

Intramolecular inclusion in novel octaester cavitands†

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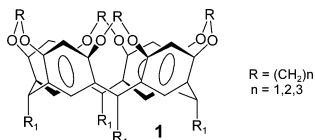
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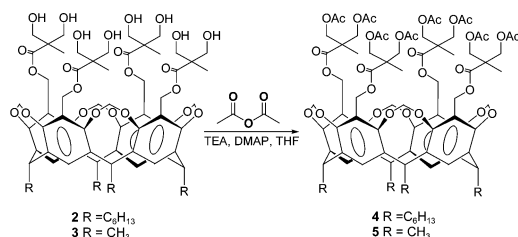
Novel octaester cavitands show intramolecular inclusion of ester moieties within the cavitand cavity.

Cavitands such as **1** contain a rigid enforced concave cavity satisfactorily large enough to encapsulate small neutral molecules or ions.¹ Cram showed that cavitands of the general structure **1** are able to encapsulate small neutral molecules such as CH₂Cl₂, CHCl₃, CS₂, and CH₃C≡CH, although such inclusion complexes are usually kinetically unstable in solutions.² In a recent report, Rebek and coworkers describe 'self inclusion', an intramolecular phenomenon in which the "guest" occupying the cavity is a covalently bonded portion of the cavitand structure, in deepened cavity cavitands. However, the inclusion was observed only at temperatures below 223 K.^{3,4a-d} Here we report intramolecular inclusion of covalently bonded esters in novel octaester cavitands at room temperature. To the best of our knowledge, intramolecular inclusion in cavitands has never been observed at room temperature, and has not been reported in non-deepened cavitands.



We prepared **2** and **3** in eight steps from resorcinol and the corresponding aldehydes.⁵ Reactions of **2** and **3** with 8.0 equiv of acetic anhydride in dry THF at room temp. in the presence of triethylamine and DMAP readily gave **4** and **5** (Scheme 1). Structure elucidation and assignment of ¹H and ¹³C resonances in **2–5** were accomplished using ¹H NMR, ¹³C NMR, MALDI analysis and COSY.⁵

The ¹H NMR spectrum of **4** recorded in CDCl₃ at 20 °C (Fig. 1) shows a singlet corresponding to the four aromatic protons (H₁) of the resorcinarene rings at 7.2 ppm. A double doublet characteristic of methylene-bridged protons² is observed at 5.7 ppm (four outer protons (H₂)), and at 4.1 ppm (four inner protons (H₃)). An 8H singlet corresponding to the methylene protons (H₄) adjacent to the resorcinarene rings at 5.0 ppm, a triplet at 4.7 ppm corresponding to four benzylic protons (H₇), and a singlet corresponding to the methylene groups (H₆) adjacent to the prochiral center at 4.0 ppm were also observed. Further upfield were three separate resonances for the alkyl chains; a quartet for the methylene groups (H₈) at 2.2 ppm, a broad multiplet at 1.5–1.2 ppm for the methylene groups



Scheme 1

† Electronic supplementary information (ESI) available: experimental; spectral data. See <http://www.rsc.org/suppdata/cc/b3/b316498e/>

(H₉–H₁₂), and a triplet at 0.88 ppm for the terminal methyl groups (H₁₃). Finally, a 12H singlet corresponding to the methyl groups (H₅) adjacent to the prochiral center was observed at 1.1 ppm. Interestingly, acetate group resonances that would be consistent with literature at around 2 ppm were not present in the ¹H NMR spectrum of **4**.⁶ Similarly, the ¹H NMR spectrum of **5** recorded in CDCl₃ at 20 °C (Fig. 1) showed all proton resonances at expected chemical shift values but did not exhibit acetate signals at chemical shift values consistent with literature.⁶ Instead, a signal upfield at 1.5 ppm that integrated to 24 protons was observed for the acetate groups.

In the ¹H NMR spectra of **4** and **5**, the upfield signal shifts in the acetate methyl resonances are characteristic of aromatic shielding and we suspected that intramolecular inclusion of the acetate groups within the cavitand cavity was responsible. The inclusion is believed to be intramolecular as evidenced by the fact that the spectra do not change within the concentration range of 5–25 mM.^{3a,7a,b}

Fig. 2 shows the ¹H NMR spectra of **5**, recorded at different probe temperatures in CDCl₃ at 360 MHz.^{7c} A downfield shift of

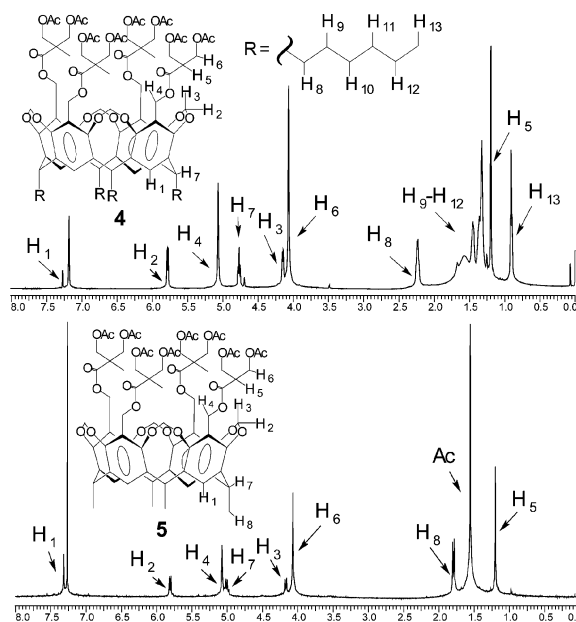


Fig. 1 ¹H NMR spectra of octaacetates **4** and **5** in CDCl₃ at 20 °C at 360 MHz.

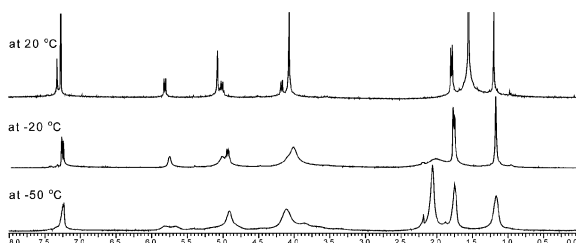


Fig. 2 ¹H NMR spectra of octaacetate **5** in CDCl₃ at 360 MHz.

0.7 ppm from 1.5–2.2 ppm in the acetate methyl resonance was observed upon cooling from 20 to -50 °C. This suggests that the intramolecular inclusion is temperature dependent. At 20 °C, it seems, there is a higher percentage of the bound species present, however exchange is fast on the NMR timescale and an averaged signal is observed at 1.5 ppm. At intermediate temperature, *i.e.* -20 °C, broadened signals are observed, which correspond to both the free and bound species being present and in intermediate-rate exchange. At -50 °C a higher percentage of the free species is favored giving rise to a single signal at 2.2 ppm.^{7c}

In order to examine more closely the inclusion phenomenon, we synthesized octaester cavitands **6–9** (Scheme 2) of varied sizes and steric bulk. Proceeding from cavitand **2** and the corresponding electrophiles (**6** mesyl chloride, **7** isobutryl chloride, **8** *p*-anisoyl chloride and **9** *p*-biphenylcarbonyl chloride) cavitands **6–9** were synthesized in excellent yield without need of chromatographic purification.⁵ The reactions were performed in dry THF at room temp. using triethylamine and a catalytic amount of DMAP.

Similar to octaacetates **4** and **5**, octamesylate **6** showed the mesylate methyl signal shifted upfield at 1.5 ppm. The ¹H NMR spectra of **6**, recorded at different temperatures, show a downfield shift for the mesylate functionalities occurred. Upon cooling from 20 to -50 °C a sharp peak that integrated for 24 hydrogens was observed at 2.2 ppm.^{7c}

The octaisopropionate **7** (Fig. 3) showed only a small upfield resonance shift ($\Delta\delta = 0.07$) to 1.06 ppm compared to literature values of 1.13–1.11 ppm for the methyl protons in the isopropyl esters. Interestingly, a double doublet-splitting pattern for the

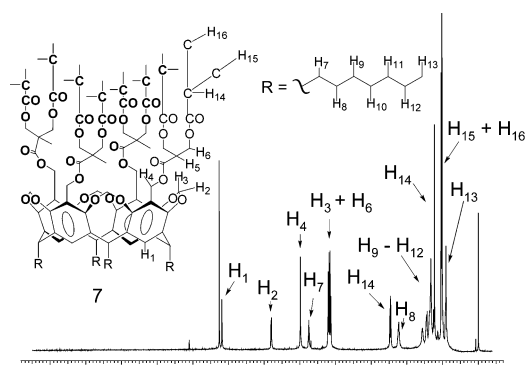
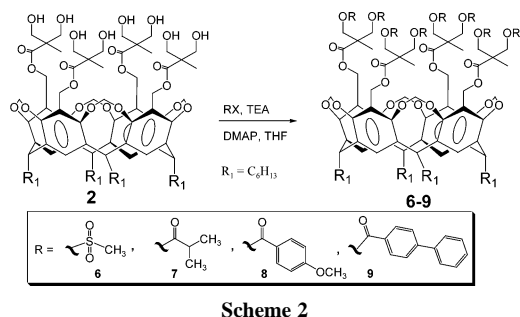


Fig. 3 ¹H NMR spectrum of octaisopropionate **7** in CDCl₃ at 500 MHz at 20 °C.

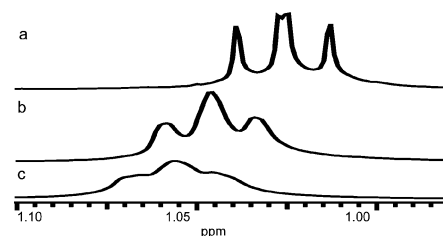


Fig. 4 Parts of the ¹H NMR spectrum of octaisopropionate **7** in CDCl₃ at 500 MHz (a) at 20 °C (b), at -5 °C (c), at -20 °C.

isopropyl moiety was observed suggesting chemical non-equivalence of the two methyl groups. Partial inclusion, such that the methyl groups are oriented towards and away from the aromatic region, cannot be discounted for the non-equivalence of the isopropyl groups. During acquisition of the ¹H NMR of **7**, cooling from 20 to -20 °C (Fig. 4), the isopropyl group signals begin to merge and shift downfield.

Finally, in **8** and **9**, interactions of the cavitand cavity and the methoxy benzoyl group or the phenyl benzoyl group were not observed.

In summary the phenomenon described herein is size dependent for the ester moieties among cavitands **4–9**. Such cavitands offer unique molecular platforms for host–guest chemistries, sensor development, metal complexation, as well as new polymers and self-assembled systems, and as potential reaction sites, and novel catalytic chambers.

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Notes and references

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- 7 (a) ¹H NMR spectra recorded at 5, 10, 15, 20, and 25 mM concentrations resulted in no change of the spectra (b) ¹H-NMR spectral data recorded in deuterated solvents of different polarity, *viz.*, benzene-*d*₆, 1,2-dichlorobenzene-*d*₄, dimethylsulfoxide-*d*₆, and methanol-*d*₄, resulted in no change of the spectrum (c) for ¹H-NMR variable temperature experiments please see ESI†.