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Synthesis of tris-(azacrown) ethers for carboxylic acid recognition

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The synergistic enhancement of metal ion extraction by azacrown ethers in the presence of carboxylic acids has been attributed to a ligand assembly effect in which these two ligands form a complex, facilitated by proton transfer, prior to complexation of the metal ion. In order to investigate the first steps in this multi-component complexation procedure, six tris-(azacrown) ethers were synthesised in high yields and their ability to complex mono- and tri-carboxylic acids was investigated by ^{1}H NMR in methanol-d_4. All six compounds bound to benzoic acid with 1:3 host–guest stoichiometry and four of them bound tricarboxylic acids with 1:1 host–guest stoichiometry, providing good support for the proposed first step in the ligand assembly effect.

1. Introduction

The ability of crown ethers and azacrown ethers to selectively bind metal ions and (alkyl)ammonium ions has been widely studied.[1–7] Given their unique properties, these compounds are frequently used in the formation of supramolecular and supermolecular structures and a number of molecular hosts containing multiple (aza)crowns have been investigated.[8–18] They have been employed as selective hosts for a wide range of guest molecules and ions and many systems have been investigated as selective extractants/ionophores in solvent extraction and/or bulk membrane transport studies.[19] In this context, it has been found that synergistic enhancement of ion extraction can occur when azacrown ethers are employed in combination with carboxylic acid derivatives.[20] This synergy has been attributed to the assembly of components required to occupy the coordination sphere of the metal, prior to metal binding and termed the 'ligand assembly effect' (Scheme 1).[21–23] The first step in the ligand assembly effect requires binding to occur between the azacrown ether and a carboxylic acid, facilitated by proton transfer between the acid and amino groups, which results in the formation of both hydrogen bonds and electrostatic interactions between the two species.[23] However, only a few investigations of this type of association between carboxylic acids and azacrown ethers have been reported previously and these have focused on single macrocycles.[22,23] In order to investigate this effect, we have designed a number of tris-azacrown derivatives, which are expected to have multiple interactions with appropriate tricarboxylic acids. We report here the synthesis of these compounds and our preliminary investigations into the ability of these compounds to bind to tricarboxylic acid derivatives.

2. Results and discussion

Tripodal molecular receptors have frequently been observed to provide multiple interactions with suitable guests and thus provide stronger host–guest interactions.[24] We therefore designed tripodal tris-azacrown derivatives to investigate the ability of the ligand assembly effect to preorganise these polytopic systems for the transport of multiple metal ions. 1,3,5-Substituted-benzene, -2,4,6-trimethylbenzene and -2,4,6-triethylbenzene derivatives were selected as 'cores' for the synthesis of a series of tripodal receptors to enable an investigation of the effect of steric gearing[25] on the molecular recognition process. It was anticipated that an increase in scaffold preorganisation, as expected for the sterically geared 2,4,6-triethylbenzene derivative[25,26] would lead to improved recognition of an appropriately sized guest molecule.

Reaction of either 1-aza-15-crown-5 (**1**) or 1-aza-18-crown-6 (**2**) with the appropriate tribromide **3**–**5** in the presence of Na_2CO_3 gave the tris-azacrown derivatives **6**–**11** in excellent yields (93–95%) (Scheme 2).[27]

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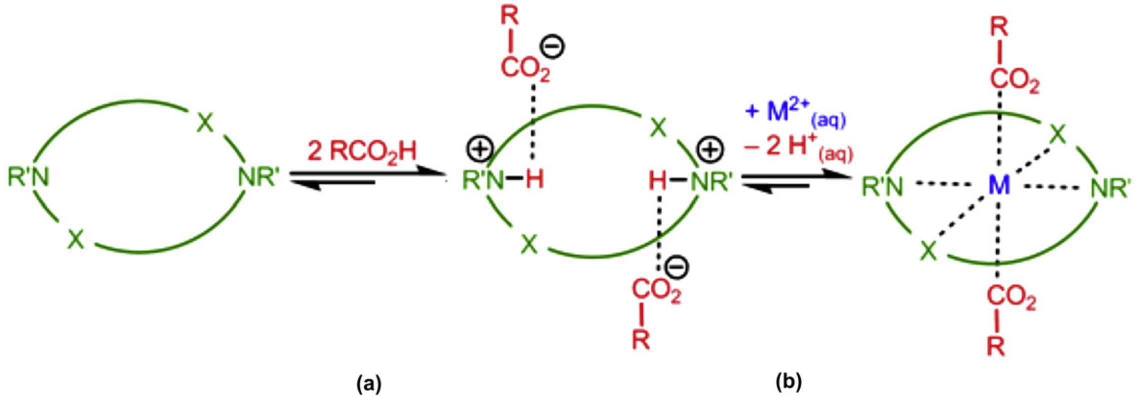
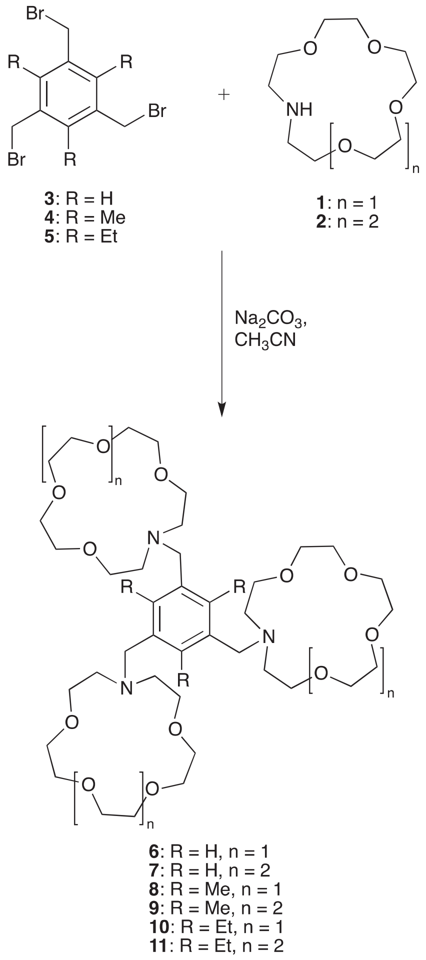


Scheme 1. The ligand assembly effect: (a) formation of a host–guest complex between a macrocycle and an organic acid. (b) Coordination of a metal ion in the host–guest complex, accompanied by the displacement of protons (X=NR′, O or S. R′=alkyl or aromatic group.).



Scheme 2. Synthesis of tris-azacrown ethers **6**–**11**.

To determine whether the tris-azacrown ether derivatives would bind to carboxylic acids, ^{1}H NMR titrations were performed in methanol-d_4 solution with trimesic acid (**12**), citric acid (**13**), Kemp's triacid (**14**), and benzoic acid (**15**). Apparent stability constants were obtained by non-linear curve fitting of the resulting data using WinEQNMR2 computer software (Table 1).[28] In all cases, addition of tricarboxylic acids **12**–**14** to **6**–**11** resulted in downfield shifts of the signals attributable to the protons adjacent to the azacrown nitrogen atoms ($\Delta\delta$=0.5–0.6 ppm in all cases), as would be expected if this nitrogen atom is protonated. Additional downfield shifts of similar magnitude were also observed for the aromatic protons in the case of receptors **6** and **7**. Titration data for compounds **6**–**9** fit well to a 1:1 binding model. The 1:1 stoichiometry was confirmed by Job plots of the complexes with **6** and **7** (Fig. 1). However, data for the 2,4,6-triethylbenzene derivatives **10** and **11** could not be fit to a simple binding model, suggesting the presence of multiple equilibria in solution. It appears that, in this case, steric gearing does not provide improved recognition, but instead the increased steric bulk around the benzene core in **10** and **11** results in the formation of complexes with different stoichiometry to that observed for complexes of **6**–**9** with the same guests. Given the multiple recognition sites present in both the tripodal hosts and tricarboxylic acid guests, it is possible that oligomeric complexes form in these cases. However, it was not possible to determine the exact nature of the species formed. In all cases, the apparent stability constants for complexes between the

Table 1
Apparent stability constants (K_a; M^{-1}) of the tris-azacrown ethers **6**–**11** for tricarboxylic acids **12**–**14** determined by ^{1}H NMR titration in methanol-d_4 at 298 K, following the protons adjacent to the azacrown nitrogen atom. Data fitted to a 1:1 binding model. Errors <15%

	12	**13**	**14**
6	600	330	115
7	120	430	140
8	1010	670	70
9	470	880	190
10	—[a]	—[a]	—[a]
11	—[a]	—[a]	—[a]

[a] Data could not be fit to 1:1, 1:2 or 1:3 host–guest binding models.

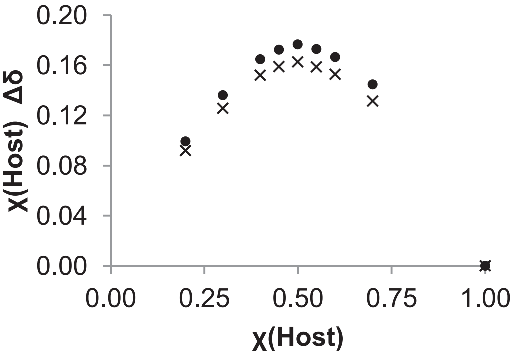


Fig. 1. Job plot for the complex between receptor **7** and trimesic acid **12** showing the observed 1:1 stoichiometry (•=signal for protons adjacent to nitrogen atom; ×=signal for protons on aromatic ring).