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Creation of a Ternary Complex between a Crown Ether and 4-Aminobenzoic acid and 3,5-Dinitrobenzoic acid

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Synopsis Inclusion of 18-crown-6 into the co-crystallisation of 3,5-dinitrobenzoic acid/4-aminobenzoic acid results in the creation of a **ternary complex**. The enhanced match between the crown and the protonated form of 4-aminobenzoic acid directs the formation of the complex system.

Abstract The creation of ternary multi-component crystals through the introduction of 18-crown-6 to direct the hydrogen bonding motifs of the other components was investigated for 3,5-dinitrobenzoic acid (3,5-dnba) with 4-aminobenzoic acid (4-aba). The creation of a binary complex between 18-crown-6 and 4-aba and a ternary salt between 3,5-dnba, 18-crown-6 and 4-aba were confirmed by single crystal structure determination. The amino derivatives bind to the crown ether through NH...O hydrogen bonding, leaving a single donor site available with restricted geometry to bind to 3,5-dnba. While 3,5-dnba and 4-aba form a binary co-crystal, the shape selective nature of 18-crown-6 preferentially binds the protonated amino molecules leading to the formation of ternary salt despite the predicted low concentration of this species in the **crystallising solution**. Thus through the choice of crown ether it may be possible to control both location and nature of the available bonding sites for the designed creation of ternary crystals.

Keywords: crystal engineering; salts; co-crystals; crown ethers

1. Introduction

A key aim of crystal engineering is the designed formation of novel functional materials through the control and application of intermolecular interactions. One route for this involves the creation of multi-component crystalline materials such as salts or co-crystals, which has recently expanded due to the interest in the application of such materials as new formulations for active pharmaceutical ingredients (APIs) (Almarsson & Zaworotko, 2004; Caira, 2007; Babu et al., 2008; Berry et al., 2008; Childs et al., 2008; Ainouz et al., 2009; Rager & Hilfiker, 2010; Braga et al., 2012). While the

creation of binary systems has been frequently investigated (Etter & Reutzel, 1991; Lynch et al., 1994; Aakeröy et al., 2003; Bis et al., 2007; Corvis et al., 2010) and an understanding of the structural and experimental factors that contribute to the successful formation of such materials is beginning to be constructed (Nehm et al., 2006; Chiarella et al., 2007; Shattock et al., 2008; Horst et al., 2009; Issa et al., 2009; Karamertzanis et al., 2009; Boyd et al., 2010; Leyssens et al., 2012; Croker et al., 2013), the development of ternary and higher complexes is significantly less developed.

The major design process in the creation of multi-component materials is the consideration of supramolecular synthons between the components (Desiraju, 1995). These are frequently occurring intermolecular interactions that are expected to bind the components together in the resulting crystal structure. In the case of a binary complex, a single supramolecular synthon is required between the two components, while for a ternary system two such synthons are required. This can be achieved either by a central molecule exhibiting two binding sites for the other components or through the formation of framework by two components with the third component included within the structure. The first route has been utilised more frequently as it exists as a straightforward extension of the binary complex creation process. However, it does require the two binding sites of the bridging molecule to be able to successfully distinguish between the two other components and reduce the potential for the formation of a 2:1 composition binary co-crystal. This has been achieved by use of hydrogen bond acceptor/donor sites of differing strengths and second and third components of differing strengths (Aakeröy et al., 2001; Aakeröy & Salmon, 2005; Aakeröy et al., 2005; Bhogala et al., 2005; Aakeröy et al., 2006; Tan et al., 2006; Aakeröy et al., 2007; Dabros et al., 2007; Bhogala & Nangia, 2008) or the use of differing but complementary types of interaction such as charge transfer and hydrogen bonding (Thomas et al., 2010; Seaton et al., 2013). Examples of the second approach are rarer but the creation of co-crystal frameworks with interchangeable solvent molecules in the lattice has been demonstrated (Friščić et al., 2006). Related to this is the inclusion of NH_4^+ /18-crown-6 or HONH_3^+ /18-crown-6 into the framework of 1,3-cis 5-cis-cyclohexanetricarboxylic acid forming the inverse concept (single component framework and binary inclusion) (Bhogala & Nangia, 2006). Indeed, building on this methodology, another potential route for ternary co-crystal formation is the inclusion of co-crystal forming dimer into a macrocyclic container. This would require a bifunctional co-crystal former that could selectively bind to both the macrocycle and the other component.

4-Aminobenzoic acid (4-aba) forms a binary co-crystals with both 3,5-dinitrobenzoic acid (3,5-dnba) (Etter & Frankenbach, 1989; Chadwick et al., 2009) and 18-crown-6 (Figure 1) (Elbasyouny et al., 1983). The binary acid/acid co-crystal forms through a heteromolecular $R_2^2(8)$ acid dimer. **Only the unit cell** of the complex with 18-crown-6 has been reported, however, the related methyl ester complex binds through the amino group to the ring oxygens through $\text{NH}\dots\text{O}$ hydrogen bonds. Thus the hydrogen bonding interactions between the three components are potentially complementary to each allowing for the formation of the desired ternary co-crystal (Figure 2). Additionally, the crown

ether may play a secondary role in directing the direction of the interactions between the remaining components. The initial study of this project was the synthesis of the binary co-crystal between 4-aba and 18-crown-6 (**I**) to confirm the expected hydrogen bonding interactions followed by the creation of a ternary complex between 3,5-dnba, 4-aba and 18-crown-6 (**II**).

2. Experimental

All starting materials were purchased from Sigma-Aldrich and used as received.

2.1. Synthesis of I

18-crown-6 (0.27 g, 0.001 mol) in methanol (2 cm³) and 4-aminobenzoic acid (0.3 g, 0.002 mol) in methanol (5 cm³) were mixed and heated until all solid was dissolved. The solution was left to cool and clear **block-shaped** crystals were formed. Comparison of PXRD data with simulated pattern from the determined crystal structure confirmed the identity of the bulk sample.

IR: $\nu_{\max}/\text{cm}^{-1}$ 3445 and 3363 (s, NH₂), 3258 (s br, OH), 2886 (m, CH₂), 1656 (s, C=O), 1595 (s, NH₂), 1107 cm⁻¹ (s, CH₂).

2.2. Synthesis of II

18-crown-6 (0.27 g, 0.001 mol) in methanol (2 cm³) and 4-aminobenzoic acid (0.14 g, 0.001 mol) in methanol (7 cm³) were mixed and heated until all solid was dissolved. To this solution, 3,5-dinitrobenzoic acid (0.42 g, 0.002 mol) was added. The resulting solution was left to cool and colourless block crystals were formed. Comparison of PXRD data with simulated pattern from the determined crystal structure confirmed the identity of the bulk sample.

IR: $\nu_{\max}/\text{cm}^{-1}$ 3450 (s br, OH), 3370 (m, NH₃⁺), 1536 (s, C=O), 1347 cm⁻¹ (s, NO₂).

2.3. X-ray Crystallography

The crystal structures of **I** and **II** were determined using intensity data collected on a Bruker APEX II X8 diffractometer using Mo K_α radiation at 173 K (Table 1). The data were collected and processed using the Bruker APEX2 software (Bruker 2008) and the structures were solved using SHELXS97 (Sheldrick, 2008) and refined with SHELXL2013 (**I**) and SHELXL97 (**II**) (Sheldrick, 2008) within the program Olex2 (Dolomanov et al., 2009). Hydrogen atoms were treated by a mixture of independent and constrained refinement. **Hydrogens bound to carbon atoms were treated as riding atoms (AFIX 23 or 43), while the hydrogens bound to nitrogen or oxygen were located in the Fourier difference map and refined freely except for H1D which displayed significant shorting of the O-H bonds on refinement and so was treated as a riding atom in the final refinement (AFIX 83).**

X-Ray powder diffraction data **were** collected on a Bruker D8 FOCUS in Bragg-Brentano $\theta-\theta$ geometry with Cu K_α radiation using a zero background silicon holder and a scintillation counter.

3. Results and Discussion

3.1. Crystal Structure of I

Complex **I** has a 2:1 acid/crown ether ratio and packs in a monoclinic crystal with three symmetry unrelated trimers (Figure 3 and Table 2). The components of the asymmetric unit cell are labelled **A** to **I** for identification (**A**, **H**, **I** are the crown ethers, **B**, **C**, **D**, **E**, **F**, **G** the 4-aba molecules). Comparison of the geometries of each complex within the asymmetric cell (Table 3) shows that all conformations differ from the expected range of torsion angles for the D_{3d} geometry commonly observed for such complexes ($\angle_{\text{OCCO}} = 180^\circ$, $\angle_{\text{COCC}} = 70^\circ$) (Watson et al., 1984). The crown ether binds to the two 4-aba molecules through N-H...O hydrogen bonding. In each system five of the six ether oxygens are involved in hydrogen bonding. In the case of crown ether **A** the oxygen free from hydrogen bonding and the neighbouring methyl group are disordered over two possible conformations (68:32% occupancy). There may be further disorder in crown ether **I** where the majority of the residual electron density is located. However, attempts to refine a disordered model were unstable. The flexibility in conformation for the complexes is further demonstrated by the geometry of binding for the 4-aba molecules into the complex, where one 4-aba is pulled closer to the centre of the crown ether ring and features shorter hydrogen bonding than the other in trimers **Ib** and **Ic** (Table 2). The hydrogen bonding occurs from both 4-aba molecules to oxygens on either side of the ring, with a bifurcated bond forming for one 4-aba to use the five acceptor sites.

All three trimers are bound together through $R^2_2(8)$ carboxylic acid dimers to generate a 1-D ribbon motif (Figure 4) with the molecules in the order E-H-D-C-A-G-F-I-B-B-I-F-G-A-C-D-H-E. As with the binding between the acid and the crown ether a range of geometries is observed for this interaction (Table 3). The inversion centre of the crystal structure generates two of these carboxylic acid dimers (4-aba **B** and **E**), while the remaining pairs are created between symmetry unrelated molecules (4-aba **D/C** and **F/G**). In general the distances observed are shorter than those observed in the α -form of 4-aminobenzoic acid (O...O distances: 2.65 and 2.616 Å respectively, $Z' = 2$) suggesting that the complexation of the crown ether causes a stronger hydrogen bond formation to occur. This is supported by the apparent disorder in the hydrogen location in the dimer, especially between complexes **F** and **G** where the proton appears to be centrally located between the oxygen atoms. While the level of residual electron density reduces the accuracy in location of the hydrogen atoms in this system, the similarity in measured C—O distances within the **F/G** carboxylic acid groups supports this interpretation (Table 4). The final crystal structure is assembled through the packing of these 1-D ribbons along the *a*- and *c*-axes through weaker C-H...O and C-H... π interactions forming a herringbone motif.

3.2. Crystal Structure Analysis of II

Complex **II** forms with a 1:1:2 4-aminobenzoic acid/crown ether/3,5-dinitrobenzoic acid composition in a triclinic crystal with a single complex forming the asymmetric cell (Table 1). The crown ether displays a closer match to the expected D_{3d} geometry ($\angle_{\text{COCC}} = 178^\circ, 177^\circ, 173^\circ, 173^\circ, 172^\circ, 177^\circ$; $\angle_{\text{OCCO}} = 59^\circ, -62^\circ, 65^\circ, -65^\circ, 61^\circ, -63^\circ$) than **1**. The molecular geometry of the benzoic acids shows no unusual features. Unlike the binary co-crystal formed between 3,5-dnba and 4-aba (Etter & Frankenbach, 1989; Chadwick et al., 2009), this system forms a salt between the acids through the deprotonation of 3,5-dnba and the protonation of the amino group of 4-aba. **The remaining 3,5-dnba molecule remains protonated and so 3,5-dnba is present in two protonation states in the crystal structure.** The ΔpK_a for these acids is 2.05, which is on the boundary for salt formation by the empirical rules (Childs et al., 2007). **However, the difference in composition does limit the ability to compare the two systems and recent work has demonstrated the importance of local crystal structure on level proton transfer in hydrogen bonded systems and these changes may have a greater contribution than changes in pK_a (Wilson, 2007; Thomas et al., 2010; Jones et al., 2013; Seaton et al., 2013).**

The protonated amino group on the 4-aba molecule binds through $^+\text{NH}\dots\text{O}$ hydrogen bonds strengthened by the symmetrical match between the crown ether and the tetragonal amino group ($\text{N}\dots\text{O}$ distances 2.881, 2.764, 2.827 Å; $\text{H}\dots\text{O}$ distances: 1.85, 1.89, 1.92 Å). **The charged 3,5-dnba bridges the 4-aba/18-crown-6 complex and the neutral 3,5-dnba molecule, through a pair of $\text{OH}\dots\text{O}^-$ hydrogen bonds** (Figure 5). These clusters are bound into a 2-D sheet in the (100) plane through a combination of weaker $\text{C-H}\dots\text{O}$ interactions ($\text{C}_{\text{arom}}\text{-H}\dots\text{O}_{\text{nitro}}$ chains along the c -axis, $\text{C}_{\text{ether}}\text{-H}\dots\text{O}_{\text{nitro}}$ along b -axis, Figure 6). The sheets feature alternating layers of crown ethers and 3,5-dinitrobenzoic acids. These sheets are stacked along the a -axis through $\text{C-H}\dots\pi$ and $\text{C-H}\dots\text{O}$ interactions to form the final 3-D structure.

The solution speciation in this system was determined using the literature values for the pK_a of the carboxylic acid groups in 3,5-dinitrobenzoic acid and 4-aminobenzoic acid in methanol (Rived et al., 1998), while the pK_a of the amino group of 4-aba in methanol was estimated from the literature aqueous value by the methods detailed by Rived *et al.* These plots (Figure 7) indicate that under the conditions of the experiment, very little of either species would be present in an ionised form and so the selective binding by the crown ether promotes the formation of the salt phase observed. However, the presence of any water in the system would readily shift the distribution of these curves, with the pK_a of 3,5-dnba in water being 2.82 compared to 7.38 in methanol (Rived et al., 1998). **As the vials were open to the air during crystallisation variable levels of water may be present, influencing the solution speciation. Understanding the influence of moisture on crystallisation of these systems is a topic for future study.**

3.3. Acid...Carboxylate Bonding Motif

The frequency of the acid to carboxylate motif between different carboxylic acids displayed in complex **2** was investigated through a database search.¹ A total of 1357 structures were identified which featured a close contact between a carboxylic acid and carboxylate group, of these only 134 featured this interaction between different acids (9 %). As these systems must feature both a carboxylic acid and a carboxylate, positively charged species must also be present in all cases for charge balance. This is achieved either by formation of salt where different charges are present on different species or a co-crystal between a neutral acid and zwitterionic species, frequently an amino acid.

Of the 134 systems, the results display an even split between salts (53 %) and co-crystals of zwitterions (45 %) with the remaining 2 % comprising a mixture of the two types. To identify any structural preferences to the salt or co-crystal formation, those acids that were involved in 5 or more systems were studied further (oxalic acid, tartaric acid, 4-hydroxybenzoic acid, mandelic acid, maleic acid, trichloroacetic acid, trifluoroacetic acid, fumaric acid, 2-phenyloxypropionic acid and (18-crown-6)-2, 3, 11, 12-tetracarboxylic acid). As the strength of the acid increases (lower pK_a) the number of salts located increased (Figure 8). For the strong acids with pK_a s less than two (oxalic, maleic, trichloroacetic and trifluoroacetic acid) only salts were obtained. Thus it appears that consideration of pK_a may be a factor in designing such motifs. However, is a selected subset and so consideration of all systems without the desired motif would need to be studied to draw final conclusions.

3.4. Computational Studies

The improved match between the crown ether and the protonated amino group would be expected to drive the selection of the salt form. To confirm this, a computational study into the binding preferences of the 18-crown-6 ring was carried out through the optimisation of the binding energy between a protonated and an unprotonated 4-aminobenzoic acid molecule with 18-crown-6 using the differential evolution global optimisation algorithm (DE) (Storn & Price, 1997; Price et al., 2006). The calculations were performed using locally developed code (mol_dimer). DE is an evolutionary algorithm (EA) and operates on similar principles to genetic algorithms or evolutionary strategies. It works through the evolution of a population of trial solutions to the problem through recombination, mutation and selection. The difference from traditional EAs is that in DE the recombination and mutation processes are combined into a single procedure and a deterministic selection is used. Each member of the population is a real valued vector (P_i) representing a solution to the problem. Initially each member of the population is randomly generated. The size of the population is a user defined

¹ Cambridge Structure Database (CSD, v 5.33 with 4 updates) was searched using Conquest v1.14 for systems with a close contact between the oxygens of a carboxylic acid and a carboxylate group with the negative charge on either oxygen. The search was limited to only organic systems, with no disorder, errors or powder structure determinations included.

variable (N_p). For each member of the population a child solution is generated by the application of equation 1:

$$C_i = P_i + K(P_{r_3} - P_i) + F(P_{r_2} + P_{r_1}) \quad (1)$$

where P_{r_1} , P_{r_2} , P_{r_3} are randomly selected members of the population, K and F are user-defined parameters controlling the level of recombination and mutation respectively. Boundary conditions on each parameter may be introduced at this stage to ensure the values remain meaningful. The better solution out of the child and parent is then retained in the population. This process is then repeated until the population converges onto one solution or a user-defined number of generations (G_{max}) have passed. DE is a general-purpose optimisation method and has been successfully applied to many problems in science and engineering including crystal structure determination from powder diffraction data (Seaton & Tremayne, 2002; Tremayne et al., 2002; Chong & Tremayne, 2006; Chong et al., 2006), optimisation of atomic clusters and hydrocarbon isomers (Ali et al., 2006), modelling e-coli metabolism (Ceric & Kurtanjek, 2006) and the analysis of X-ray absorption fine structure (Dimakis & Bunker, 2006). **This methodology was selected as for this problem since a large number of potential minima would be expected to form in this case and an efficient optimisation algorithm would be required to interrogate such a complicated hypersurface. Given the large number of energy evaluations required, the use of *ab initio* quantum mechanical calculations to evaluate the energy would be prohibitive and so the use of an empirical forcefield was required in this case. While this any limit the accuracy of the absolute energies calculated, the relative trends and structural features would be expected to suitable for analysis.**

For this problem the trial structures were encoded as the position and orientation of the 4-aba molecule relative to the centre of the 18-crown-6 molecule ($x, y, z, \theta, \phi, \gamma$). Boundaries of $-15 \leq x, y, z \leq 15 \text{ \AA}$ and $0 \leq \theta, \phi, \gamma \leq 360^\circ$ on the six parameters were maintained during the runs. The intermolecular binding energy between the molecules was minimised. This was determined using the non-bonding interactions of the force field described by No *et al.* (No et al., 1995) with the electrostatic interaction calculated from single point charges on each atom. The point charges were calculated by fitting to the electrostatic potential calculated at the PBE/def2-TZVP/def2-TZVP/J level (Schaefer et al., 1992; Weigend & Ahlrichs, 2005) using the RJCOSX option in the orca program (Neese, 2012) for each molecule. The original model for each molecule was extracted from the crystal structure of the dimer, optimised using the QuickOpt option and then the single point energy was calculated at the above level. The DE control parameters were $K, F, G_{max}, N_p = 0.1, 0.5, 5000, 60$. The DE calculation was performed ten times for each pair and the same solution located each time.

The optimal solution in each case has the amino group within the crown ether as expected (Figure 9), with the protonated system displaying a significantly stronger binding than the unprotonated amino group ($E_{4abaH^+} = -170.00 \text{ kJ}\cdot\text{mol}^{-1}$, $E_{4aba} = -68.74 \text{ kJ}\cdot\text{mol}^{-1}$). This indicates a strong preference for the

protonated system over the deprotonated. Therefore even a low level of salt within the solution would be preferentially extracted. Optimisation of three component clusters between 4-aba/18c6 and either 4abaH⁺, 4aba or 3,5-dnba offers insight into the competition between hydrogen bonding sites. The translational boundaries were increased to $-25 \leq x, y, z \leq 25$ Å and N_p to 120. In the case of 4aba/4-aba/18c6 the second acid forms the expected acid/acid dimer with a total energy of -152.30 kJ·mol⁻¹. For 4aba/4abaH⁺/18c6, the crown ether selects the protonated acid and an acid/acid dimer is formed between the two 4-aba molecules with a total energy of -264.85 kJ·mol⁻¹ (Figure 10). The difference in energy between the dimer pairs and the trimer clusters gives the binding energy for the acid/acid dimer, which are relatively similar in this case ($E_{4aba/4aba} = -83.60$ kJ·mol⁻¹, $E_{4abaH^+/4aba} = -94.85$ kJ·mol⁻¹).

Optimisation of the 3,5-dnba/4-aba/18-crown-6 trimer proved to be more problematic. Initial runs failed to converge, often suffering from convergence of the majority of the population to a single solution but a small proportion of the population stuck in a different solution with only a slightly higher energy. As the DE generates trial structures based on the difference of randomly selected members of the population, this situation causes a stagnation of the population, as the majority of the differences generated for the higher energy solution are close to zero and so no movement occurs. To overcome this stagnation, optimisation with the recently developed Drift-Bias Free Differential Evolution (DBFDE) algorithm was attempted (Price, 2008). In this case, the generation of trial structures proceeds by equation 2 instead of 1.

$$c_i = x_i + \begin{cases} F \cdot m_{r_1, r_2} & \text{if } \text{Rand}(0,1) \leq P_\mu \\ \sqrt{D} \cdot (m_{r_1, r_2} \cdot e_{r_1, r_2}) \cdot e_{r_1, r_2} & \text{otherwise} \end{cases} \quad (2)$$

where

$$m_{r_1, r_2} = (x_{r_1} - x_{r_2})$$

$$e_{r_1, r_2} = \frac{x_{r_3} + x_{r_4} - 2x_i}{\|x_{r_3} + x_{r_4} - 2x_i\|}$$

F and P_\square are user defined parameters in the range 0 to 1 and D is the number of parameters to be determined. This formulation has been shown to remove bias in the generation and selection of trial positions and ensure that each operation has a unique function during the search (mutation explores the surface, recombination homogenises the population and selection improves the population) (Price, 2008). This methodology has been shown to be effective on complex multi-modal surfaces with a high dimensionality, where the traditional DE can stagnate (Price, 2008).

DBFDE was run using control parameters: P_\square , F , G_{max} , N_p of 0.5, 0.98, 5000, 120 respectively and displayed a more robust searching for the 3,5-dnba/4-aba/18-crown-6 case than the traditional DE. Ten independent runs all successfully converged showing with the 4-aba molecule binding to the crown ether through NH...O hydrogen bonds. The interaction of the 3,5-dnba with this dimer was more varied including OH...O hydrogen bonds and π ... π stacking interactions (Figure 11) giving

interaction energies in the range -148.16 to -161.67 $\text{kJ}\cdot\text{mol}^{-1}$, corresponding to acid/acid interactions of -79.41 to -92.93 $\text{kJ}\cdot\text{mol}^{-1}$ comparable to those obtained in the 4-aba/4-aba case. This suggests that a wider number of binding modes are possible in this case, unlike the previous systems where a single low energy solution was located in all runs. Given the successful convergence of the each run of the DBFDE method compared to the traditional DE, this is likely due to the existence of numerous minima on the hypersurface of similar energy instead of a limitation of the search method. This change in hypersurface morphology a contributing factor for the selectivity as the binding of 4-abaH⁺ or 4-aba to an existing 4-aba/crown ether complex follows a straight-forward route to a single low energy solution, while the 4-aba /3,5-dnba system has a number of competing routes.

4. Conclusions

The creation of ternary multi-component crystals through the binding of a binary co-crystal through additional hydrogen bonding to the crown ether has been demonstrated for 18-crown-6 with the binary pairs of 4-aminobenzoic acid/3,5-dinitrobenzoic acid. The selectivity of the crown ether for the protonated amino group is highlighted by the selection of the salt form of 4-aminobenzoic acid/3,5-dinitrobenzoic acid in favour of the neutral co-crystal that is obtained from solutions lacking the crown ether. This system also displays a carboxylic acid/carboxylate hydrogen bond between differing benzoic acids. This is a relatively rare supramolecular synthon, however variations in crystal type (e.g. salt or co-crystal) appear to be selective depending on the strength of the acid used.

Computational studies support the bonding preference for the protonated 4-aba with the crown ether showing a lower energy of binding and preferential selection when both options are present. Binding of 3,5-dnba to the created 4-aba/crown ether complex is complicated by a number of potential binding modes of similar energy. Thus the creation of novel multicomponent crystal materials with more than two components through selection of specific protonated or deprotonated states by selection of components with selected binding preferences may be a route to the creation of novel new materials.

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Table 1 Experimental details

	I	II
Crystal data		
Chemical formula	$C_{14}H_{14}N_2O_4 \cdot 3(C_{12}H_{24}O_6) \cdot 4(C_7H_7NO_2)$	$C_{12}H_{24}O_6 \cdot C_7H_7NO_2 \cdot C_7H_3N_2O_6 \cdot C_7H_4N_2O_6$
M_r	1615.75	825.69
Crystal system, space group	Monoclinic, $P2_1/n$	Triclinic, $P\bar{1}$
a, b, c (Å)	10.3947 (3), 17.5546 (5), 47.2700 (14)	7.6055 (2), 16.0157 (4), 16.4476 (4)
α, β, γ (°)	90, 91.321 (2), 90	73.156 (2), 85.540 (2), 89.562 (1)
V (Å ³)	8623.3 (4)	1911.45 (8)
Z	4	2
μ (mm ⁻¹)	0.10	0.12
Crystal size (mm)	0.79 × 0.65 × 0.53	0.24 × 0.21 × 0.17
Data collection		
Absorption correction	None	None

No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	132140, 16030, 10452	50498, 10356, 6338
R_{int}	0.045	0.047
$(\sin \theta/\theta)_{\text{max}}$ (\AA^{-1})	0.620	0.703
Refinement		
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.073, 0.199, 1.06	0.047, 0.112, 0.99
No. of reflections	16030	10356
No. of parameters	1114	543
No. of restraints	6	0
$\Delta\rho_{\text{max}}$, $\Delta\rho_{\text{min}}$ (e \AA^{-3})	0.91, -0.37	0.30, -0.27

Table 2 Geometric analysis of acid/crown ether trimers in I.

	Trimer Ia (Crown A, 4-aba C/G)	Trimer Ib (Crown H, 4-aba D/E)	Trimer Ic (Crown I, 4-aba B/F)
COCC torsion angles of 18-crown-6 ring [†] / $^\circ$	170 (139), -174 (-63), - 173, -172, -165, 174	178, 140, 167, 179, 171, 167	-170, -179, -167, -167, 179, -170
OCCO torsion angles of 18-crown-6 ring [†] / $^\circ$	51 (-64), -64.9 (-42), - 63, -59, 76, -67	61, 63, -81, 59, 60, -74	76, -54, -59, 81, -56, - 61
Distance of N to centre of crown ether / \AA	1.74, 1.75	1.63, 1.80	1.63, 1.73
N...O distances/ \AA	N1C/O1A: 2.998(5) N1C/O4A: 3.152(5) N1C/O5A: 3.055(6) N1G/O3A: 3.352(5) N1G/O4A: 3.058(4) N1G/O6A: 3.058(5)	N1D/O4H: 2.960(5) N1D/O6H: 3.148(5) N1E/O1H: 3.069(4) N1E/O2H: 3.124(5) N1E/O5H: 3.404(5)	N1B/O2I: 3.279(5) N1B/O3I: 3.062(5) N1B/O6I: 3.137(5) N1F/O1I: 3.166(5) N1F/O3I: 3.083(5) N1F/4I 3.379(5)
Tilt angle of 4-aba to crown ether/ $^\circ$	144, 157	160, 140	140, 148

[†]Values in parenthesis reflex values for 2nd geometry in disordered system.

Table 3 Geometric analysis of acid/acid interactions in **I**.

System	O...O distance/Å	OH...O distance/Å	OHO angle/°
4-aba D...4-aba C	2.616(4)	1.83(5)	168(6)
4-aba C...4-aba D	2.601(3)	1.61(6)	170(5)
4-aba F...4-aba G	2.601(4)	1.39(7)	171(6)
4-aba G...4-aba F	2.605(4)	1.36(7)	178(6)
4-aba B...4-aba B	2.603(4)	1.55(6)	173(6)
4-aba E...4-aba E	2.620(4)	1.51(7)	170(6)

Table 4 Intramolecular Geometries in Carboxylic Acid Groups of 4-aba in **I**.

System	C=O distance/Å	C-OH distance/Å	O-H distance/Å
4-aba B	1.274(4)	1.281(5)	1.03(6)
4-aba C	1.241(4)	1.308(4)	1.02(5)
4-aba D	1.236(4)	1.317(4)	0.840(2)
4-aba E	1.268(4)	1.284(4)	1.12(7)
4-aba F	1.268(5)	1.280(5)	1.15(7)
4-aba G	1.273(5)	1.273(5)	1.25(7)

Figure 1 Molecular structures for compounds used in this study.

Figure 2 Envisioned intermolecular interactions between species in ternary complex.

Figure 3 Molecular conformations of the three trimers in 4-aba/18-crown-6 complex in an ORTEP style (50 % probability ellipsoids). The atomic labelling is also shown. Trimer **Ia** is formed from 4-aba C, crown ether A, 4-aba G. Trimer **Ib** is formed from 4-aba D, crown H and 4-aba E. Trimer **Ic** is formed by 4-aba F, crown ether I and 4-aba B. Carbon atoms are coloured green, oxygen red, nitrogen blue and hydrogen in grey.

Figure 4 View of the 1-D ribbon motif constructed through acid/acid dimers in crystal structure of **1**. The packing of two chains is displayed. The colour scheme is the same as Figure 3.

Figure 5 Formation of a four-component complex in **2**. The colour scheme is the same as Figure 3.

Figure 6 Formation of a hydrogen bonded chain along the *c*-axis, viewed down the *a*-axis.

Figure 7 Calculated speciation curves for (a) 3,5-dnba (protonated species: red open squares, deprotonated species: blue open diamonds) and (b) 4-aba in methanol (protonated amino group: red open squares, neutral species: blue open diamonds and deprotonated acid: green open circles). Lines between points have been added as a guide to the eye.

Figure 8 Variation in percentage of zwitterionic co-crystals located with the pK_a of the acid used in the co-crystallisation.

Figure 9 Optimised geometries for interactions between 18-crown-6 and (a) protonated and (b) neutral 4-aba.

Figure 10 Comparison of optimised trimers between 18-crown-6, 4-aba and (a) protonated, (b) neutral 4-aba. In the protonated case the third hydrogen of the amino group points into the page.

Figure 11 Structures of the three lowest energy minima on the 3,5-dnba/4-aba/18-crown-6 hypersurface with associated total energy of interaction.