

The first water-soluble hemicarceranes

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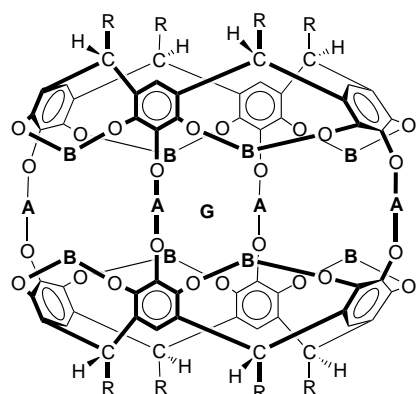
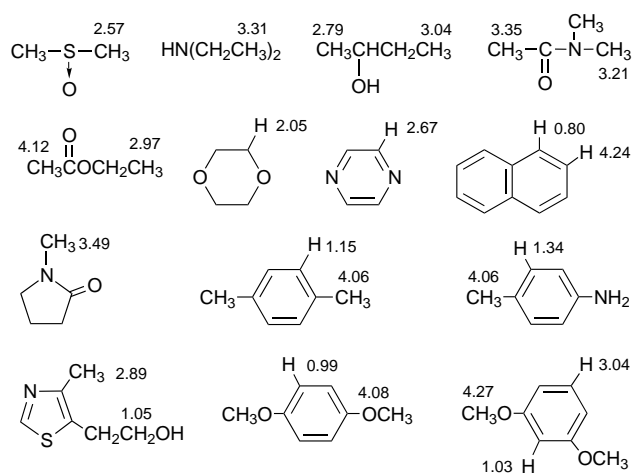
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The synthesis of the first water-soluble hemicarcerand and its spectral and binding properties with 14 guests in water are described.

Many hemicarcerands and hemicarceranes of general structures **1** and **1**⊙G, respectively, have been reported in which the carbon chains of the bridging A groups, the spanning B groups, the feet (R groups) and guests (G) have been widely varied.¹ The host which binds the largest number and variety of guests is **2** [A = (CH₂)₄, B = CH₂, R = CH₂CH₂Ph].² Recently a family of hosts has been synthesized in which A = 3-CH₂C₆H₄CH₂, B = (CH₂)_n (n = 1–3) and R = (CH₂)₄Me.³ Of the hundreds of known hemicarceranes,⁴ all have been too lipophilic to be soluble in water. If hemicarcerands are to be candidates for drug delivery systems, they should not only bind a wide variety of guests but they and their complexes should be soluble in water not far from physiological pH values. Here we report the synthesis, spectra and host-binding properties toward representative organic guests of the first water-soluble hemicarcerand **4**.^{†,‡}

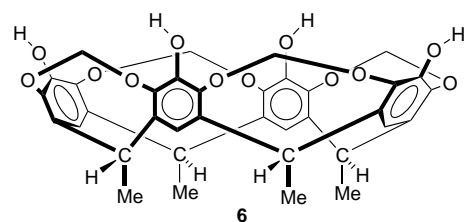
For complexation studies, a stock 1.5 mmol dm⁻³ solution of octaacid **4** in 0.1 mol dm⁻³ deuteriated sodium borate buffer (adjusted to pH 9 with NaOD in D₂O)⁷ was prepared, and its 400 MHz ¹H NMR spectrum was recorded. About 10 equiv. of each listed guest were added to the host solution, the pH was again adjusted if necessary, and the ¹H NMR spectrum of the aqueous solution was taken at 25 °C. The effects of incarceration for 14 guests on important signals in their ¹H NMR spectra in D₂O at 25 °C are recorded in values of Δδ, which equals δ_{free} – δ_{complexed}. These Δδ values (ppm) are placed close to their assigned protons in the 14 guest formulas. The fact that the

exchange of places of free and incarcerated guest was slow on the NMR time scale allowed the inner-phase guests to be differentiated from those in the bulk phase. Complexation appeared to be complete in a few minutes for all guests formulated except naphthalene, whose limited solubility in D₂O made dissolution of the solid in D₂O the rate-limiting step rather than complexation. The insolubility of naphthalene in D₂O coupled with the 12 h it took for all of the free host to become complexed indicates that complexation was the cause of dissolution of naphthalene in D₂O. All complexes were 1:1, a conclusion drawn from peak intensity comparisons.

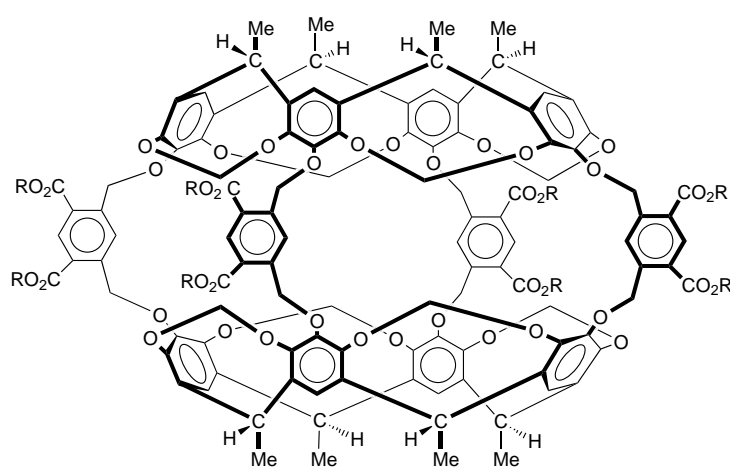


1 ⊙G, **2** ⊙G, A = (CH₂)₄, B = CH₂, R = CH₂CH₂Ph

3 ⊙G, A = 3-CH₂C₆H₄CH₂, B = CH₂, R = CH₂CH₂Ph

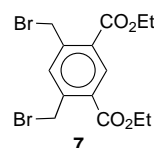


6



4 R = H

5 R = Et



7

The four salts Me_4NBr , PhNMe_3Br , BnNMe_3Br and $3\text{-MeC}_6\text{H}_4\text{CO}_2\text{Na}$ failed to complex **4** in D_2O buffer, probably because D_2O solvates their charges much better than does the interior of **4**. Although the release of many inner-phase-solvating water molecules for each host and from bulk-phase water for each guest molecule would provide a substantial entropic driving force for complexation of the cations the enthalpic solvation energies of their charges by water appear to be dominant in inhibiting complexation.

The guests formulated that are incarcerated in **4** which is dissolved in D_2O provide a wide range in size, polarity and water solubility. The smallest one is Me_2SO containing 4 heavy atoms (non-hydrogen), which is highly polar, is miscible with D_2O in all proportions, and is a good hydrogen bond acceptor. The next largest are $\text{MeCH}(\text{OH})\text{CH}_2\text{Me}$ and $(\text{MeCH}_2)_2\text{NH}$ with 5 heavy atoms, which are both moderately polar, good hydrogen bond acceptors and donors, and are rather soluble in D_2O . Of the four guests containing 6 heavy atoms, MeCONMe_2 and MeCO_2Et are highly polar, $\text{O}(\text{CH}_2\text{CH}_2)_2\text{O}$ and $\text{C}_4\text{N}_2\text{H}_4$ (1,4-diazine) are polarizable, all are highly soluble in D_2O , and are excellent hydrogen bond acceptors. The only 7-heavy atom guest is $\text{C}_5\text{H}_9\text{NO}$ (*N*-methylpyrrolidinone or NMP), which is very polar, water soluble and a good hydrogen bond acceptor. Of the two guests containing 8 heavy atoms, $4\text{-MeC}_6\text{H}_4\text{NH}_2$ and $1,4\text{-(Me)}_2\text{C}_6\text{H}_4$, the former is of intermediate polarity, is somewhat soluble in D_2O and is a good hydrogen bond acceptor and donor, whereas the latter is slightly polarizable, slightly soluble in D_2O , and is a poor hydrogen bond acceptor. The only 9-heavy atom guest is 4-methyl-5-(2-hydroxyethyl)thiazole, which is an intermediate in the synthesis of vitamin B_1 and is a sedative. This guest is rather polar, is very soluble in water, and is a good donor and acceptor of hydrogen bonds. Of the three 10-heavy atom guests that complexed **4**, 1,4-dimethoxybenzene and 1,3-dimethoxybenzene are relatively nonpolar compounds slightly soluble in D_2O with low hydrogen bond-accepting ability, whereas naphthalene is even less polar, is an even poorer hydrogen bond acceptor, and is essentially insoluble in D_2O .

Corey–Pauling–Koltun (CPK) molecular models of the 14 guests listed can be pushed, the larger ones only with difficulty, through the portals of CPK models of **4** containing new atom connectors which survive the encapsulation. Experimentally, the 1 : 1 complexes all appeared stable at ambient temperature in the medium containing excess guest in which they were prepared. It is likely that other guests that complex **3** and are stable in CDCl_3 at 25°C should be stable as complexes of **4** in D_2O at 25°C , since the hosts' interiors are essentially the same. The only guests common to this study and those involving **3** are $1,4\text{-Me}_2\text{C}_6\text{H}_4$ and $1,4\text{-(MeO)}_2\text{C}_6\text{H}_4$, whose complexes with **3** were stable to formation at high temperatures and even isolation, but decomposed rapidly enough at 25°C in CDCl_3 to inhibit recording reportable ^1H NMR spectra. Particularly with these two lipophilic guests, we expect hydrophobic binding to contribute more stability to 4OG in D_2O than solvophobic binding in CDCl_3 does to 3OG .

The ^1H NMR results provide the following interesting conclusions. (1) All inner volumes occupied (on average) by guest protons of 4OG are shielding, but vary widely. At the extremes, the β protons of 4Onaphthalene (in D_2O) give a $\Delta\delta$ value of 4.24, whereas the α protons give 0.80 ppm. Similarly, the six methyl protons of $4\text{O}1,3\text{-(MeO)}_2\text{C}_6\text{H}_4$ provide a $\Delta\delta$ value of 4.27, while the Ar–H flanked by the two MeO groups gives 1.03 ppm. Model examination of both complexes shows that the longer axes of both guests must be aligned along the longer (polar) axis of the inner phase of **4**, and the shorter guest axes along the shorter equatorial axis of **4**. The seven-heavy atom MeOCCCOMe moiety of $1,3\text{-(MeO)}_2\text{C}_6\text{H}_4$ is the longest axis of this guest. These alignments place the β protons of

naphthalene and the methyl protons of $1,3\text{-(MeO)}_2\text{C}_6\text{H}_4$ in the highly shielding polar caps of **4**, and the α protons of naphthalene and the methoxy-flanked Ar–H protons of $1,3\text{-(MeO)}_2\text{C}_6\text{H}_4$ in the much lower shielding, bridge region of the inner phase of **4**. The other $\Delta\delta$ values lend themselves to similar analysis. (2) The patterns of $\Delta\delta$ values for the protons of the same guest incarcerated in 2OG and 4OG in eight sets of available comparisons are very similar, although those of 2OG without exception are between 0.02 and 0.38 ppm higher valued than those of 4OG . This reflects the fact that although the cavities of **2** and **4** are similarly shaped, the $\text{O}(\text{CH}_2)_4\text{O}$ bridges of **2** are one atom shorter than the $3\text{-OCH}_2\text{C}_6\text{H}_4\text{CH}_2\text{O}$ bridges of **4**. (3) Generally the $\Delta\delta$ values for all the complexes fall into three groups. Values of 1 ± 0.3 are observed for protons that do not terminate chains [e.g. CH_2 of $4\text{O}4\text{-methyl-5-(2-hydroxyethyl)thiazole}$, $\Delta\delta = 0.88$, or Ar–H of $1,4\text{-(MeO)}_2\text{C}_6\text{H}_4$, $\Delta\delta = 0.99$ ppm], are close to the centre of the guest, and therefore cannot approach closely the generally shielding inner surfaces of the cavities. Values of $\Delta\delta = 2\text{--}3$ ppm are found for protons which are forced to occupy the equatorial regions of the host (e.g. CH_2 protons of NMP), or are small enough to average many locations by rapid rotations within the host's cavity [e.g. protons of Me_2SO , $\text{O}(\text{CH}_2\text{CH}_2)_2\text{O}$ or 1,4-diazine]. Values of 3.0–4.5 ppm occur for guests whose protons are forced into the faces of the host's aryl groups [e.g. the β protons of naphthalene, the Me protons of MeCO_2Et and of MeCONMe_2].

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Footnote

† Tetrol **6**⁵ (1 equiv.) was stirred under argon at 25°C with 2.1 equiv. of dibromide **7**⁶ in dry *N*-methylpyrrolidinone (NMP)– CS_2CO_3 for 24 h under high dilution conditions. An additional 1.5 equiv. of **7** were added and the stirring continued at 40°C for 24 h. The mixture was filtered, the filtrate was evaporated under high vacuum, and the residue was dissolved in CHCl_3 . The mixture was filtered, the filtrate was evaporated to ca. 5 ml and mixed with 100 ml of MeOH which precipitated octaester **5**. This material was filtered and purified by chromatography on a TLC plate (silica gel– CH_2Cl_2) to give a 15% yield of **5**. This ester was hydrolysed to give octaacid **4** in THF –1 mol dm^{-3} aqueous KOH –18-crown-6 (4 h at reflux). The solvent was evaporated, and the aqueous solution acidified to pH 1 with 1 mol dm^{-3} aqueous HCl. The octaacid **4** was extracted with EtOAc, the organic layer was dried, and the solvent evaporated to give pure **4** in 90% yield.

‡ New compounds, **4** and **5**, gave elemental analyses within 0.30% of theory, and the expected ^1H NMR spectra and FABMS (m/z , $\text{M}^+ + \text{H}$).

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