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Simultaneously bound guests and chiral recognition: a chiral self-assembled supramolecular host encapsulates hydrophobic guests

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Abstract—Driven by the hydrophobic effect, a water-soluble, chiral, self-assembled supramolecular host is able to encapsulate hydrophobic organic guests in aqueous solution. Small aromatics can be encapsulated in the supramolecular assembly, and the simultaneous encapsulation of multiple guests is observed in many cases. The molecular host assembly is able to recognize different subtitutional isomers of disubstituted benzenes with *ortho* substitution leading to the encapsulation of two guests, but *meta* or *para* substitution leading to the encapsulation of only one guest. The scope of hydrophobic guest encapsulation is further explored with chiral natural product guests. Upon encapsulation of chiral guests into the racemic host, diastereomeric host-guest complexes are formed with observed diastereoselectivities of up to 78:22 in the case of fenchone. © 2008 Elsevier Science. All rights reserved.

1. Introduction

A major driving force for complexation processes in water is the hydrophobic effect (or hydrophobic bond).[1,2] This effect stems from the energetically costly reorganization of solvent water molecules required to maintain a normal hydrogen-bonding network around the nonpolar solute.[3] This often causes hydrophobic species to aggregate in aqueous solution and can lead to rate enhancements of organic reactions taking place in aqueous media due to the increased local concentration upon aggregation.[4] This desolvation effect is also prevalent in nature where hydrophobic portions of substrates can be sequestered from aqueous solution by binding in hydrophobic receptor pockets in proteins. The magnitude of this desolvation interaction is dependent on the surface area of the hydrophobic molecule and is estimated to be 0.03-0.05 kcal/molÅ^2 which corresponds to ~0.7 kcal/mol per methyl group for simple alkanes.[5-7]

Supramolecular systems that operate in water have exploited this driving force in the encapsulation of

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hydrophobic guests. By binding reactants for bimolecular reactions in synthetic hosts, the increased local concentration can lead to large rate accelerations. Such encarceration in synthetic hosts can dramatically change the reactivity of the bound reactants, often creating unusual or unexpected reactivity. Similarly, hydrophobic surfaces of detergents[8,9] and steroids[10] have been shown to prefer complexation in synthetic receptors. Furthermore, the distinct shape of certain molecular hosts allows for the analysis of static guest conformations of otherwise dyanmic molecules such as alkanes.[11,12]

Our group has developed and extensively studied a water-soluble metal ligand cluster (M = Ga(III), Al(III), Fe(III), Ti(IV), Ge(IV), L = 1,5-biscatecholamide naphthalene) of the M_4L_6 stoichiometry ($[Ga_4L_6]^{12-}$ = (**1**)) (Figure 1).[13] The interior cavity of **1** provides a unique environment for encapsulated guests which is isolated from bulk solution. The self-assembled tetrahedron is homochiral, adopting either the Δ,Δ,Δ,Δ or the Λ,Λ,Λ,Λ configuration with respect to the metal verticies, and the two enantiomers are resolvable and isolable.[14] The majority of work using **1** has explored the encapsulation of monocationic guests such as tetraalkylammonium,[15] phosphonium,[16] iminium,[17] and organometallic cations.[18,19] The driving forces for these guest-binding events are thought to be both enthalpic (CH-π, cation-π, electrostatic interactions) and entropic (release of many weakly-bound solvent molecules from host interior) in nature. Recently, during our studies of the enzyme-like acid-catalyzed hydrolysis of orthoformates[20] and acetals[21] by **1** in basic solution, kinetic evidence suggested that encapsulation of the neutral substrate occurred during the initial step of the catalytic cycle. Intrigued by these results, we examined the ability of **1** to bind simple hydrocarbons such as linear or cyclic alkanes.[22] Here we expand our initial communication of neutral guest encapsulation to include small aromatics, for which multiple guests encapsulation occurs, and the diastereoselective encapsulation of small chiral natural products.

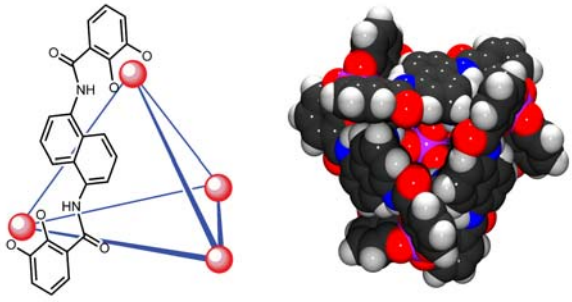

Figure 1. Left: Schematic of the molecular host **1** with only one ligand shown for clarity. Right: Space filling model of **1**.

2. Results and Discussion

2.1. Preparation and Characterization of Host-guest Complexes

Although **1** is primarily soluble in polar solvents such as H_2O, MeOH, DMF, and DMSO, the interior cavity of **1** provides a hydrophobic cavity distinctly different from bulk solution. Host-guest complexes are most easily characterized by ^{1}H NMR. Upon encapsulation in **1**, the ^{1}H-NMR resonances corresponding to the guest are characteristically shifted upfield by 2–3 ppm due to the magnetic anisotropy of the nearby naphthalene walls. Also indicative of encapsulation is the change in the local symmetry environment of the guests. Encapsulation in *T*-symmetric **1** renders enantiotopic hydrogens diastereotopic due to the loss of mirror symmetry. These characteristic observations allow for facile detection and characterization of host-guest complexes.

2.2. Encapsulation of Arenes

Having previously demonstrated the encapsulation of both linear and cyclic saturated hydrocarbons in **1,** we expanded our investigation of neutral hydrophobic guests by encapsulating a variety of arenes. We began our investigation by subjecting **1** to a range of substituted benzenes in aqueous solution (Figure 2). Many small arenes (**2-21**) are readily encapsulated in **1**. However, the presence of water-solubilizing substituents on the arene, such as in the case of phenol, acetophenone and styrene oxide, prohibited encapsulation (Figure 3). Treatment of **1** with any of the arenes in organic solution did not produce host-guest complexes. These observations are consistent with the hydrophobic effect driving guest encapsulation.

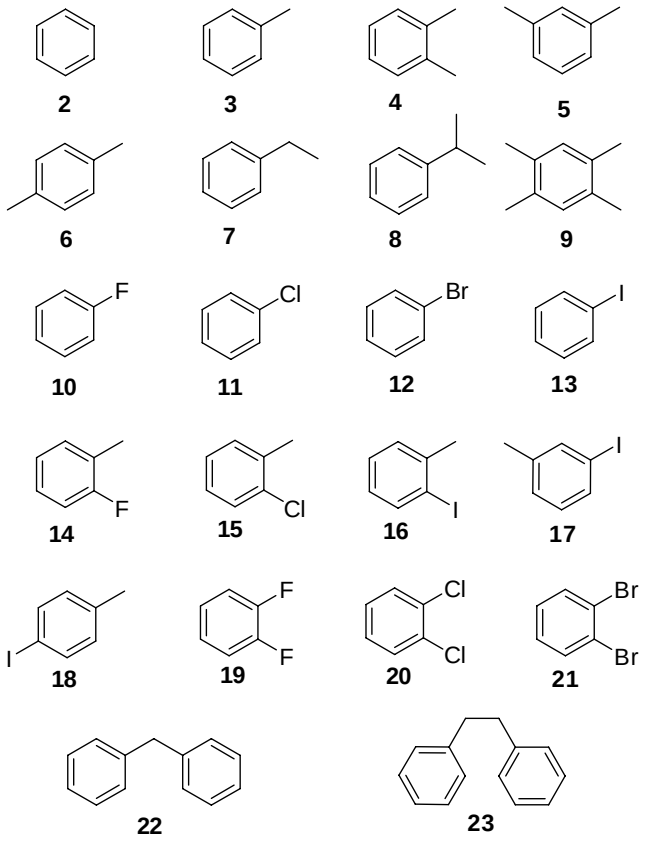

Figure 2. Scope of arenes encapsulated in **1**.

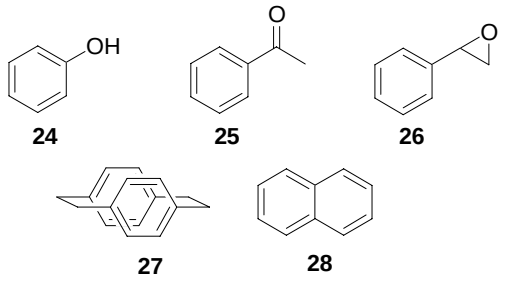

Figure 3. Arenes not encapsulated in **1**.

Based on the ^{1}H NMR spectra of host-guest complexes, further information was obtained about the stoichiometry Depending on the guest, between one and three equivalents of the substituted benzenes were encapsulated. The number of guests encapsulated in **1** seems to be dependent both on the guest size and the substitution pattern. For example, three molecules of benzene (**2**) are encapsulated, whereas two molecules of the slightly more sterically demanding toluene (**3**) or monohalo benzenes (**10-13**) are encapsulated. For monosubstituted toluenes, *ortho* substitution leads to pairwise encapsulation (**14-16**) whereas *meta* or *para* substitution leads to the encapsulation of a single guest molecule (Figure 3). Two molecules of orthosubstituted dihalobenzenes (**19-21**) are also simultaneously encapsulated.. Similarly, 1,2,4,5-tetramethylbenzene (**9**) is encapsulated as a pair whereas the monosubtituted ethylbenzene (**7**) or isopropylbenzene (**8**) are only encapsulated as monomers.

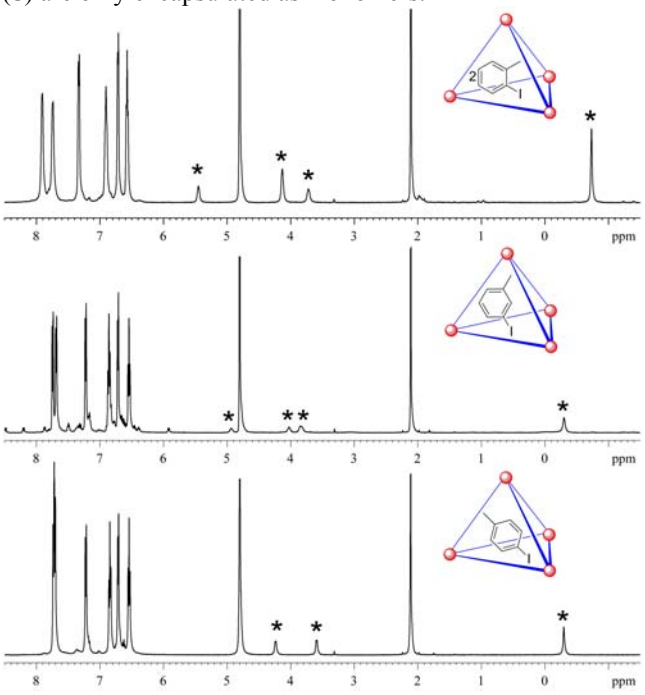

Figure 4. Comparison of the ^{1}H NMR spectra of *ortho* (top), *meta* (middle), and *para* (bottom) substitutional isomers of iodotoluene (**16-18**) encapsulated in **1**. Guest resonances are denoted (*).

For host-guest complexes containing multiple guest molecules, the ^{1}H NMR resonances corresponding to the encapsulated guest are broadened. Furthermore, the encapsulated guests are equivalent on the NMR time scale, suggesting that the multiply-bound guests do not attain a static conformation in **1**, but rather are rapidly tumbling. Cooling the samples to 5 ^{o}C did not decoalesce the averaged signals, thus prohibiting further investigation of the relative conformations of these guests.

The encapsulation of multiple guest molecules may be driven by a number of different forces (*vide infra*) such as packing forces, desolvation, or enthalpic π-π or CH-π interactions. Studies conducted by the Rebek group suggest that host-guest complexation is most favorable when the ratio of guest volume to interior host volume, or packing coefficient, is approximately 0.55.[23,24] Guided by this empirical observation, we sought to further our understanding of the binding of multiple arene guests in **1** by examination of the packing coefficients. While **1** is able to distort to accomodate guests of varying sizes,[25] it may be too rigid to provide an adequate environment for a single molecule of benzene, for example. In calculating the packing coefficients for guests, the previously published[13] crystal structure $K_5(NEt_4)_6[NEt_4 \subset Fe_4L_6]$ (where $\subset$ denotes encapsulation) was used and produced an interior cavity of 274 Å^3. The packing coefficients of a single molecule of benzene (0.27), toluene (0.34), and *o*-xylene (0.39) are all well below the ideal value of 0.55, suggesting that cavity filling may contribute to the multiple encapsulation of guests.

These packing coefficients do not, however, account for the preference for encapsulation of two *ortho*-disubstituted benzenes but only one *meta*- or *para*-substituted benzene. In the absence of structural data that might imply the relative conformations of multiply-bound guests, any attempts to explain this selectivity would be speculative. However, it seems likely that two arenes must pack in a manner that both maximizes favorable edge-to-face interactions between the arene rings, or between the arene and the guest-accessible naphthalene walls of **1**, while minimizing unfavorable steric interactions.[26] It is possible that the less-compact *meta* or *para* substituted isomers are unable to efficiently pack in **1** without incurring unfavorable steric interactions between the guest methyl groups and the naphthalene walls of **1**.

Having observed the simultaneous encapsulation of multiple aromatic guests, we sought to encapsulate molecules containing multiple aromatic rings. While both diphenylmethane (**22**) and 1,2-diphenylethane (**23**) are cleanly encapsulated in **1**, neither 2,2-paracyclophane (**27**) nor naphthalene (**28**) are encapsulated. The exclusion of the more rigid cyclophane and naphthalene suggests that the freedom to adopt a suitable conformation is beneficial for efficient packing in **1**. Also of interest is that **23** is encapsulated but paracyclophane is not. This suggests that although paracyclophane is more compact, it is not a compatible shape for **1.** This result is consistent with the observation that *para*-substituted benzenes are only encapsulated as monomers.

A unique aspect of the ^{1}H NMR spectrum of **23** ⊂ **1,** when compared to the spectra of other arenes encapsulated in **1,** is that the spectrum was not broadened and the enantiotopic methylene protons in the backbone of **23** are rendered diastereotopic. This suggests that **23** is in a static configuration in **1** and not rapidly converting between C_{2v} to C_{2h} conformations. In solution, the C_{2h} geometry of **23,** which limits the steric interactions of the two phenyl groups, is the more stable conformation, although rotation around the C-C bond to the C_{2v} conformation occurs readily. When considering the conformation of **23** encapsulated in **1**, the lower energy C_{2h} geometry has a longest linear dimension of ~11.5Å, but the distance between the metal vertices in **1** is only ~12Å. This suggests that the phenyl groups of **23** are in closer proximity to each other in the encapsulated form than in bulk solution. Upon heating the host-guest complex, the ^{1}H NMR resonances corresponding to the ethylene backbone broadened and eventually coalesced. Based on the coalescence temperature and the chemical shift difference between the two decoalesced resonances, an activation barrier 17.0(2) kcal/mol was determined for the coalescence process.[27] In order for the geminal methylene hydrogens on **23** to become equivalent, rotation around the dihedral angle must be occurring. Since the cavity of **1** is not large enough to accomodate this conformational change, the only possible way for rotation to occur is by ejection of **19** from **1** followed by rotation of **19** in free solution followed by re-encapsulation. The activation barrier of 17.0(2) kcal/mol is consistent with previous activation barriers determined for the extrusion tetraalkylammonium or protonated amine substrates.[28,29]

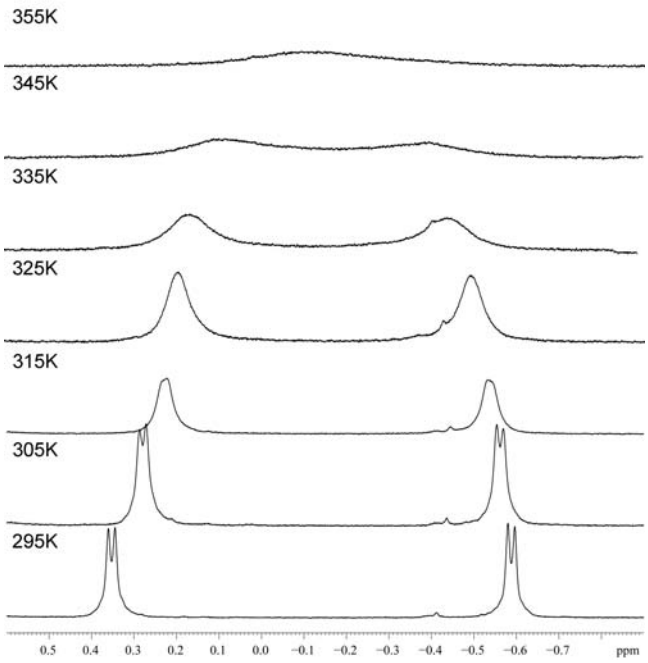

Figure 5. Variable temperature ^{1}H NMR spectra of **19** encapsulated in **1**

2.3. Diastereoselective Recognition of Natural Products

In nature, host-guest binding often features the recognition of a chiral molecule by a chiral receptor, thereby allowing for stereoselective discrimination. For example, the enantiomers of limonene are distinctly recognized by the olfactory system and L-dopa is a potent drug in the treatment of Parkinson's disease while its enantiomer is inactive.[30] Such biological specificity is often utilized in enzymes, which are capable of selectively stabilizing one enantiomeric transition state over another, leading to natural asymmetric catalysis.[31,32]

The chirality of **1**, generated by the helical twist at each metal vertex, can in principle be transmitted to encapsulated guest molecules. When a racemic guest is encapsulated in racemic **1**, each enantiomer of the guest can be bound by either the Δ,Δ,Δ,Δ or the Λ,Λ,Λ,Λ enantiomer of **1**, thereby forming two host-guest diastereomeric pairs of enantiomers. A difference in the association constant associated with each host-guest diastereomer leads to preferential formation of one host-guest diastereomer over the other.

To test the chiral recognition properties of **1** toward neutral guests, a number of sufficiently hydrophobic chiral natural products were encapsulated in **1** (Figure 5). In all cases, the resultant host-guest complexes showed two host-guest diastereomers by ^{1}H NMR. Assignments of the ^{1}H NMR signals corresponding to each diastereomer were accomplished by 2D ^{1}H COSY and NOESY experiments. In all cases, suitable ^{1}H NMR resonances could be used to determine the diastereoselectivity for host-guest complex formation (Table 1).

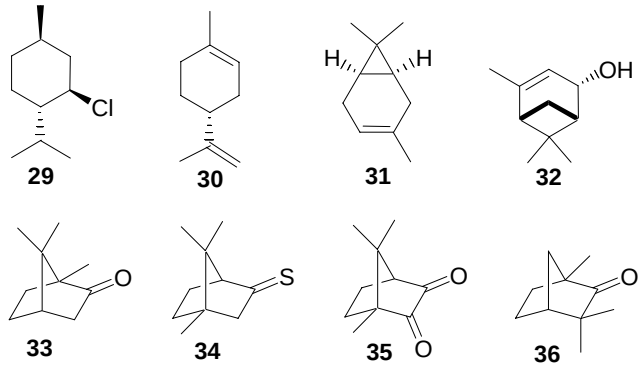

Figure 6. Scope of chiral guests encapsulated in **1**.

Relatively high levels of diastereoselectivity were observed for some species, such as limonene (**30**), camphor (**33**), and fenchone (**36**). The differing levels of diastereoselectivity are hard to rationalize based on guest structure. For instance, **33** is bound with a 66:34 diastereomeric ratio, while no selectivity is observed for the larger thiocamphor (**34**) or the more oxidized camphorquinone (**35**)**.** While **33** and **36** differ only in the placement of two methyl groups, **33** is bound with greater diastereoselectivity. Similarly**, 30** is encapsulated with higher diastereoselectivity than its isomer carene (**31**). This highlights the sensitivity of **1** toward small changes in guest size and shape.

Table 1. Diasteromeric ratios and excesses for encapsulation of chiral guests in **1**.

Entry	Compound	d.r.[a]	d.e. (%)
1	29	50:50	0
2	30	67:33	34
3	31	55:45	10
4	32	62:38	24
5	33	66:34	32
6	34	50:50	0
7	35	50:50	0
8	36	77:23	54

[a]The estimated uncertainty on the d.r. is ± 3%..

3. Conclusions

The ability of **1** to selectively encapsulate different substitutional isomers of aromatic guests shows that small changes in geometry can lead to large changes in the host-guest dynamics of supramolecular systems. Furthermore, the diastereoselective encapsulation of neutral, chiral molecules suggests that use of an enantiopure assembly could allow for asymmetric catalysis to take place in **1**. Similarly, the encapsulation of enantiopure neutral guests could be used as a strategy for the dynamic resolution of racemic **1**.

4. Experimental

4.1. General Methods

All NMR spectra were obtained using an AV-500 MHz spectrometer at the indicated frequency. The temperature of all variable temperature NMR experiments was calibrated with an ethylene glycol standard. All organic substrates were purchased from commercial suppliers and used as received. The host assembly **1** $K_{12}[Ga_4L_6]$ was prepared as described in the literature and precipitated with acetone.[13]

4.2. General Procedure for Sample Preparation.

In an N_2-filled glovebox, 15mg (4.17 μmol) of **1** was added to an NMR tube with 500 μL D_2O. An excess of the neutral guest (20 mg or 20 μL) was added to ensure that the water solution was saturated. The NMR tube was allowed to equilibrate overnight before a ^{1}H spectrum was obtained. To ensure accurate integrations of host-guest complexes, all spectra were acquired using a calibrated 90° pulse with a delay time of 10 seconds between scans.

4.3. ^{1}H NMR Characterization

[3x **2** ⊂ **1]$^{12-}$** ^{1}H NMR (500 MHz, D_2O): δ 7.74 (d, *J* = 7.6 Hz, 12H, *aryl*), 7.69 (d, *J* = 7.6 Hz, 12H, *aryl*), 7.27 (d, *J* = 8.0 Hz, 12H, *aryl*), 6.90 (t, *J* = 8.0 Hz, 12H, *aryl*), 6.69 (d, *J* = 7.6 Hz, 12H, *aryl*), 6.53 (t, *J* = 8.0 Hz, 12H, *aryl*). Guest: 6.13 (bs, 18H, 18 x CH).

[2x **3** ⊂ **1]$^{12-}$** ^{1}H NMR (500 MHz, D_2O): δ 7.87 (bs, 24H, *aryl*), 7.25 (d, *J* = 7.5 Hz, 12H, *aryl*), 6.91 (t, *J* = 8.0 Hz, 12H, *aryl*), 6.82 (d, *J* = 7.6 Hz, 12H, *aryl*), 6.65 (t, *J* = 7.6 Hz, 12H, *aryl*). Guest: 5.81 (s, 2H, 2 x CH), 5.17 (s, 4H, 4 x CH), 4.67 (s, 4H, 4 x CH), 0.42 (s, 6H, 2 x CH_3).

[2x **4** ⊂ **1]$^{12-}$** ^{1}H NMR (500 MHz, D_2O): δ 7.90 (d, *J* = 7.6 Hz, 12H, *aryl*), 7.72 (d, *J* = 7.6 Hz, 12H, *aryl*), 7.15 (d, *J* = 8.0 Hz, 12H, *aryl*), 6.92 (t, *J* = 8.0 Hz, 12H, *aryl*), 6.72 (d, *J* = 7.6 Hz, 12H, *aryl*), 6.57 (t, *J* = 8.0 Hz, 12H, *aryl*). Guest: 4.79 (s, 4H, 4 x CH), 4.03 (s, 4H, 4 x CH), -0.51 (s, 12H, 4 x CH_3).

[5 ⊂ **1]$^{12-}$** ^{1}H NMR (500 MHz, D_2O): δ 7.78 (bs, 24H, *aryl*), 7.20 (d, *J* = 7.6 Hz, 12H, *aryl*), 6.81 (d, *J* = 7.6 Hz, 12H, *aryl*), 6.68 (d, *J* = 7.6 Hz, 12H, *aryl*), 6.56 (t, *J* = 8.0 Hz, 12H, *aryl*). Guest: 4.82 (s, 1H, CH), 3.89 (s, 2H, 2 x CH), 3.32 (s, 1H, CH), -0.07 (bs, 6H, 2 x CH_3).

[6 ⊂ **1]$^{12-}$** ^{1}H NMR (500 MHz, D_2O): δ 7.71 (d, *J* = 8.0 Hz, 12H, *aryl*), 7.67 (d, *J* = 8.0 Hz, 12H, *aryl*), 7.21 (d, *J* = 8.0 Hz, 12H, *aryl*), 6.83 (t, *J* = 8.0 Hz, 12H, *aryl*), 6.68 (d, *J* = 8.0 Hz, 12H, *aryl*), 6.51 (t, *J* = 8.0 Hz, 12H, *aryl*). Guest: 3.87 (s, 4H, 4 x CH), -0.10 (bs, 6H, 2 x CH_3).

[7 ⊂ **1]$^{12-}$** ^{1}H NMR (500 MHz, D_2O): δ 7.76 (d, *J* = 8.0 Hz, 12H, *aryl*), 7.68 (d, *J* = 8.0 Hz, 12H, *aryl*), 7.23 (d, *J* = 8.0 Hz, 12H, *aryl*), 6.88 (t, *J* = 7.6 Hz, 12H, *aryl*), 6.71 (d, *J* = 7.6 Hz, 12H, *aryl*), 6.60 (t, *J* = 8.0 Hz, 12H, *aryl*). Guest: 5.40 (s, 1H, CH), 5.03 (s, 2H, 2 x CH), 4.41 (s, 2H, 2 x CH), -0.19 (bs, 2H, CH_2), -0.99 (bs, 2H, CH_3).

[8 ⊂ **1]$^{12-}$** ^{1}H NMR (500 MHz, D_2O): δ 7.62 (d, *J* = 8.0 Hz, 12H, *aryl*), 7.55 (d, *J* = 8.0 Hz, 12H, *aryl*), 7.11 (d, *J* = 7.6 Hz, 12H, *aryl*), 6.79 (t, *J* = 7.6 Hz, 12H, *aryl*), 6.70 (d,

J = 7.6 Hz, 12H, *aryl*), 6.47 (t, *J* = 8.0 Hz, 12H, *aryl*). Guest: 5.55 (s, 1H, CH), 3.91 (s, 2H, 2 x CH), 3.54 (s, 2H, 2 x CH), -1.08 (s, 1H, CH), -1.93 (bs, 6H, 2 x CH_3).

[9 ⊂ 1]$^{12-}$ ^{1}H NMR (500 MHz, D_2O): δ 7.74 (bs, 24H, *aryl*), 7.16 (bs, 12H, *aryl*), 6.83 (bs, 12H, *aryl*), 6.71 (d, *J* = 7.6 Hz, 12H, *aryl*), 6.55 (t, *J* = 7.6 Hz, 12H, *aryl*). Guest: 3.31 (s, 2H, 2 x CH), -0.14 (s, 12H, 4 x CH_3).

[2x **10 ⊂ 1]$^{12-}$** ^{1}H NMR (500 MHz, D_2O): δ 7.69 (bs, 24H, *aryl*), 7.13 (d, *J* = 7.6 Hz, 12H, *aryl*), 6.77 (t, *J* = 8.0 Hz, 12H, *aryl*), 6.57 (d, *J* = 8.0 Hz, 12H, *aryl*), 6.40 (t, *J* = 8.0 Hz, 12H, *aryl*). Guest: 5.77 (bs, 4H, 4 x CH), 5.53 (bs, 2H, 2 x CH), 5.43 (bs, 4H, 4 x CH).

[2x **11 ⊂ 1]$^{12-}$** ^{1}H NMR (500 MHz, D_2O): δ 7.72 (d, *J* = 7.6 Hz, 12H, *aryl*), 7.64 (d, *J* = 7.6 Hz, 12H, *aryl*), 7.17 (d, *J* = 7.5 Hz, 12H, *aryl*), 6.84 (t, *J* = 8.0 Hz, 12H, *aryl*), 6.58 (d, *J* = 8.0 Hz, 12H, *aryl*), 6.44 (t, *J* = 8.0 Hz, 12H, *aryl*). Guest: 5.06 (bs, 2H, 2 x CH), 4.53 (bs, 4H, 4 x CH), 4.21 (bs, 4H, 4 x CH).

[2x **12 ⊂ 1]$^{12-}$** ^{1}H NMR (500 MHz, D_2O): δ 7.73 (d, *J* = 7.5 Hz, 12H, *aryl*), 7.64 (d, *J* = 7.6 Hz, 12H, *aryl*), 7.04 (d, *J* = 7.5 Hz, 12H, *aryl*), 6.83 (t, *J* = 8.0 Hz, 12H, *aryl*), 6.59 (d, *J* = 8.0 Hz, 12H, *aryl*), 6.44 (t, *J* = 8.0 Hz, 12H, *aryl*). Guest: 5.12 (bs, 2H, 2 x CH), 4.27 (bs, 4H, 4 x CH), 4.03 (bs, 4H, 4 x CH).

[2x **13 ⊂ 1]$^{12-}$** ^{1}H NMR (500 MHz, D_2O): δ 7.65 (m, *overlapping*, 24H, *aryl*), 7.05 (d, *J* = 7.5 Hz, 12H, *aryl*), 6.77 (t, *J* = 8.0 Hz, 12H, *aryl*), 6.58 (d, *J* = 8.0 Hz, 12H, *aryl*), 6.42 (t, *J* = 8.0 Hz, 12H, *aryl*). Guest: 5.20 (bs, 2H, 2 x CH), 4.20 (bs, 4H, 4 x CH), 4.11 (bs, 4H, 4 x CH).

[2x **14 ⊂ 1]$^{12-}$** ^{1}H NMR (500 MHz, D_2O): δ 7.94 (d, *J* = 7.6 Hz, 12H, *aryl*), 7.78 (d, *J* = 8.0 Hz, 12H, *aryl*), 7.34 (d, *J* = 8.0 Hz, 12H, *aryl*), 6.95 (t, *J* = 8.0 Hz, 12H, *aryl*), 6.72 (d, *J* = 7.6 Hz, 12H, *aryl*), 6.58 (t, *J* = 7.6 Hz, 12H, *aryl*). Guest: 4.43 (d, *J* = 45 Hz, 2H, 2 x CH), 4.92 (bs, 4H, 4 x CH), 3.67 (bs, 2H, 2 x CH), -0.53 (s, 6H, 2 x CH_3).

[2x **15 ⊂ 1]$^{12-}$** ^{1}H NMR (500 MHz, D_2O): δ 7.88 (bs, 12H, *aryl*), 7.31 (bs, 12H, *aryl*), 7.31 (bs, 12H, *aryl*), 6.97 (bs, 12H, *aryl*), 6.71 (bs, 12H, *aryl*), 6.57 (bs, 12H, *aryl*). Guest: 5.16 (s, 2H, 2 x CH), 4.22 (bs, 4H, 4 x CH), 3.86 (bs, 2H, 2 x CH), -0.09 (s, 6H, 2 x CH_3).

[2x **16 ⊂ 1]$^{12-}$** ^{1}H NMR (500 MHz, D_2O): δ 7.91 (bs, 12H, *aryl*), 7.78 (bs, 12H, *aryl*), 7.32 (d, *J* = 7.6 Hz, 12H, *aryl*), 6.90 (t, *J* = 7.6 Hz, 12H, *aryl*), 6.71 (bs, 12H, *aryl*), 6.56 (bs, 12H, *aryl*). Guest: 5.45 (s, 2H, 2 x CH), 4.13 (bs, 4H, 4 x CH), 3.71 (bs, 2H, 2 x CH), -0.74 (s, 6H, 2 x CH_3).

[17 ⊂ 1]$^{12-}$ ^{1}H NMR (500 MHz, D_2O): δ 7.46 (d, *J* = 7.6 Hz, 12H, *aryl*), 7.61 (d, *J* = 7.6 Hz, 12H, *aryl*), 7.29 (bs, 12H, *aryl*), 6.84 (t, *J* = 8.0 Hz, 12H, *aryl*), 6.84 (t, *J* = 8.0 Hz, 12H, *aryl*), 6.56 (t, *J* = 8.0 Hz, 12H, *aryl*). Guest: 4.93 (s, 1H, CH), 4.08 (s, 2H, 2 x CH overlapping), 3.82 (s, 1H, CH), -0.31 (s, 3H, CH_3).

[18 ⊂ 1]$^{12-}$ ^{1}H NMR (500 MHz, D_2O): δ 7.73 (d, *J* = 7.6 Hz, 12H, *aryl*), 7.71 (d, *J* = 7.8 Hz, 12H, *aryl*), 7.22 (d, *J* = 8.0 Hz, 12H, *aryl*), 6.83 (t, *J* = 8.0 Hz, 12H, *aryl*), 6.71 (d, *J* = 8.0 Hz, 12H, *aryl*), 6.54 (t, *J* = 8.0 Hz, 12H, *aryl*). Guest: 4.22 (s, 2H, 2 x CH), 3.56 (s, 2H, 2 x CH), -0.30 (s, 3H, CH_3).

[2x **19 ⊂ 1]$^{12-}$** ^{1}H NMR (500 MHz, D_2O): δ 7.84 (d, *J* = 8.0 Hz, 12H, *aryl*), 7.76 (d, *J* = 8.0 Hz, 12H, *aryl*), 7.28 (d, *J* = 8.0 Hz, 12H, *aryl*), 6.96 (t, *J* = 7.6 Hz, 12H, *aryl*), 6.72 (d, *J* = 8.0 Hz, 12H, *aryl*), 6.56 (t, *J* = 8.0 Hz, 12H, *aryl*). Guest: 5.06 (bd, *J* = 47 Hz, 4H, 4 x CH), 4.76 (bs, 4H, 4 x CH).

[2x **20 ⊂ 1]$^{12-}$** ^{1}H NMR (500 MHz, D_2O): δ 7.96 (bs, 12H, *aryl*), 7.76 (bs, 12H, *aryl*), 7.34 (d, *J* = 8.0 Hz, 12H, *aryl*), 6.94 (bs, 12H, *aryl*), 6.73 (d, *J* = 7.6 Hz, 12H, *aryl*), 6.59 (t, *J* = 8.0 Hz, 12H, *aryl*). Guest: 4.45 (bs, 4H, 4 x CH), 4.01 (bs, 4H, 4 x CH).

[2x **21 ⊂ 1]$^{12-}$** ^{1}H NMR (500 MHz, D_2O): δ 7.91 (bs, 12H, *aryl*), 7.66 (d, *J* = 8.0 Hz, 12H, *aryl*), 7.41 (d, *J* = 8.0 Hz, 12H, *aryl*), 6.79 (bs, 12H, *aryl*), 6.81 (d, *J* = 7.6 Hz, 12H, *aryl*), 6.61 (t, *J* = 8.0 Hz, 12H, *aryl*). Guest: 4.38 (bs, 4H, 4 x CH), 4.21 (bs, 4H, 4 x CH).

[22 ⊂ 1]$^{12-}$ ^{1}H NMR (500 MHz, D_2O): δ 7.88 (d, *J* = 7.6 Hz, 12H, *aryl*), 7.73 (d, *J* = 7.6 Hz, 12H, *aryl*), 7.37 (bs, 12H, *aryl*), 6.69 (t, *J* = 8.0 Hz, 12H, *aryl*), 6.56 (d, *J* = 7.6 Hz, 12H, *aryl*), 6.52 (t, *J* = 7.6 Hz, 12H, *aryl*). Guest: 5.15 (bs, 4H, 4 x CH), 5.04 (bs, 2H, 2 x CH), 4.51 (bs, 4H, 4 x CH), 1.32 (s, 2H, CH_2).

[23 ⊂ 1]$^{12-}$ ^{1}H NMR (500 MHz, D_2O): δ 7.71 (bs, 24H, *aryl*), 7.25 (d, *J* = 8.0 Hz, 12H, *aryl*), 6.84 (t, *J* = 7.6 Hz, 12H, *aryl*), 6.71 (d, *J* = 8.0 Hz, 12H, *aryl*), 6.53 (t, *J* = 8.0 Hz, 12H, *aryl*). Guest: 5.97 (t, *J* = 7.5 Hz, 2H, 2 x CH), 4.90 (t, *J* = 7.5 Hz, 4H, 4 x CH), 3.30 (d, *J* = 7.5 Hz, 4H, 4 x CH), 0.35 (d, *J* = 8.0 Hz, 2H, CH_2), -0.60 (d, *J* = 8.0 Hz, 2H, CH_2).

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Supplementary Data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.05.131.

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