

On the Nature of the Host–Guest Interaction Between Cyclam and 4-*tert*-Butylbenzoic Acid—A System Pre-assembled for Metal Complex Formation

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The host–guest interaction between cyclam and 4-*tert*-butylbenzoic acid has been investigated by NMR titration, X-ray diffraction, neutron diffraction and semi-empirical MO calculations; the product represents a system pre-assembled for metal-ion complexation.

The use of molecular design to achieve spatial and/or electronic complementarity between different molecular entities is a continuing theme underlying many of the recent studies in host–guest chemistry.¹ In the present study, we have demonstrated that aromatic and aliphatic carboxylic acid moieties interact with the 14-membered tetraaza macrocycle cyclam, such that discrete assemblies are formed. One such assembly, the host–guest complex between 4-*tert*-butylbenzoic acid and cyclam, has proved an ideal model for investigating the carboxylic acid–amine interaction present—a type common to a wide range of synthetic and naturally occurring host–guest systems.

Monitoring the changes in the ¹H and ¹³C NMR spectra during the incremental addition of 4-*tert*-butylbenzoic acid to a solution of cyclam in CDCl₃ indicated 2 : 1 host–guest complex formation (Fig. 1). A parallel investigation using titration calorimetry confirmed the above stoichiometry; the thermogram obtained in chloroform showed a distinct end point corresponding to formation of the 2 : 1 host guest species.

Similar behaviour was also observed when 4-*tert*-butylbenzoic acid was replaced by hexadecanoic acid, confirming the generality of the host–guest interaction with cyclam. Slow crystallization of a methanol solution containing cyclam and 4-*tert*-butylbenzoic acid in the ratio 2 : 1 yielded, however, a crystalline 4 : 1 complex. This product was investigated by both X-ray and neutron diffraction.† The structural data show that two 4-*tert*-butylbenzoic acid moieties interact directly with the cyclam molecule *via* a network of hydrogen bonds involving all four amine groups (Fig. 2). Each of these carboxylate species is joined to the cyclam by three non-equivalent hydrogen bonds (one strong, one intermediate, one weak) such that the six available hydrogen atoms (four from the amine groups and two from the acid groups) are used in host–guest binding. The two weaker hydrogen bonded

interactions between the cyclam and each of the ‘guest’ carboxylate moieties are important to the orientation of the latter with respect to the cyclam ring—spanning as they do between two diagonal amine groups. The two additional 4-*tert*-butylbenzoic acid molecules are not intimately associated with the cyclam; each exists in the lattice hydrogen bonded to an oxygen of different ‘guest’ 4-*tert*-butylbenzoic acid groups (Fig. 2).

The neutron data show that, for each of the ‘strongest’ bonded N–H⋯O groupings (as exemplified by [N(619′)–H(119′)–O(117)], the N–H [N(619′)–H(119′)] bond length is 1.033 (14) Å while for the ‘weakest’ hydrogen bond the N–H [N(619′)–H(129′)] bond length appears only marginally shorter at 0.992 (16) Å. The similarity of these bond lengths clearly demonstrates that there has been an effective transfer of a carboxylic acid proton to the amine group on formation of the ‘strongest’ bond. That is, the data confirm that the interaction is essentially between a –NH₂⁺ group and a –COO[–] group—formally analogous to formation of a ‘host–guest zwitterion’. The mean literature value for quaternary N–H bonds is 1.033 Å,² corresponding to the neutron value mentioned above. The H–N–H⋯O angle [H(129′)–N(619′)–H(119′)] at the nitrogen is 106.8°, in accordance with the presence of a near regular quaternary nitrogen group. The

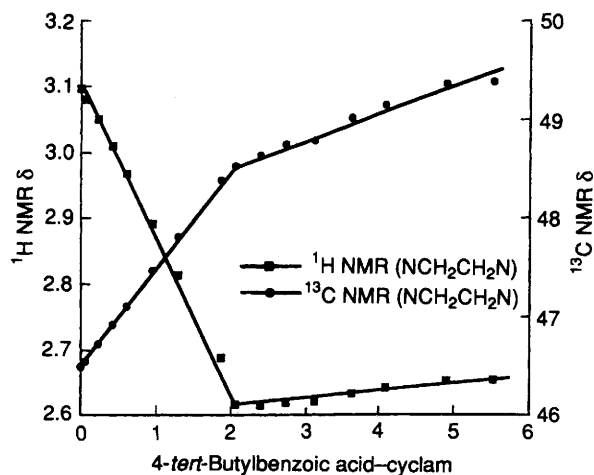


Fig. 1 Individual chemical shifts in CDCl₃ of selected methylene carbon and hydrogens of cyclam upon incremental addition of 4-*tert*-butylbenzoic acid

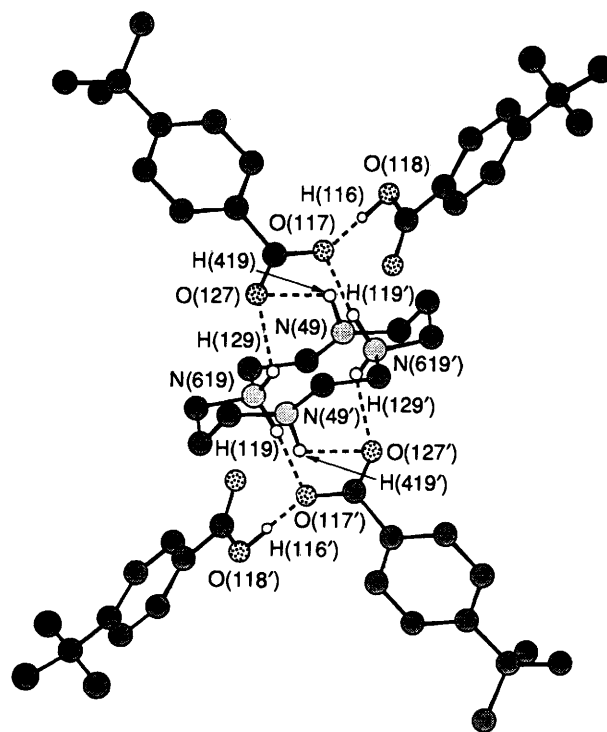
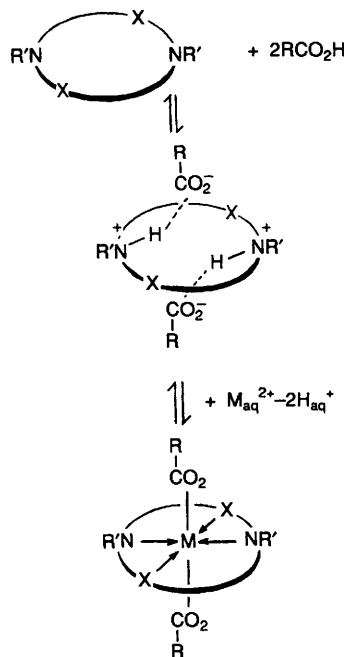


Fig. 2 The neutron diffraction structure of the 4 : 1 adduct between 4-*tert*-butylbenzoic acid and cyclam. Only hydrogen atoms participating in the hydrogen bonding network have been included.

Table 1 Observed (neutron diffraction) and calculated (AM1) hydrogen bond parameters for the 4:1 host-guest adduct between 4-*tert*-butylbenzoic acid and cyclam

	N(619)-H(119')-O(117) Neutron AM1	N(619)-H(129)-O(127) Neutron AM1	N(49)-H(419)-O(127) Neutron AM1
(N-H) Å	1.03 1.04	0.99 1.04	1.00 1.00
(H-O) Å	1.75 1.90	2.06 2.05	2.58 2.34
(N-O) Å	2.78 2.89	2.81 2.82	3.09 2.96
(N-H-O) ^a	172.2 159.3	130.9 130.2	112.0 119.2

^a Using MOPAC 6.0 on a Fujitsu VP2200 computer. Geometry optimisations were run in cartesian coordinates using the BFGS method and termination criteria set to a gnorm of <0.01. Full geometry optimisations required *ca.* 60 min of CPU time.

**Fig. 3** Metal ion complexation by the 'pre-assembled' carboxylic acid-amine macrocycle species

thermal ellipsoid for the 'transferred' proton was found to be almost spherical (within the limits of the neutron data) giving no evidence that this proton has extended occupancy in other regions between the carboxylate and amine groups.

The above hydrogen bonding behaviour (and particularly the 'proton transfer' behaviour) has been investigated using semi-empirical MO calculations based on AM1³ within the MOPAC 6 package.⁴ Reasonable agreement was obtained between the neutron structure and the calculated structure (Table 1) (PM3, within MOPAC 6.0, gave a slightly less satisfactory fit). When the calculations were repeated with the two 'peripheral' carboxylate groups removed, as expected, no significant variation within the remaining carboxylate-cyclam hydrogen bonding pattern was observed. The charge distribution within the host-guest species was found to approach that predicted for full charge separation (2⁺:1⁻:1⁻); the values obtained from AM1 are 1.89⁺:0.93⁻:0.93⁻, respectively.

The formation of host-guest species of the above type which effectively 'pre-assembles' a complete coordination sphere for a metal ion (Fig. 3) has important implications for the design of systems for metal-ion uptake. The effect of pre-assembly is to provide a more highly preorganised donor-set from the

individual components and thus should favourably influence both the strength and selectivity of metal complex formation.

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Footnote

[†] X-ray Crystal data for: C₃₂H₅₂N₄O₄, *M* = 556.80, triclinic, space group *P*1̄ (No. 2), *a* = 9.108(4), *b* = 9.798(5), *c* = 17.406(9) Å, α = 77.64(4)°, β = 75.32(4)°, γ = 63.34(5)°, *U* = 1334(1) Å³. Data were collected on a single crystal (0.18 × 0.26 × 0.30 mm); 2518 of the 4691 measured reflections with *I* > 2.5σ(*I*) were used for the structure analysis; λ = 0.71073 Å. The data were processed (B. A. Frenz and Enraf-Nonius, Structure Determination Package, Delft, The Netherlands, 1985) and corrected for Lorentz and polarisation effects and absorption (empirical, based on azimuthal for reflections). The structure was solved by heavy-atom methods SHELXS-86 (G. M. Sheldrick, *Acta Crystallogr. Sect. A*, 1990, 46, 467) and refinement with anisotropic atomic displacement parameters SHELX-92 (G. M. Sheldrick, *J. App. Cryst.*, 1994, to be published) resulted in the residuals *R* = (Σ||*F*_o| - |*F*_c||/Σ|*F*_o|) of 0.071 and *R*_w = [Σw(|*F*_o| - |*F*_c||)²/Σw(|*F*_o|²)]^{1/2} of 0.08 {*w* = 1.0/(σ²*F*_o + 0.0003*F*_o²)}.

Neutron crystal data for: [C₃₂H₅₂N₄O₄], *M* = 556.80, triclinic, space group *P*1̄ (No. 2), *a* = 9.108(4), *b* = 9.798(5), *c* = 17.406(9) Å, α = 77.64(4)°, β = 75.32(4)°, γ = 63.34(5)°, *U* = 1334(1) Å³. Data were collected on a single crystal (2.85 × 2.85 × 1.1 mm); 2511 of the 3654 measured reflections with *I* > 2.0σ(*I*) were used for structure analysis. Data were collected on the 2TANA four circle diffractometer on HIFAR, Lucas Heights Research Laboratories (Australia) using 2θ/ω scanning mode; λ = 1.221 Å, an absorption correction was applied (μ = 2.9 cm⁻¹). The coordinates obtained from the X-ray study were used as the starting point for the refinement which was carried out with SHELXL-92 (G. M. Sheldrick, *J. App. Cryst.*, 1993, to be published). The neutron refinement confirmed the hydrogen positions calculated in the X-ray determination of the structure. A final value of the residual *R* = (Σ||*F*_o| - |*F*_c||/Σ|*F*_o|) of 0.095 was obtained. Atomic coordinates, bond lengths and angles and thermal parameters have been lodged with the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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