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Gases as Guests in Benzocyclotrimer Cage Hosts

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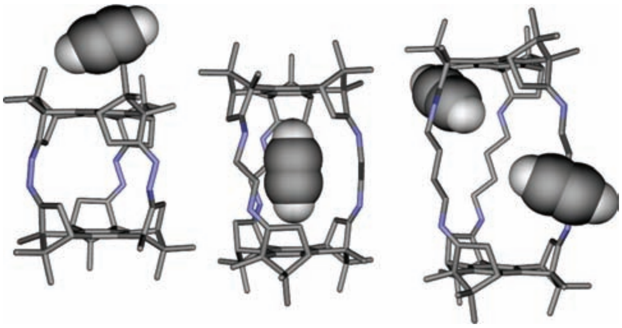
ABSTRACT



An imine-linked (+)-*syn*-benzotricamphor derivative gives access to chiral unimolecular cages exhibiting internal cavities of new shapes and volumes. One of these hosts hydrocarbon gases at low temperatures in solution through CH−π attractive interactions. No encapsulation is observed when the cage structure is too narrow or too large for the guest.

Compounds featuring an inner and outer space have a leading role in supramolecular chemistry[1,2] arising from the striking differences in behavior from hosted versus solvated molecules.[3] Self-assembled host systems, properly designed to complement a wide variety of guests, have led to *"The chemistry beyond the molecules"*.[4] In particular, charged guests—either anionic or cationic—can benefit from strong intermolecular forces with the hosts, through ion pairing, charge−dipole interaction, and cation/π interactions. In contrast, neutral apolar species, especially those lacking heteroatoms, are much more difficult to recognize: they require hosts characterized by concave surfaces to generate large reciprocal van der Waals contacts. An exception is the use of water-soluble hosts endowed with appropriate surfaces that can complement and efficiently bind neutral apolar guests driven by the hydrophobic effect. Gas absorption in solids is quite common,[5,6] but the same process is much more difficult to achieve in solution[7] since organic solvents can compete for the host. These cases require host cavities of suitable size and shape to complement the desired guest but exclude the solvent most of the time. We report the design and application of such a system here.

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Neutral, apolar hydrocarbon gases are elusive guests, but several host systems have been developed for gas binding. The field has been recently reviewed,[8] and the dynamics of binding has been analyzed.[9] In contrast to common guests which usually display packing coefficients (PC) of about 55% for encapsulation phenomena,[10] gases usually require more space, and consequently, packing coefficients decrease to 40% or less.[11] The most efficient hosts for apolar gases are unimolecular receptors characterized by small volume cavities based on scaffolds such as cycloveratrilene[12] or resorcinarene.[9,13] Nevertheless, examples of sufficiently tight self-assembled capsules displaying suitable environments for hydrocarbon gas hosting are known based on resorcinarene[11,14] or aromatic glycouril[7,15] scaffolds.

Benzocyclotrimers are rigid structures which are new scaffolds for encapsulation studies, especially suited for guests of reduced dimensions (Figure 1). Specifically, some benzocyclotrimers have recently displayed intriguing binding of neutral guest,[16] and chiral *syn*-**1** gave evidence of enantioselective ammonium ion recognition.[17] The properly modified derivative *syn*-**2**, featuring oxime residues, showed formation of a dimeric self-assembled capsule in solution capable of hosting methane, oxygen, and nitrogen.[18]

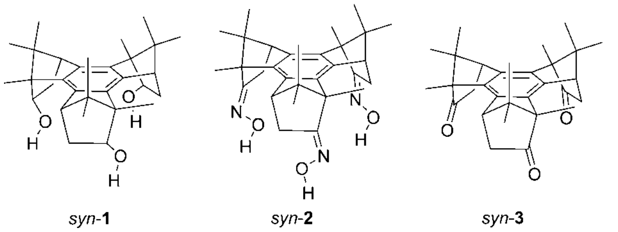
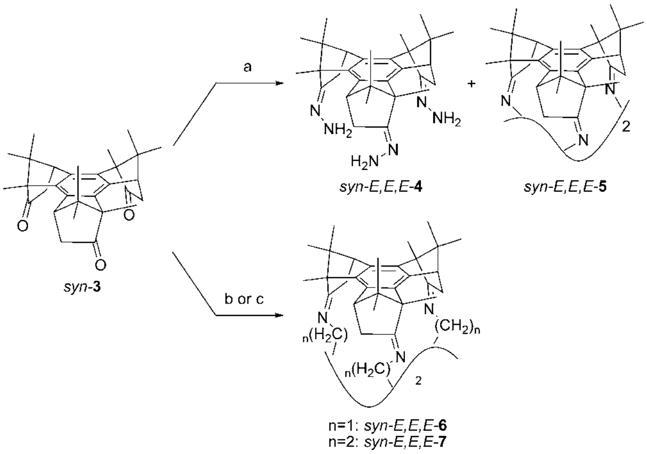


Figure 1. Benzocyclotrimeric units displaying supramolecular activity: *syn*-**1** as the chiral ammonium host; *syn*-**2** as a supramolecular self-assembled capsule for hosting gases; *syn*-**3** as a building block for the new cage compounds.

Imine linkers, obtained by reactions between carbonyl compounds and primary anilines or amines, have been successfully employed to synthesize sizable cage compounds.[19] Such systems rarely show host−guest properties because their rather large structures require suitable guests and proper experimental conditions. We pursued the synthesis of unimolecular cages bearing imine functions[20] as cross-linking groups between two benzocyclotrimeric units. The reaction of (+)-benzotricamphor *syn*-**3** with diamines ranging from hydrazine, 1,2-ethane, and 1,4-butane diamines gave the respective cage compounds.

Benzotricamphor *syn*-**3**[18] was condensed with hydrazine hydrate under azeotropic removal of water[21] and initially formed the expected trishydrazone *syn*-*E*,*E*,*E*-**4** as a single diastereoisomer. Monitoring of the reaction progress by ^{1}H NMR revealed the gradual formation of a single new C_3-symmetric compound. The latter is the main product after 64 h reaction time, and it was eventually isolated and identified as the trisazine[22] *syn*-*E*,*E*,*E*-**5** (Scheme 1). Single crystals suitable for X-ray diffraction could not be obtained for the determination of the geometrical isomerism of **4** and **5**; instead, they have been assigned from DFT calculations.[23,24]

Scheme 1[a]



[a] Reagents and conditions: (a) $H_2NNH_2{\cdot}H_2O$, H_2SO_4 (cat.), *n*-BuOH, 120 °C (18 h only *syn-E,E,E*-**4** 53% yield; 64 h only *syn-E,E,E*-**5** 91% yield); (b) $H_2N(CH_2)_2NH_2$, $BF_3{\cdot}OEt_2$ (10 mol %), PhMe, 130 °C (*syn-E,E,E*-**6** 39% yield); (c) $H_2N(CH_2)_4NH_2$, PTSA (10 mol %), PhMe, 130 °C (*syn-E,E,E*-**7** 25% yield).

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These highly ordered structures arise from the stereoregular placement of the ketone groups in the enantiomerically pure material and the high stereoselectivity in the formation of the imine double bond. 1,2-Ethanediamine and 1,4-butanediamine condensed with *syn*-**3**, providing the expected cages which were isolated as single diastereoisomers. The *E* geometry of the double bonds for *syn*-**6** and *syn*-**7** has been determined on the basis of DFT calculations and NOESY experiments.[25] It was not possible to isolate a pure compound when 1,3-propanediamine is used under the same conditions. DFT calculations[24,25] of the three cages **5**, **6**, and **7**, shown in Figure 2, allow the estimation of their internal volumes.[26]

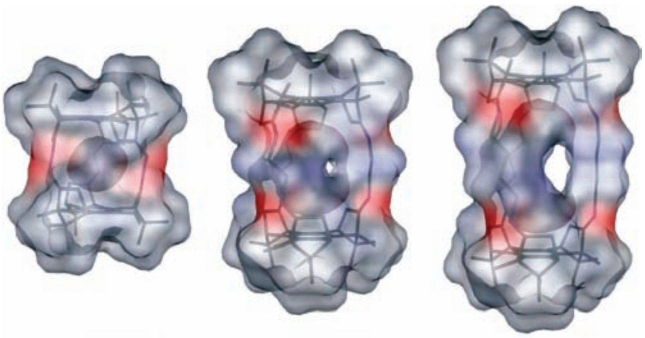
syn-E,E,E-**5** *syn-E,E,E*-**6** *syn-E,E,E*-**7**

Figure 2. Optimized structures of compounds *syn-E,E,E*-**5**, *syn-E,E,E*-**6**, and *syn-E,E,E*-**7**.

Available volumes increase from 16 Å^3 for *syn*-**5**, to 56 and 88 Å^3 for *syn*-**6** and *syn*-**7,** respectively (see Supporting Information).

The host−guest behavior of cages **5**, **6**, and **7** was studied by NMR in chloroform-*d* solution. The low molecular weight hydrocarbons (methane, ethyne, ethene, ethane, propene, butane) and H_2 were bubbled into the solution. Attempts to fill the cavity of **5** with H_2 or CH_4 as guests failed, as did the azine synthesis from **4** in the presence of dissolved H_2. Similarly, **7** provided no evidence of gas encapsulation with any of the above listed possible guests, even at low temperatures. Both (negative) results are in agreement with packing coefficient calculations showing that for **5** the internal cavity is inaccessible from outside and too small even for H_2. Exactly the opposite is true for **7**, where PCs are too small (<0.47)[10] and the openings are too large. Conversely, when gases are bubbled in NMR tubes containing **6** and spectra are recorded at low temperatures, upfield (nearly 2−4 ppm) shifted signals for encapsulated gases can be observed. The temperature at which the peaks start to appear is dependent on the gas employed. For example, encapsulated CH_4@**6** is seen at −2.00 ppm only at 238 K, the temperature below which guest exchange is slow on the chemical shift time scale, and separate signals are observed for free and encapsulated gas. Ethyne displays the best complementarity with the cavity: The upfield shifted signal for encapsulated C_2H_2@**6** appears at −1.51 already at 278 K (Figure 3). The encapsulation phenomena for C_2H_2@**6** can be confirmed by NOESY experiments (Figure 4), which show an exchange cross-peak between the free and bound guest and a scalar correlation between hosted ethyne and the bridge-head hydrogens of the cyclotrimer.

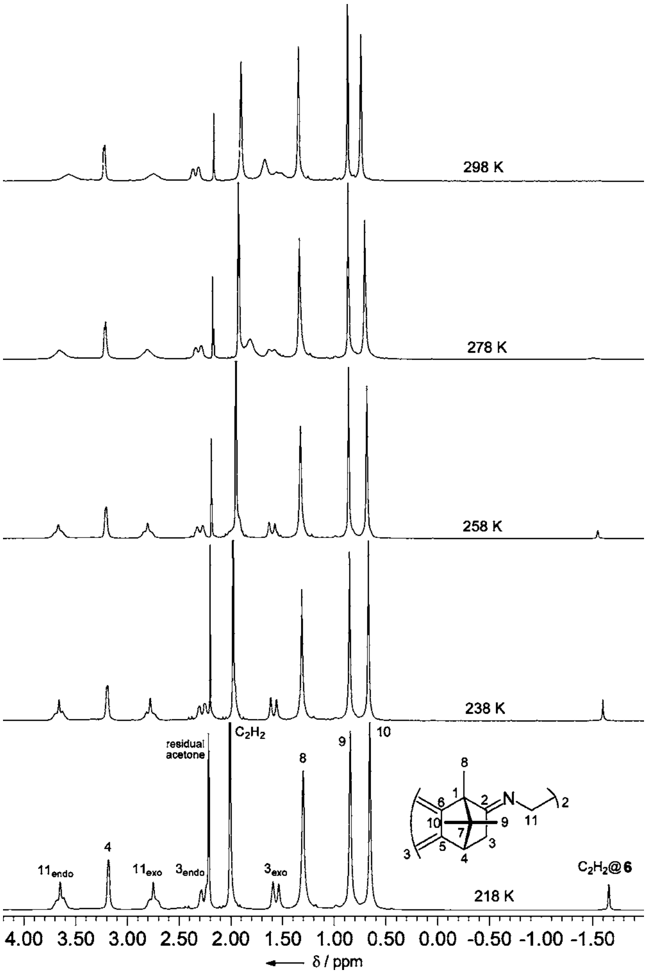

Figure 3. Temperature on the equilibrium between free ethyne and ethyne@**6** in $CDCl_3$.

The larger guests (i.e., C_2H_4 and C_2H_6) are not expected to be bound efficiently, according to their larger PC (Table 1). In fact, they showed peaks for C_2H_4@**6** and C_2H_6@**6** only at much lower temperatures: 228 and 238 K, respectively. Gases with larger volumes (propene and butane) showed no encapsulation in **6** even at 208 K, as expected on the basis of their PCs (>80%).

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[23] Calculation performed with Gaussian 03, revision D.02, on the IBM SP5 multiprocessor platform at CINECA (Bologna). DFT geometrical optimization, method RB3LYP, basis set 6-31G(d).

[24] *syn-E,E,E*-**4** was 21.84 kcal/mol more stable than *syn-Z,Z,Z*-**4**; *syn-E,E,E*-**5** was 19.62 kcal/mol more stable than *syn-Z,Z,Z*-**5** (see Supporting Information).

[25] *syn-E,E,E*-**6** was 5.23 kcal/mol more stable than *syn-Z,Z,Z*-**6**; *syn-E,E,E*-**7** was 13.12 kcal/mol more stable than *syn-Z,Z,Z*-**7** (see Supporting Information).

[26] The volume of the cavity was calculated with DeepView/Swiss PdbViewer 3.7 using a 1 Å molecular probe.

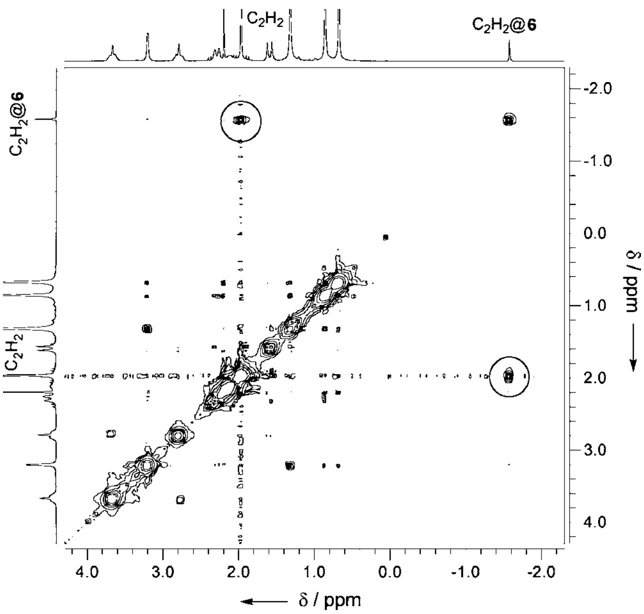

Figure 4. NOESY spectrum (300 MHz) at 228 K of **6** in ethyne-containing $CDCl_3$.

Equilibrium constants for host **6** at different temperatures can be obtained from ^1H NMR spectra, and the van't Hoff plots enabled calculation of the thermodynamic parameters for the encapsulation process at low temperatures (Table 1).

Table 1. Chemical and Thermodynamic Data for Encapsulation of Gases@**6**

gas	vol. (Å^3)	PC (%)^a	Δδ (ppm)	K_{eq}^{b}	$\Delta H^{c,d}$	$\Delta S^{c,e}$
CH_4	25	45	−2.16	3.40	−43	−0.18
HCCH	33	59	−3.67	221	−62	−0.23
H_2CCH_2	37	66	−2.55	8.99	−47	−0.19
H_3CCH_3	41	73	−2.19	1.13	−40	−0.18

[a] Packing coefficient = (guest volume)/(cavity volume), cavity volume 56 Å^3. [b] L•mol^{-1}, determined at 228 K. [c] Calculated by the van't Hoff plot (see Supporting Information), estimated error range <10%. [d] kJ•mol^{-1}. [e] kJ•mol^{-1}•K^{-1}.

Shielding effects on the resonances of the guests (Table 1) imparted by the two aromatic rings of **6** are characterized by a trend that parallels the binding affinity of the gases for the host, as commonly observed in encapsulation phenomena.[27] CH_4 and C_2H_6 are both saturated hydrocarbons, displaying the smaller binding constants of the series, probably because they do not complement the cavity well, one being too small and the other too large. Conversely, C_2H_4 and C_2H_2 have similar volumes but rather different chemical natures that are reflected on their affinity for the cavity. All the gaseous guests show similar entropic contribution to the binding, but C_2H_4 and C_2H_2 are characterized by the larger enthalpic contributions. Acetylene, in particular, is characterized by the proper size and shape and greatly benefits from the polarized C−H hydrogens. These enable strongly attractive CH−π interactions[28] with the electron-rich π-system of the benzocyclotrimer scaffold. 2D EXSY experiments at 228 K allowed the calculation of the $\Delta G^{\ddagger}$ both for the association and dissociation processes:[9] values for C_2H_2 are 52 and 61 kJ•mol^{-1}, while for C_2H_4 values are 48 and 55 kJ•mol^{-1}, respectively. Activation barriers for guest release are similar to those reported for cryptophane.[9] These two hosts share similar cavity size and three portals defined by $-CH_2CH_2-$ columns. The higher values observed with C_2H_2 are difficult to explain and are possibly related to stronger solvation in chloroform solution compared to C_2H_4.

In conclusion, chiral enantiopure molecular cages based on a cyclotrimeric scaffold provide suitable hosting structures for gaseous guests. The volume and morphology of the cavities determine the efficiency of the cages to host small organic molecules: the optimum compromise between internal space and the stiffness of the "bars" connecting the "valves" determines the efficiency of the hosting molecule. The best hemicarcerand **6** shows high complementarity in particular for C_2H_4 due to attractive CH−π interactions.

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Supporting Information Available: Detailed experimental procedures and DFT modeling of hosts. This material is available free of charge via the Internet at http://pubs.acs.org.

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