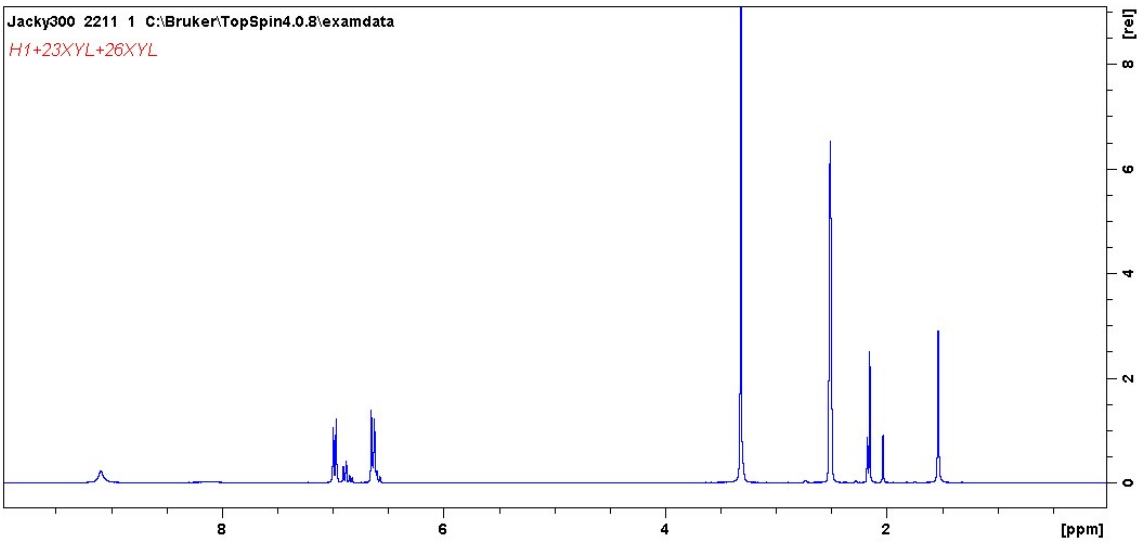


Figure S5: ^{1}H NMR spectrum for H1+ 23XYL+26XYL

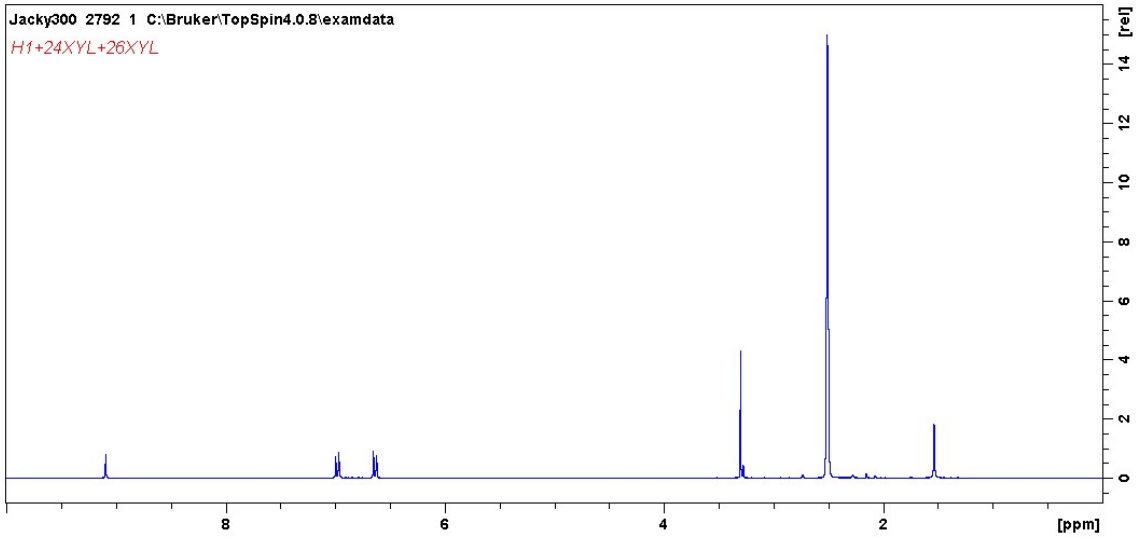


Figure S6: ^{1}H NMR spectrum for H1+ 24XYL+26XYL

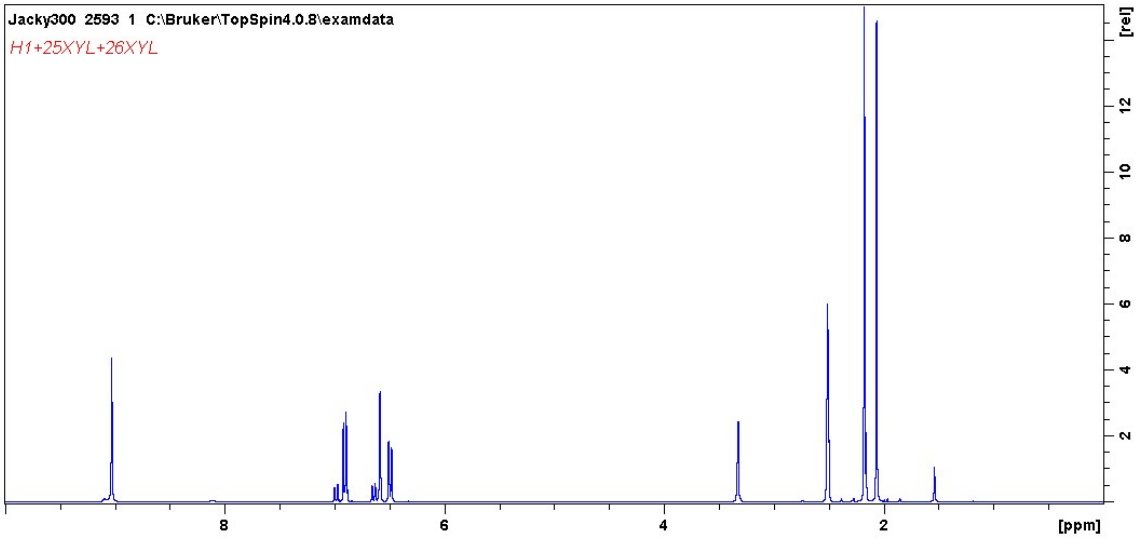


Figure S7: ^{1}H NMR spectrum for H1+ 25XYL+26XYL

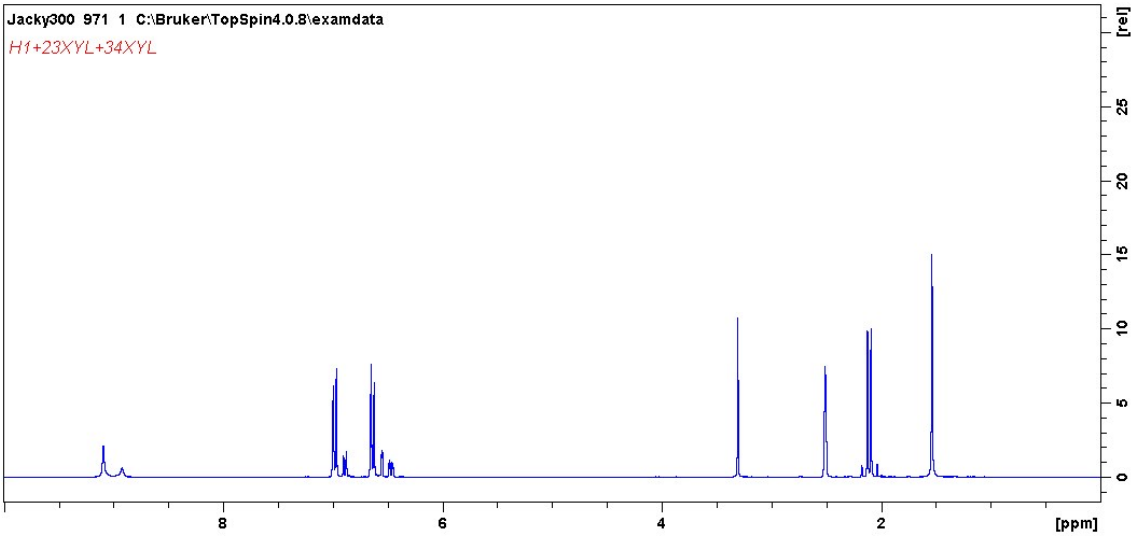


Figure S8: ^{1}H NMR spectrum for H1+ 23XYL+34XYL

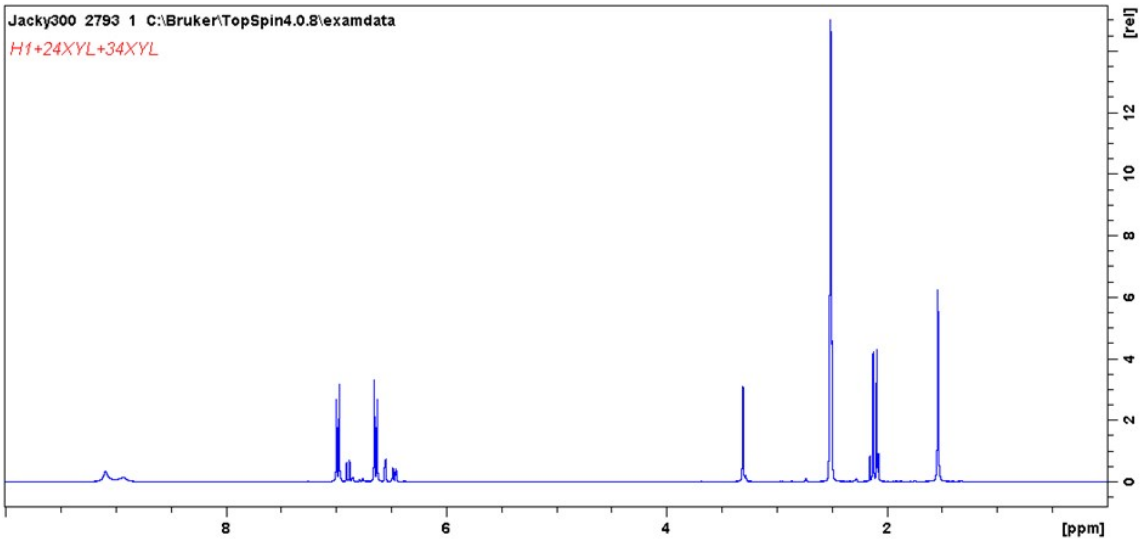


Figure S9: ^{1}H NMR spectrum for H1+ 24XYL+34XYL

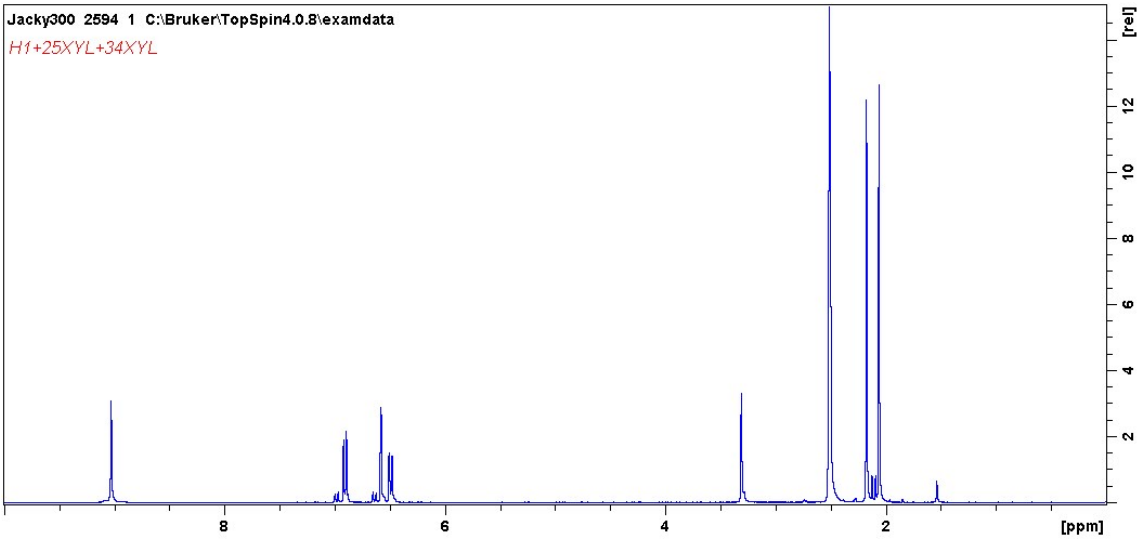


Figure S10: ^{1}H NMR spectrum for H1+ 25XYL+34XYL

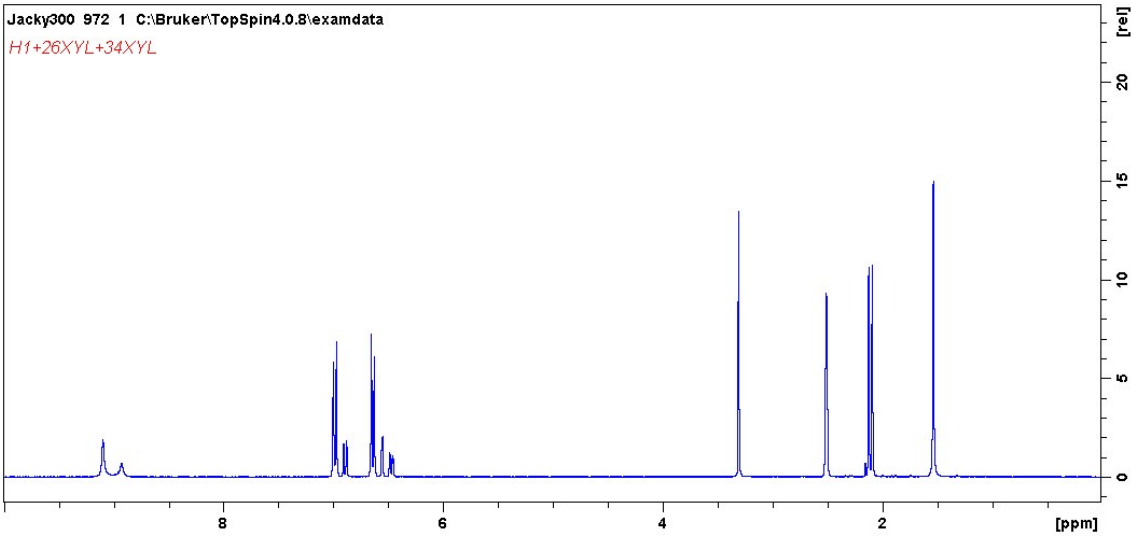


Figure S11: ^{1}H NMR spectrum for H1+ 26XYL+34XYL

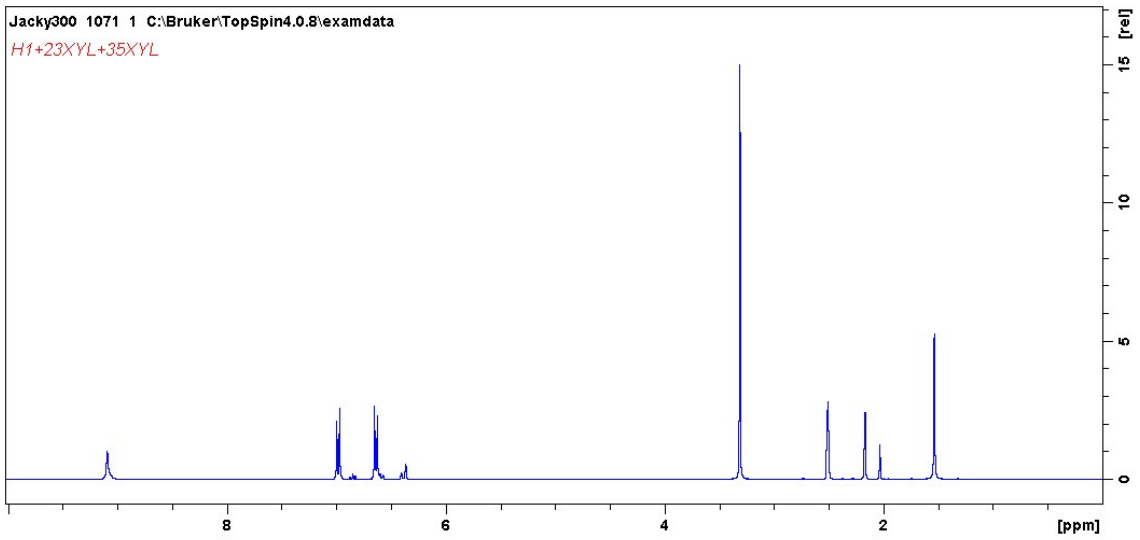


Figure S12: ^{1}H NMR spectrum for H1+ 23XYL+35XYL

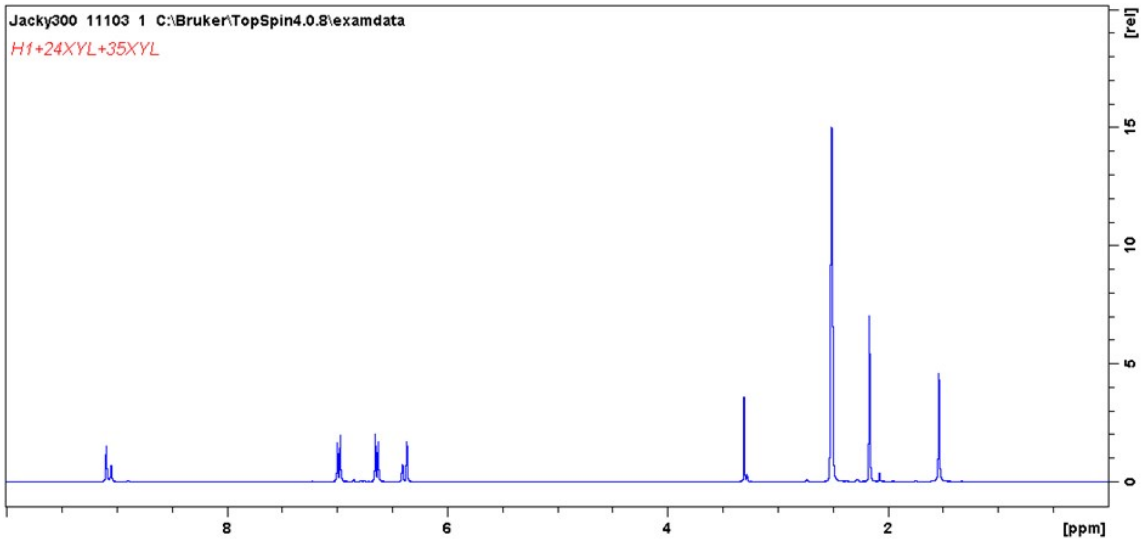


Figure S13: ^{1}H NMR spectrum for H1+ 24XYL+35XYL

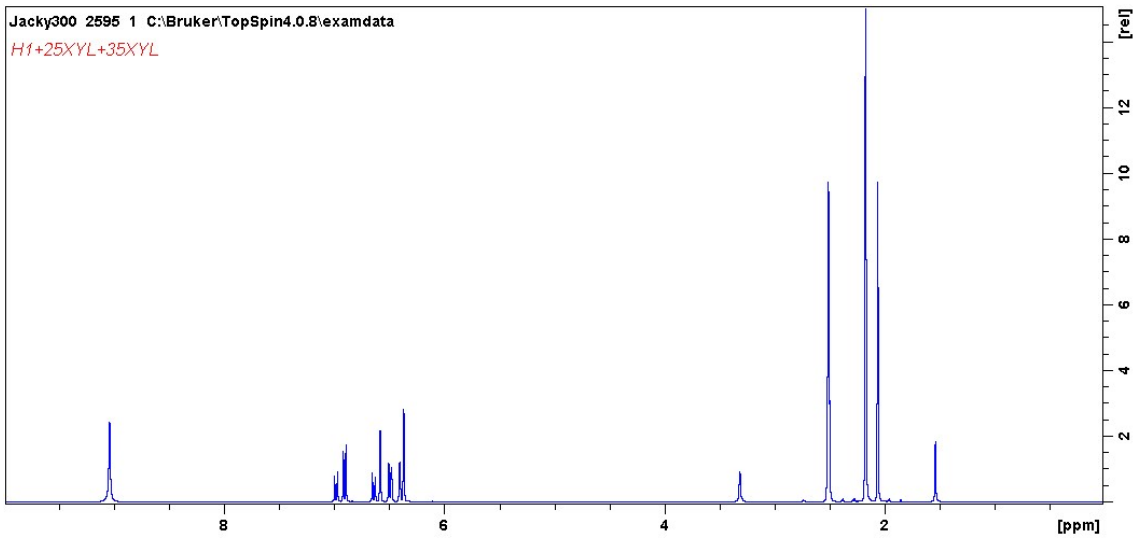


Figure S14: ^{1}H NMR spectrum for H1+ 25XYL+35XYL

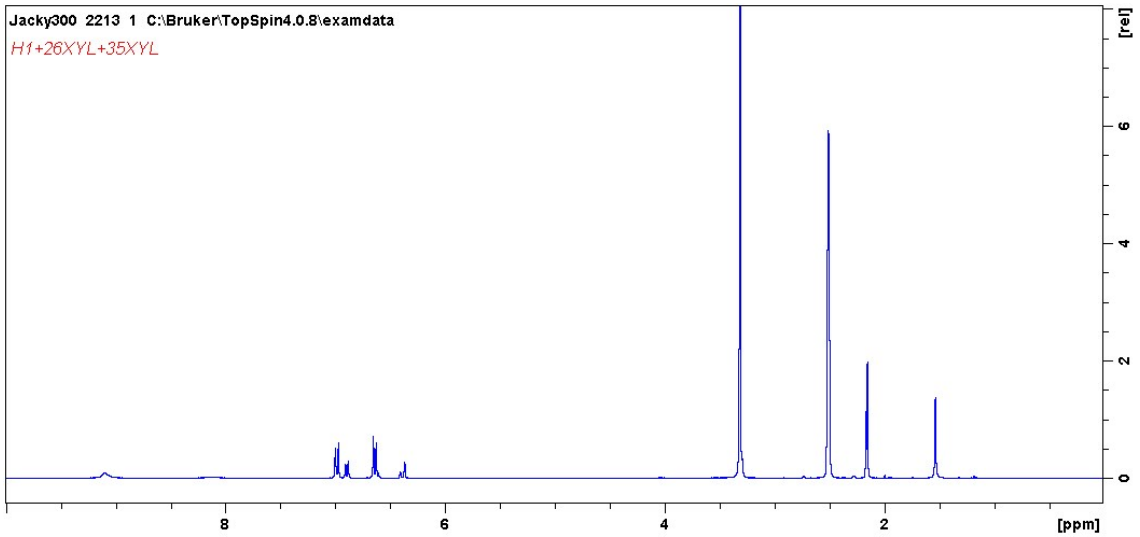


Figure S15: ^{1}H NMR spectrum for H1+ 26XYL+35XYL

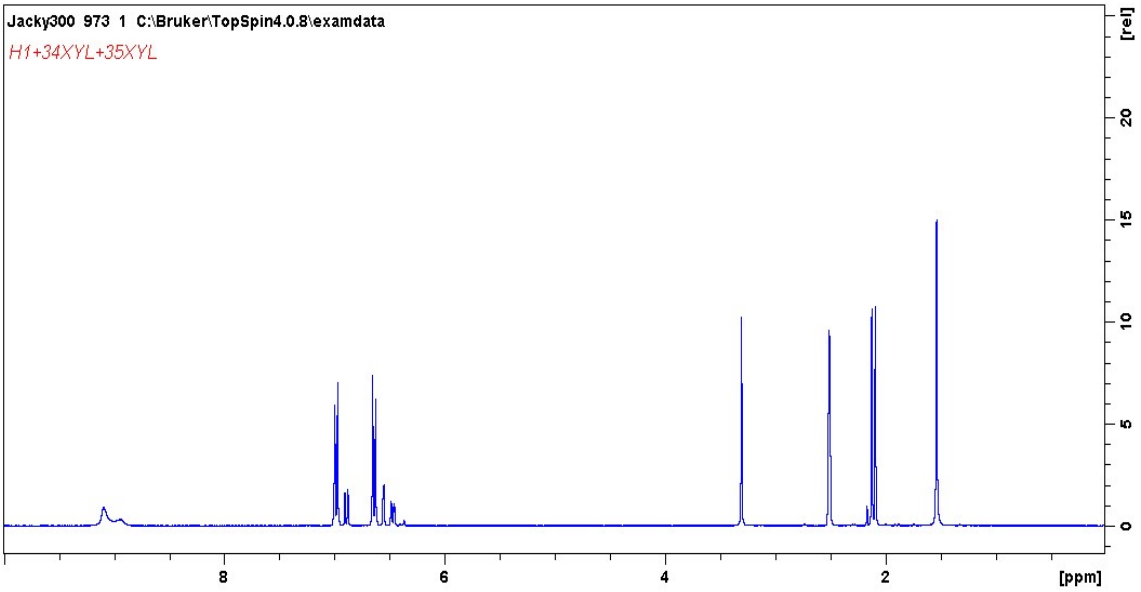


Figure S16: ^{1}H NMR spectrum for H1+ 34XYL+35XYL

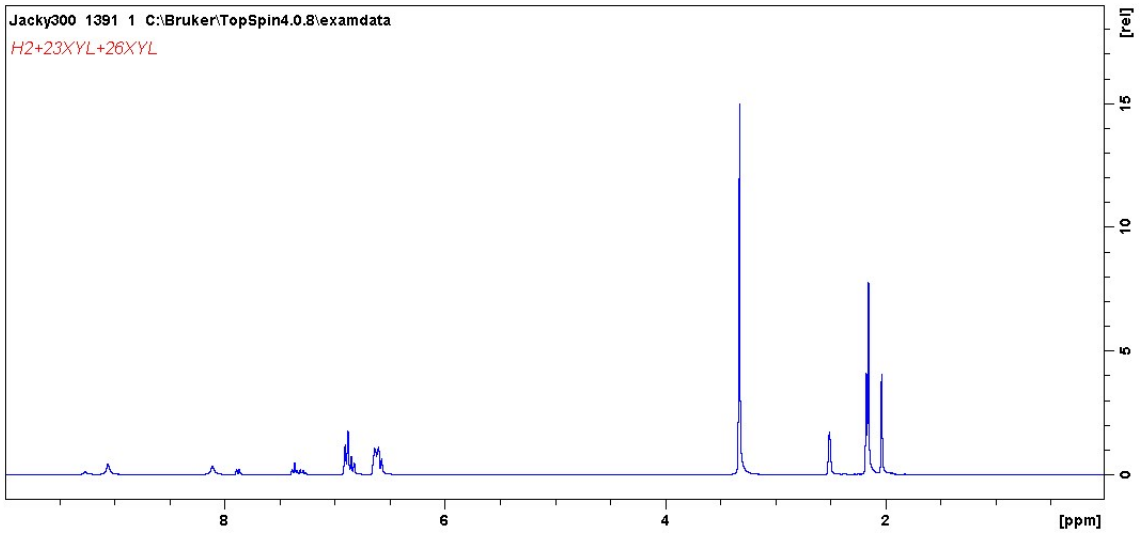


Figure S17: NMR spectrum for H2+ 23XYL+26XYL

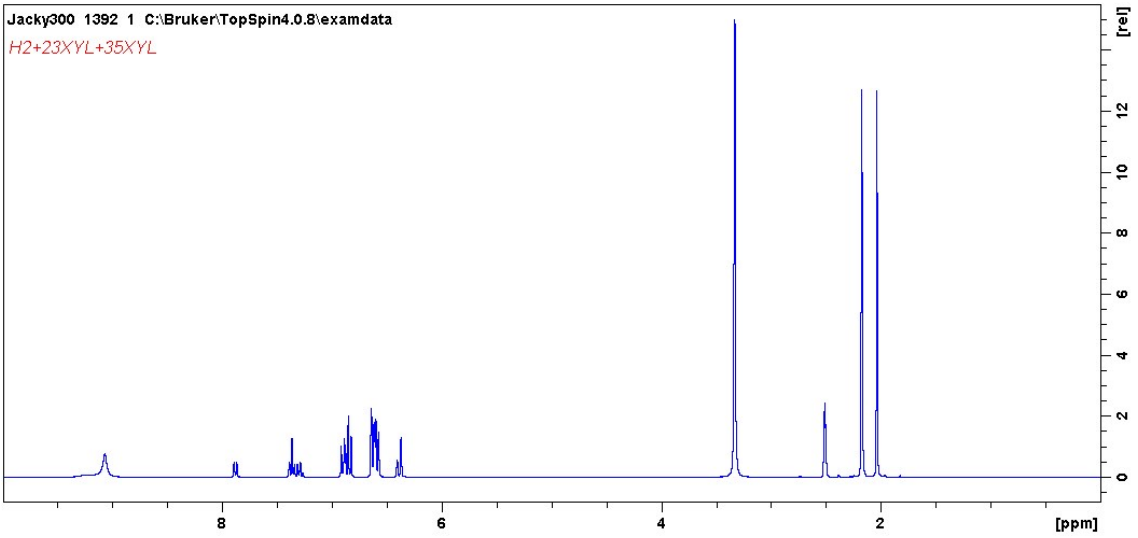


Figure S18: ^{1}H NMR spectrum for H2+ 23XYL+35XYL

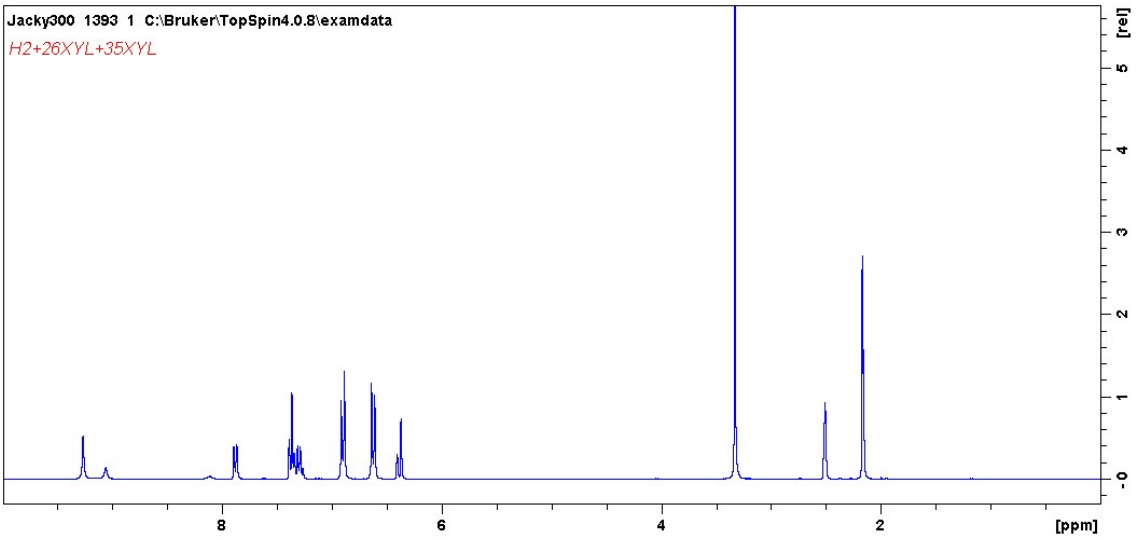


Figure S19: ^{1}H NMR spectrum for H2+ 26XYL+35XYL

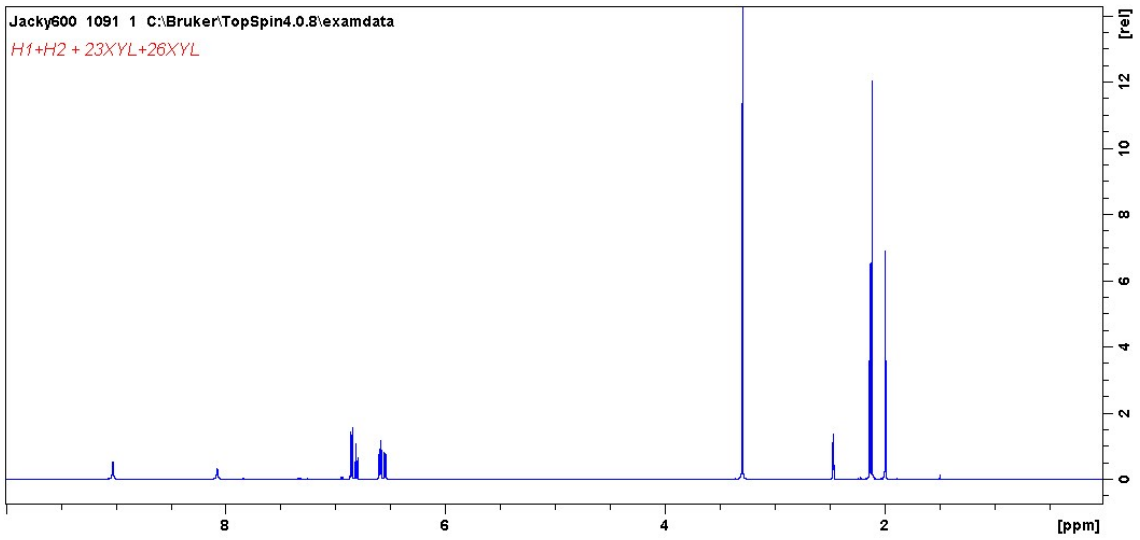


Figure S20: ^{1}H NMR spectrum for H1+H2+ 23XYL+26XYL

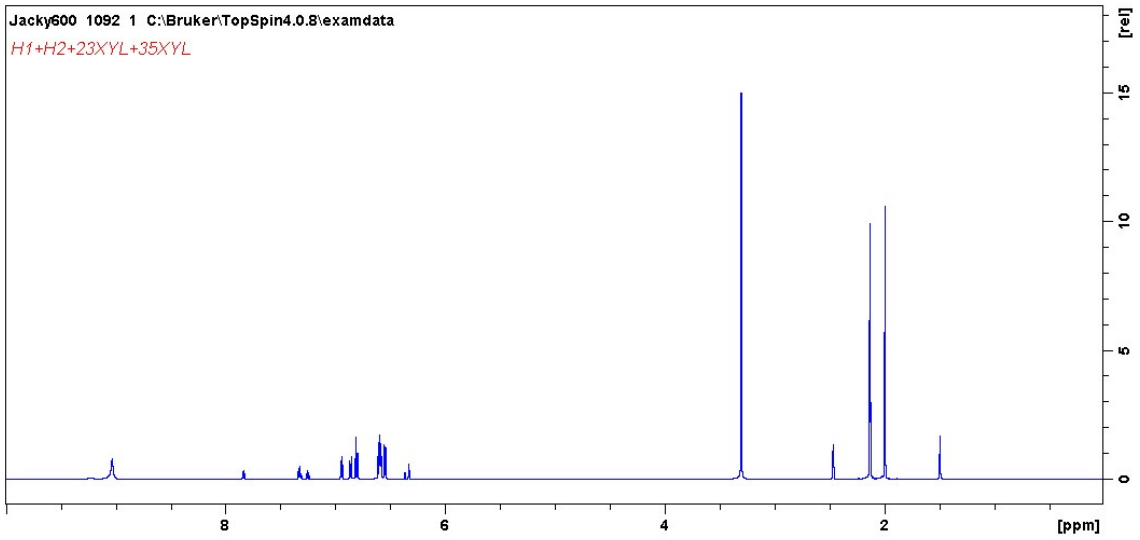


Figure S21: ^{1}H NMR spectrum for H1+H2+ 23XYL+35XYL

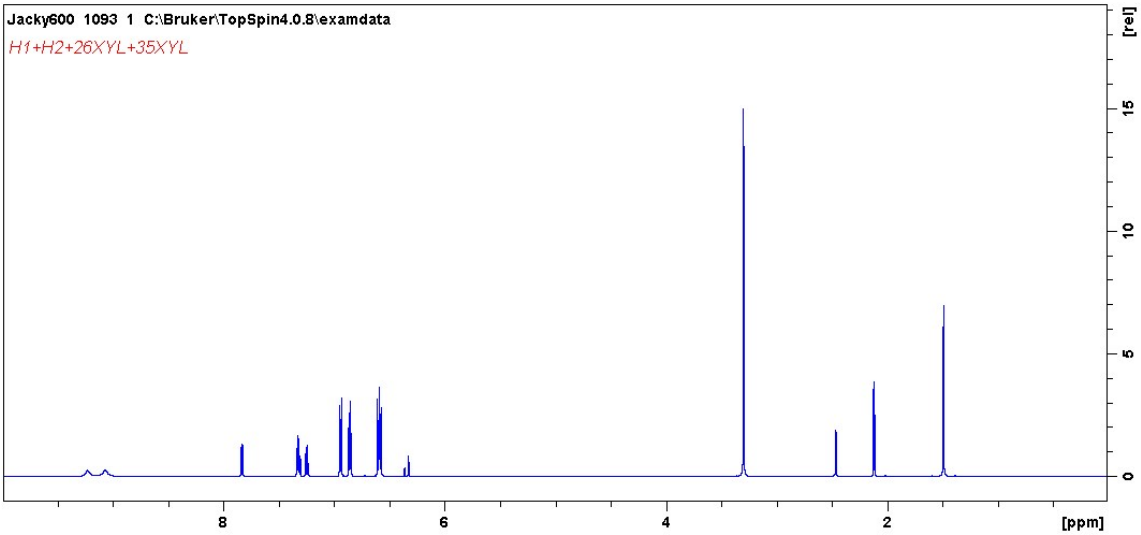


Figure S22: ^{1}H NMR spectrum for H1+H2+ 26XYL+35XYL

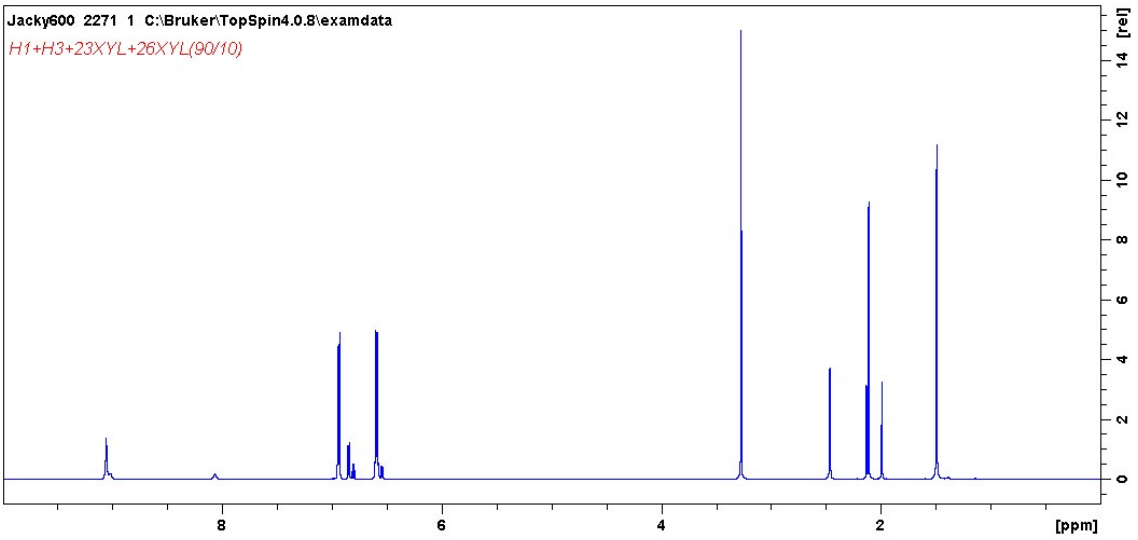


Figure S23: ^{1}H NMR spectrum for H1+H3+23XY+26XYL (ratio H1:H3 90/10)

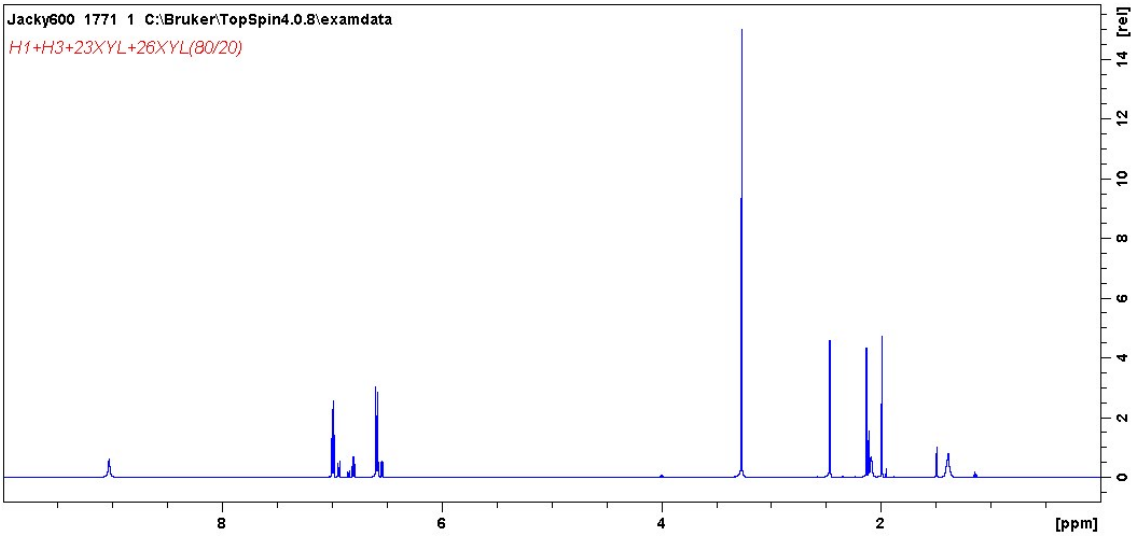


Figure S24: ^{1}H NMR spectrum for H1+H3+23XY+26XYL (ratio H1:H3 80/20)

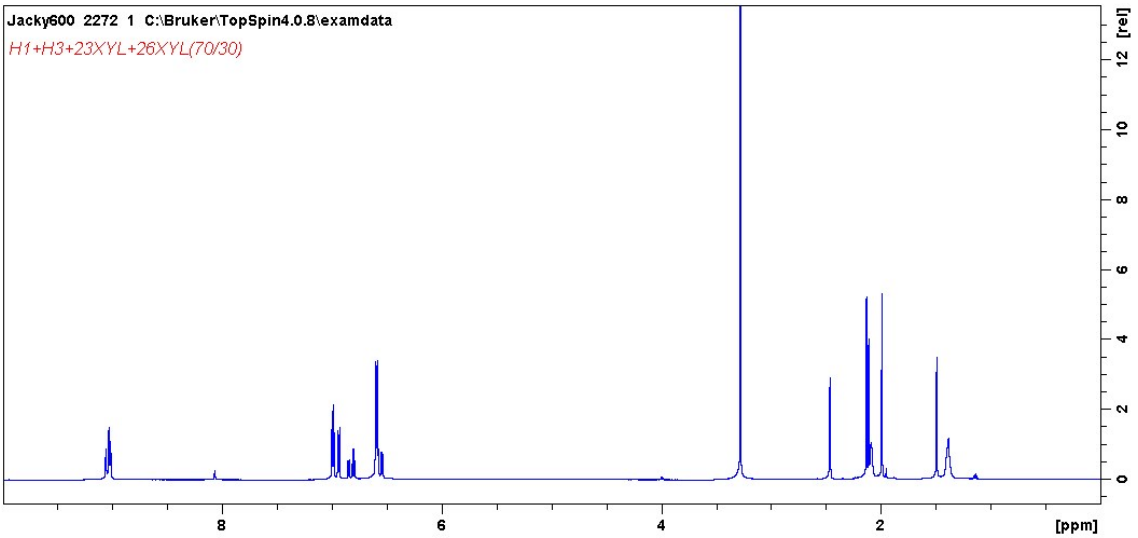


Figure S25: ^{1}H NMR spectrum for H1+H3+23XY+26XYL (ratio H1:H3 70/30)

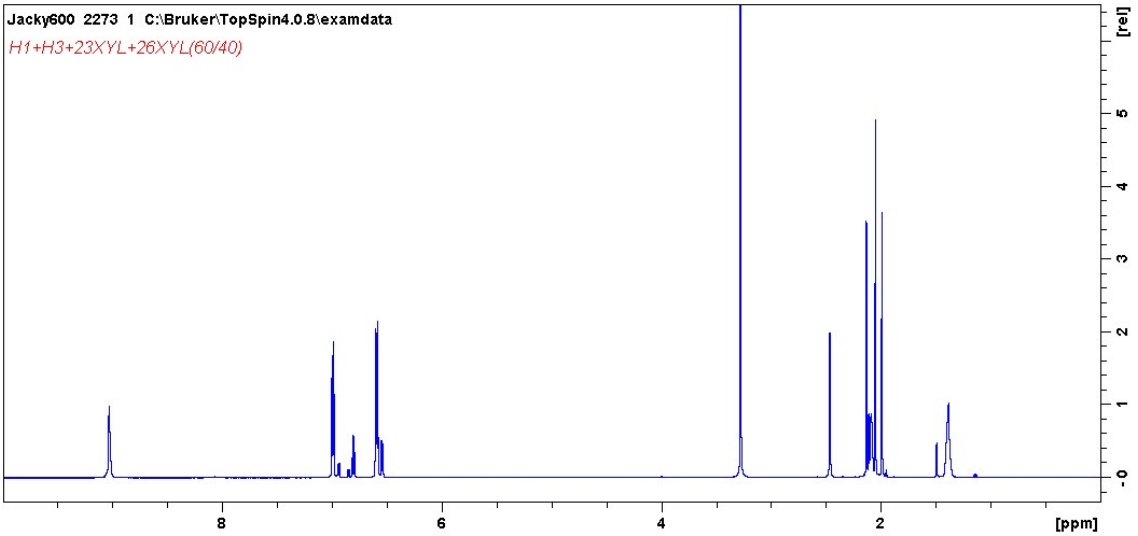


Figure S26: ^{1}H NMR spectrum for H1+H3+23XY+26XYL (ratio H1:H3 60/40)

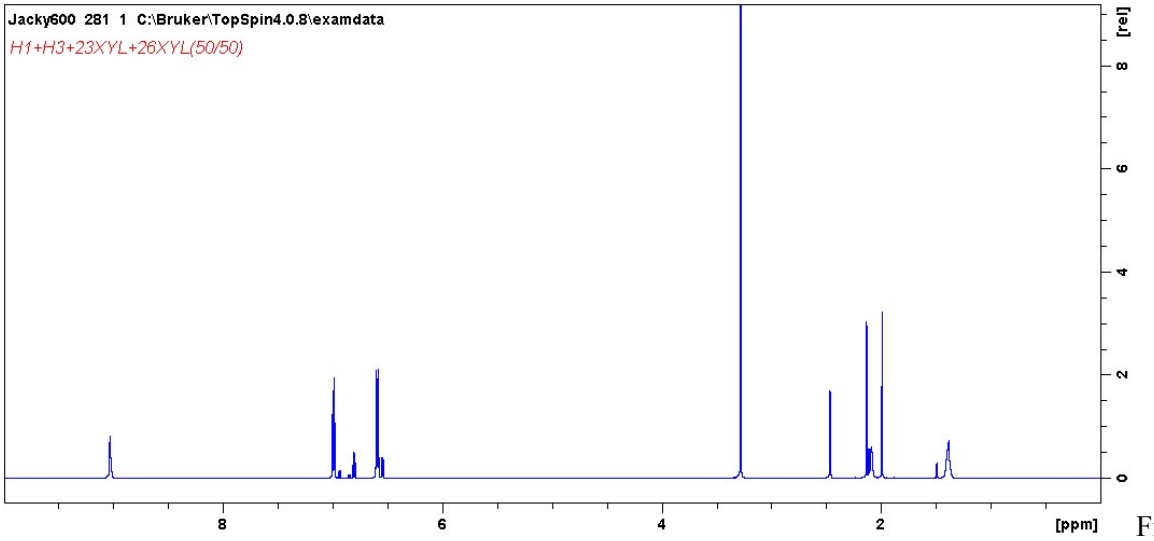


Figure S27: ^{1}H NMR spectrum for H1+H3+23XY+26XYL (ratio H1:H3 50/50)

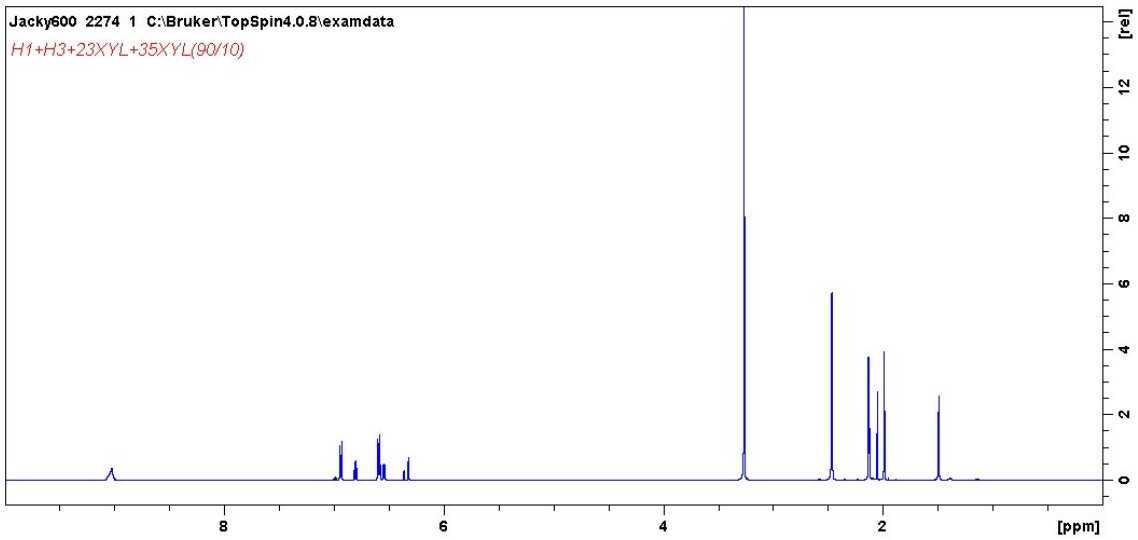


Figure S28: ^{1}H NMR spectrum for H1+H3+23XY+35XYL (ratio H1:H3 90/10)

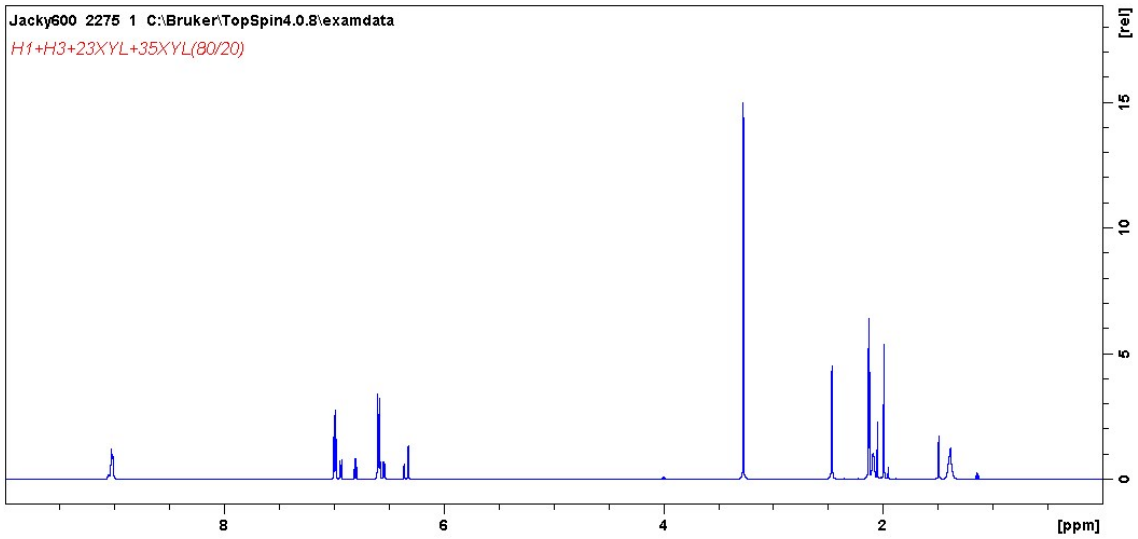


Figure S29: ^{1}H NMR spectrum for H1+H3+23XY+35XYL (ratio H1:H3 80/20)

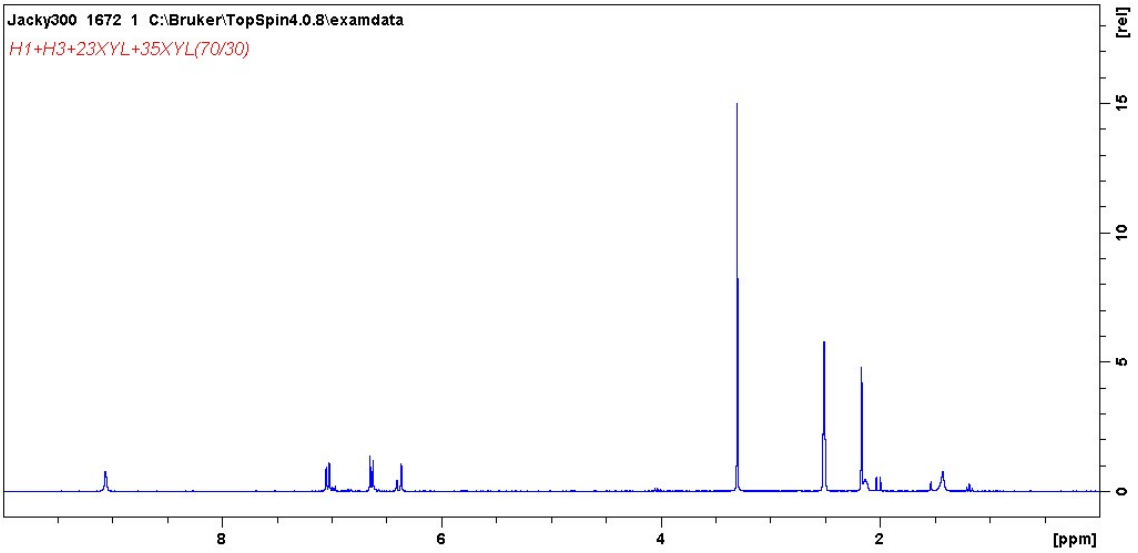


Figure S30: ^{1}H NMR spectrum for H1+H3+23XY+35XYL (ratio H1:H3 70/30)

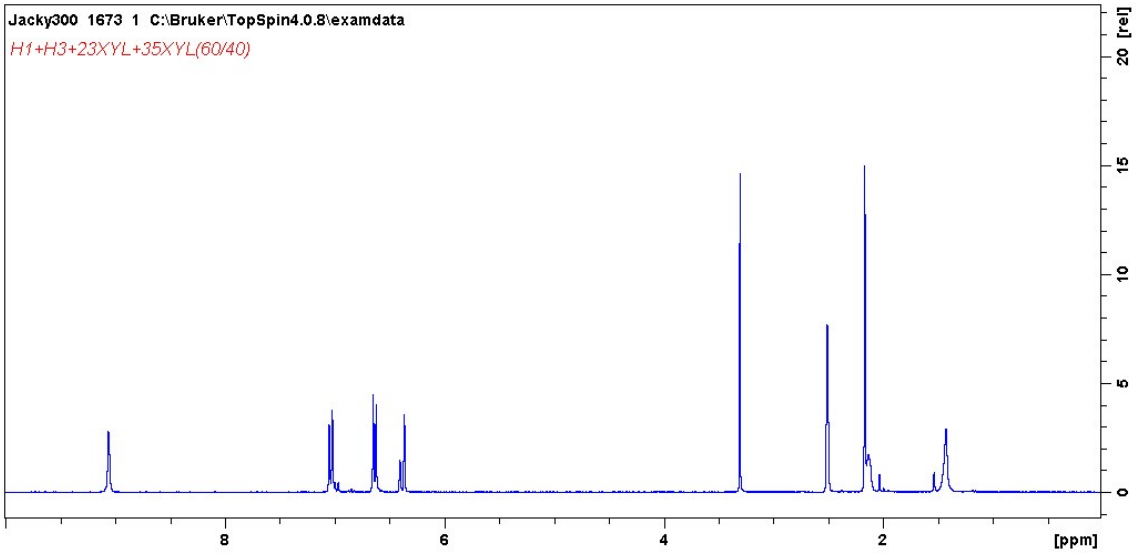


Figure S31: ^{1}H NMR spectrum for H1+H3+23XY+35XYL (ratio H1:H3 60/40)

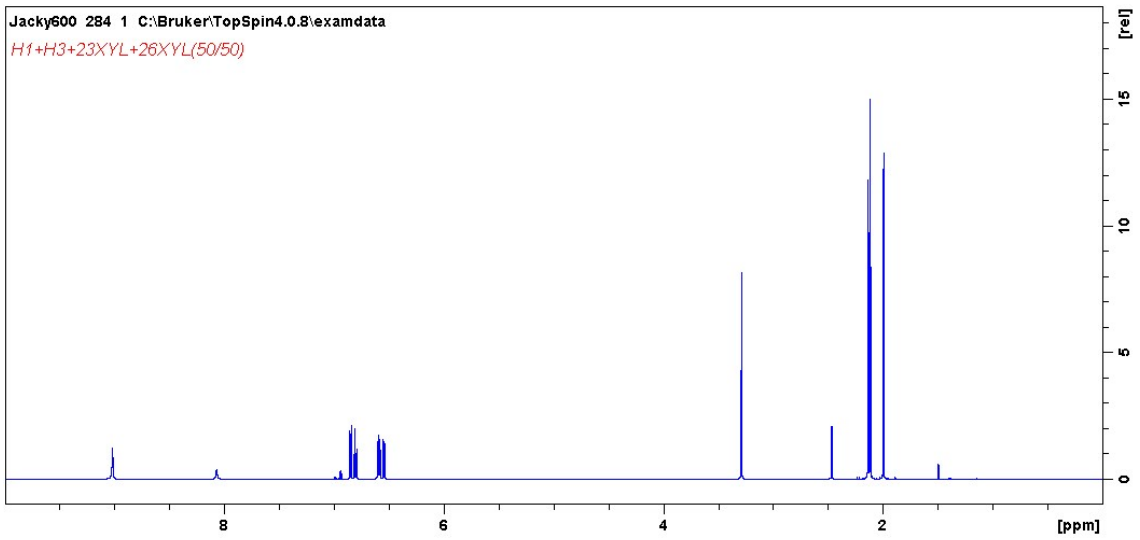


Figure S32: ^{1}H NMR spectrum for H1+H3+23XY+35XYL (ratio H1:H3 50/50)

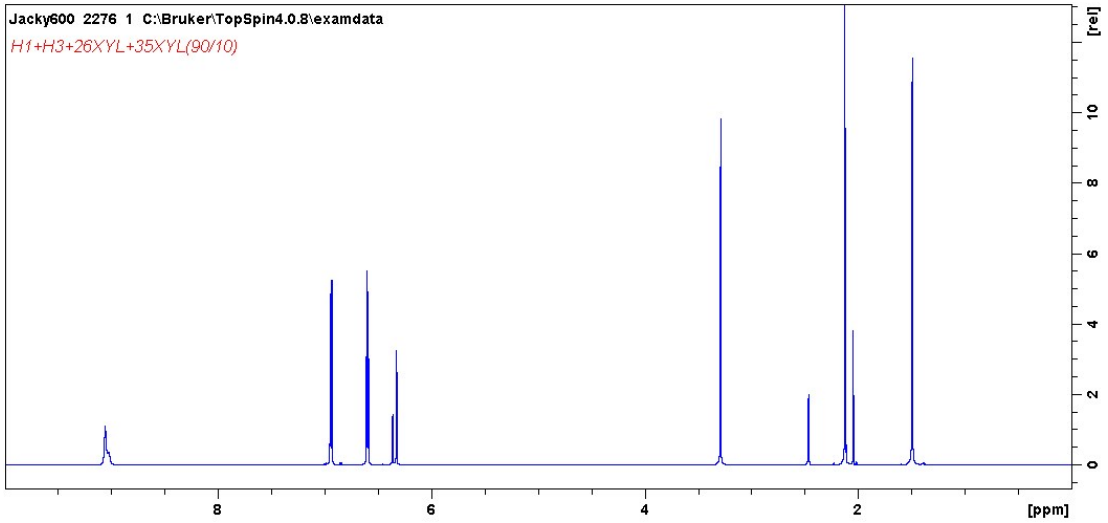


Figure S33: ^{1}H NMR spectrum for H1+H3+26XY+35XYL (ratio H1:H3 90/10)

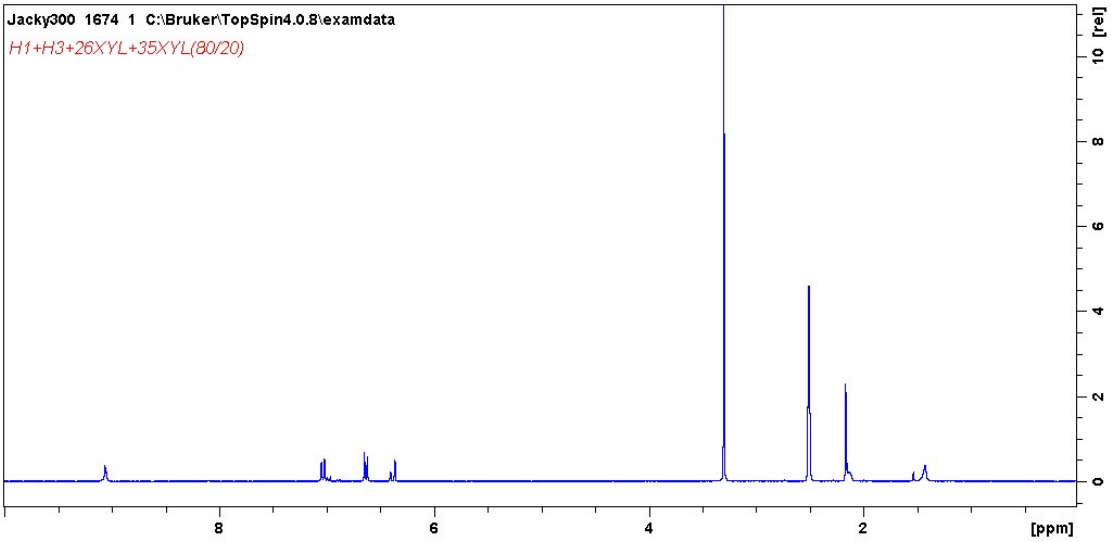


Figure S34: ^{1}H NMR spectrum for H1+H3+26XY+35XYL (ratio H1:H3 80/20)

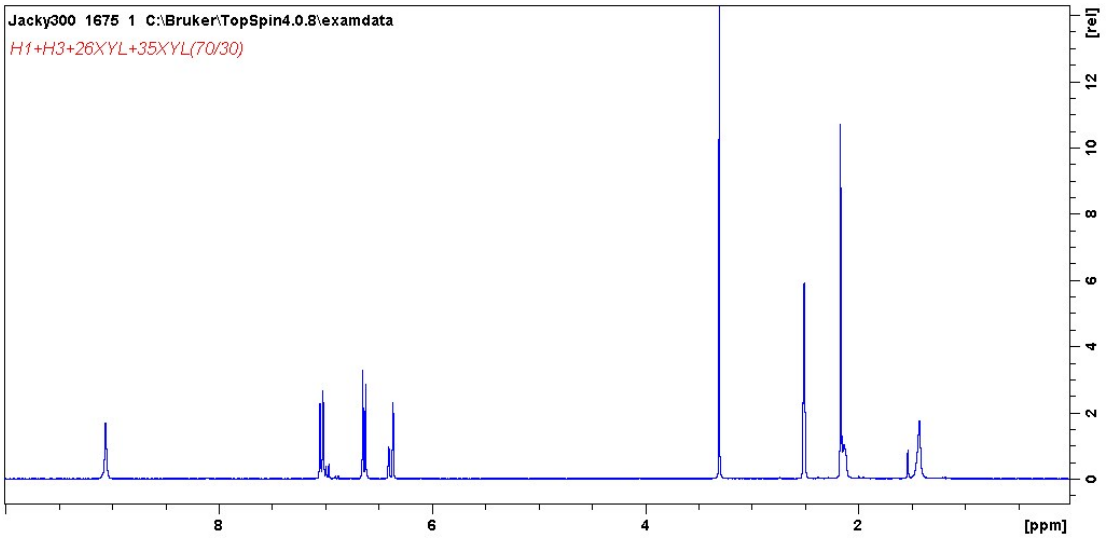


Figure S35: ^{1}H NMR spectrum for H1+H3+26XY+35XYL (ratio H1:H3 70/30)

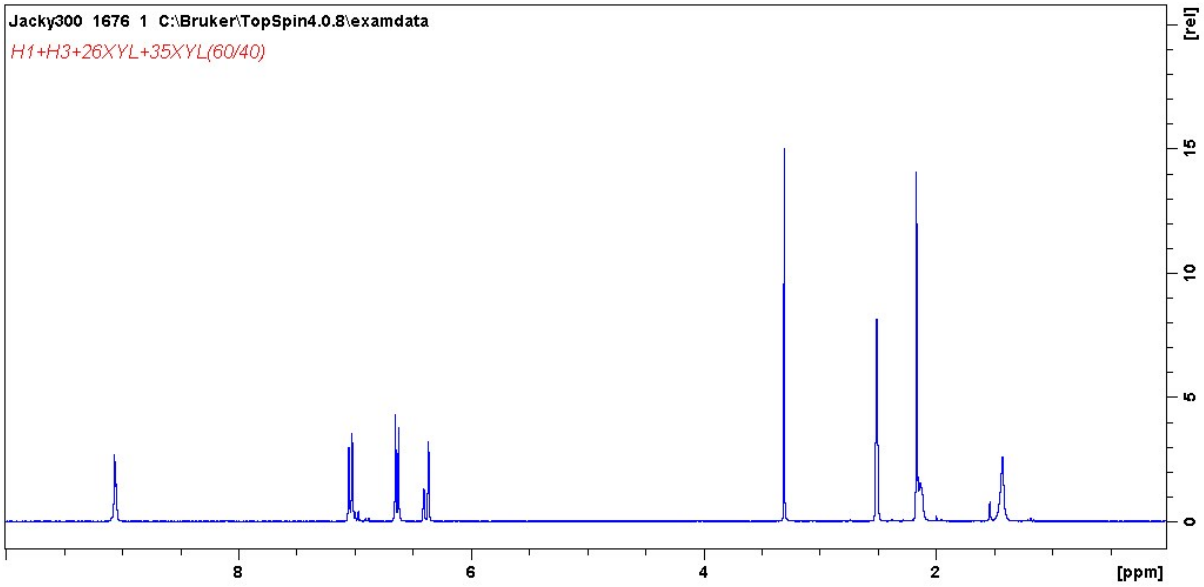


Figure S36: ^{1}H NMR spectrum for H1+H3+26XY+35XYL (ratio H1:H3 60/40)

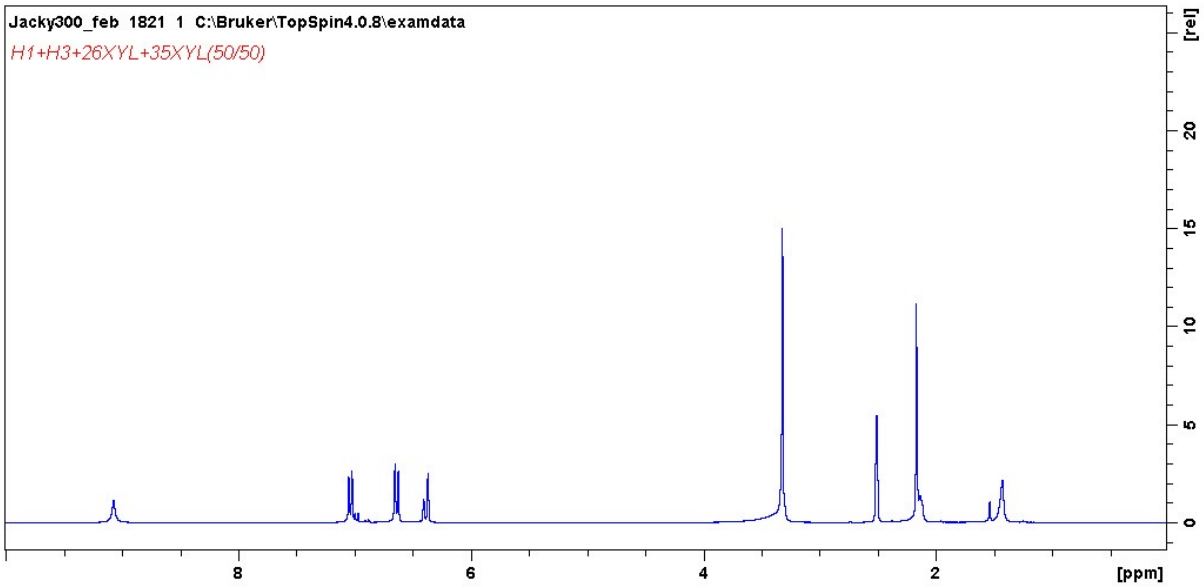


Figure S37: ^{1}H NMR spectrum for H1+H3+26XY+35XYL (ratio H1:H3 50/50)

Chapter 8.

Conclusion

Isomers are compounds with the same molecular composition but may differ in the way atoms are arranged or relate to one another. Due to the vast implication of isomers among several fields, separating specific isomers is important. In chemical engineering, isomers of xylene have been intensively examined to improve their selectivity for the petrochemical industry. In pharmaceutical, medicinal, and biochemical chemistry, racemic modifications are found. The choice of the correct enantiomer is of an important in these industries because there are possible toxicity problems. This shows the importance of separating racemic mixtures.

There are various separation methods used for mixtures of compounds. Among these approaches, one can find the chromatographic methods, absorption, extraction, distillation as well as crystallization. The different methods tend to be difficult to apply when compounds have similar macro-properties. An example is racemic mixtures where the difference of the individual components is the process in which they diffract polarised light. Additionally, for isomers which have close boiling points can also be difficult to separate by distillation. Host-guest chemistry to offer a possible solution in this instance because of its efficiency and economical aspect. The Host-guest method results from the interaction of large molecules (hosts) with small molecules (guests). It does not necessitate many materials and the experimental section is quite straight forward. The present characteristic renders the process quite common and appreciated in industries. The most crucial aspect in this method is the choice of host compound to favour the selectivity. For this aspect of the procedure, special crystal engineering principles need to be employed. In this instance, important features to consider are the robustness, the flexibility, the expected synthons that might be formed with the chosen guest as well as the channels or the voids provided by the host molecules.

The research contributes to the effort done over the separation of isomers in host-guest chemistry. The different complexes reported in here were elucidated and refined after data collection with single crystal X-ray diffraction. These complexes were also characterised by thermal analysis (TGA, DSC), NMR spectroscopy, competition experiments, kinetics of desolvation, Hirshfeld surface analysis and evaluation of activation energies of decomposition.

Isomers of trimethoxybenzene were separated with deoxycholic acid (DCA) and cholic acid (CA). The selectivity preference was found after different competitions experiment of pairwise combinations of guest with the individual host. During this process, two different trends were observed: TMB135 > TMB123 ≈ TMB124 for CA and TMB123 > TMB124 > TMB135 for DCA. The study led to four structures with cholic acid and three structures from deoxycholic

acid. Analysis of the different interactions present in the structures obtained from cholic acid with one guest compound and with no disorder showed that the **CA• TMB135** has the most closely packed structure. Additionally, it demonstrated that there was a better fit with the complexes formed by **CA• TMB135** compared to **CA• TMB124.** The aforementioned was observed despite the water molecules present in the latter structure. Packing coefficient determination was not successful over the structures obtained with CA but followed the selectivity trend of the ones obtained with DCA. Since the two hosts only changed from the presence of a hydroxyl group, an understanding of the difference in the selectivity was studied. At the end of the experiment, the packing arrangement of the two hosts were found to be dissimilar. The structures consisted of alternative hydrophilic and lipophilic double layers running in opposing direction. In all the structures the guest compounds were found to be lying in voids provided from the arrangement of the lipophilic layers. This led to the conclusion that the addition of another functional moiety does affect the reactivity and the arrangement of the host when mixed with a guest compound. Due to the lack of solubility and the presence of disordered structures, analysis of guest affinity toward a host could come to be a challenge.

The Diol host compound 3,3′-bis(9-hydroxy-9-fluorenyl)-2−2′- binaphthyl was employed to separate the isomer of lutidine in chapter 4. Fifteen competition experiments were then set. Ten structures were elucidated with five of them made of a single guest and mixture of guest and host compound. TGA analysis agreed with the ^{1}H NMR results confirming that the isomer 3,4-lutidine gave a better fit with the host compound 3,3′-bis(9-hydroxy-9-fluorenyl)-2−2′-binaphthyl. Attempting to extend the separation by the "Dutch resolution" method was partially successful because different host-guest complexes were formed while other preferences were improved towards a guest.

Separation of lutidines was further investigated with emphasis of the choice of diol host compounds and the results were reported in chapter 5. The competition experiments were repeated for the fifteen pair of guest mixtures with host 2,2'bis(1-hydroxy-4,5-dihydro-2,3:6,7-dibenzocycloheptatrien-1-yl)-biphenyl (H1). The preference pattern obtained by thermal analysis was the same as the one from ^{1}H NMR and was found to be 3,4-LUT>2,4-LUT≈3,5-LUT>2,5-LUT>2,3-LUT>2,6-LUT. Among the competition experiment four pair of guests were selected where 2,2'bis(1-hydroxy-4,5-dihydro-2,3:6,7-dibenzocycloheptatrien-1-yl)-biphenyl did not show a high selectivity preference. Then a screening process was done with four additional diol hosts namely: 2,2'-bis (diphenylhydroxymethyl) biphenyl (H2); 2,2'-bis(9-hydroxy-9*H*-xanthen-9-yl) biphenyl (H3); 2,2'- bis (9-hydroxyfluoren-9-yl) biphenyl (H4);

2,2'-bis (2,7-di-tert-butyl-9 hydroxyfluren-9-yl) biphenyl (H5). The selected host from the screening was tested in various proportions with H1. The experiment resulted into two structures H1•2,4-LUT•3,5-LUT and H2•1(2,4-LUT). The new structure of H1 showed better characteristics during its structural resolution with crystal engineering tools. Torsion angles were investigated from crystallization of each host with 2,4-lutidine and 3,5-lutidine. 2,4-LUT is preferentially selected by H3 and H4 the hosts with the least flexibility which display lower values of $\boldsymbol{\tau}1$ and $\boldsymbol{\tau}3$ (average ≈ 17°), while 3,5-LUT is preferred by H2 and H5. H2 is characterized by unbridged phenyl moieties while H5 has bulky tert-butyl groups which change the range of host•••guest non-bonded contacts.

In chapter 6, DCA was successfully applied to separate and resolve the isomers of methylacetophenones (MCH). DCA resolved the 2-methylacetophenone (2MCH) to its S-enantiomer while the 3-methylacetophenone (3MCH) was not resolved. During the competition experiment of the mixture of 2MCH and 3MCH, it was found that in the presence of 2MCH, (S)- enantiomer of the 3MCH was found. This was attributed to the templating effect of 2MCH guest when combined with Deoxycholic acid. This statement was confirmed by changing the different portion of the two isomers in the mother liquor. During the competition experiments, the preference pattern for these isomers were 2MCH > 3MCH > 4MCH. The present pattern was confirmed by thermal analysis. Additionally, it was also confirmed through the determination of the activation energies of the DCA with each isomer compound. These activation energies varied in the range of 78−81 kJ/mol for the 2MCH complex with DCA while they were ranging from 71 to 74 kJ/mol (3MCH) and 42 to 54 kJ/mol (4MCH).

Chapter 7 investigated with the synergistic effect of mixed hosts over xylenol (XYL) guests. 4,4-isopropylidene bisphenol was used to separate the six isomers compounds. The final trend resulting from the operations was 34XYL> 35XYL>26XYL>23XYL>25XYL>24XYL. Four structures were then collected from the experiments. Among the competitions experiment that were carried out, three pairs were selected and used to further analyse the synergism resulting from mixed hosts. When host 4,4'-(9-fluorenylidene) bisphenol, and 4,4'(cyclohexylidene) bisphenol were mixed with 4,4-isopropylidene bisphenol, it was observed that the selectivity pattern changed. In fact, there was an improvement when these host were combined compare to when one host was employed. Through this process, a structure of 4,4'-(9-Fluorenylidene) Bisphenol with 4,4-Isopropylidene Bisphenol and a mixture of 2,6-xylenol and 3,5-xylenol was isolated.

Solubility is quite a common problem when dissolving compound. It was observed that a less soluble guest would be easier to separate from another isomer guest. This idea is quite important when two isomers are dissolve with a particular host. If one could not crystallize with the host used, it would facilitate the selectivity of that host compound and that was the case of deoxycholic acid with 1,3,5-trimethoxybenzene. Solubility issues can also restrain the analysis and comparison of the crystal compounds found since they tend to change the starting materials. Since cholic acid and deoxycholic acid crystal with the trimethoxybenzene were obtained in various cosolvents, important conclusive remarks were difficult to be reached. Structure of guest compound also influences how they would be selected. When the space provided by the host is not suitable, some disorder may be observed, or the guest may be rejected.

The choice of host is most important to improve selectivity toward a given guest compound. Choosing a host that does have a structural backbone close to the starting material used for crystallization would improve its selectivity during mixed hosts' process. Additionally, hosts that are not too bulky can also improve the quality of crystals obtained.

The templating effect of compound is quite an important strategy to improve selectivity. Adding a host or guest that present a particular feature can lead to the selection of a desired guest molecule. That was observed with the use of 4,4-Isopropylidene Bisphenol which from the research reported by Nassimbeni presented a selectivity toward 3,5-xylenol. Additionally, when it was mixed with 4,4'-(9-Fluorenylidene) Bisphenol, the same selectivity was observed. Synergism is an interesting theme that should be explored more carefully. Although applied in the medicinal, pharmaceutical and biological industries, crystal engineering has not shown a good interest in this field. Exploring such areas might open doors to new crystal engineering tools in the future. The South African company SASOL is a petrochemical enterprise that produces petrol and diesel from coal. In this process, it also produces various aromatic compounds, many of which are mixtures of isomers. These have similar boiling points and are sometimes difficult to separate. The best-known example is that of C8 hydrocarbons, namely ortho-xylene, meta-xylene, paraxylene, and ethyl xylene. Sasol also produces mixtures of cresols (methyl phenols) and xylenols (dimethyl phenols). The latter are the subject of chapter 7 which are dealt of the thesis; and tetrahydro cresols which are mixtures of methyl cyclohexanones and form the subject of chapter 6.