Facile Synthesis of Some Novel Dicarboxylic Acid Crown Ethers†

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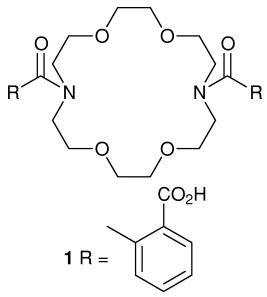
Two procedures for the synthesis of a series of novel dicarboxylic acid functionalised aza-crown ethers from dicarboxylic acid anhydrides and 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane are reported.

Many heavy metals, such as cadmium, lead, mercury and the lanthanides, are currently of great environmental concern due to their toxic effects. Several analytical methods, such as atomic absorption spectroscopy, are available for the detection of these cations. However, the task of their removal from, for example, water supplies or the body following ingestion is somewhat more demanding. Clearly, extraction agents that could remove these metals from a given system would be of considerable value.

Published work has highlighted lariat ethers containing carboxylate functionality within the pendant arms as being selective hosts with high association constants for a great variety of metal cations, including transition metals, lanthanides and actinides.[1–7] Such ionisable crown ethers possess the distinct advantage over neutral crown compounds in that extraction or transport of the metal cations from the aqueous phase does not involve concomitant transfer of the aqueous phase anion.[8]

Recently, our work has focused upon the preparation of dicarboxylic acid functionalised crown ethers as highly selective complexing agents for specific heavy metal cations with a view to constructing solid phase extraction systems based upon those we find to have greatest potential. When developing the design for our receptors we aimed primarily for a procedure that avoided lengthy and time-consuming synthetic procedures and one that may ultimately be translatable to commercial production. Therefore, we sought a methodology involving high yield and a minimum number of steps. Here, we report the synthesis of four novel dicarboxylic acid functionalised crown ethers (Fig. 1). In each case, the synthetic attachment of the pendant arms to the aza-crown ether was accomplished, together with the incorporation of the desired carboxylic acid functionality, and without the need for protecting group strategies and in high yielding, single step reactions.

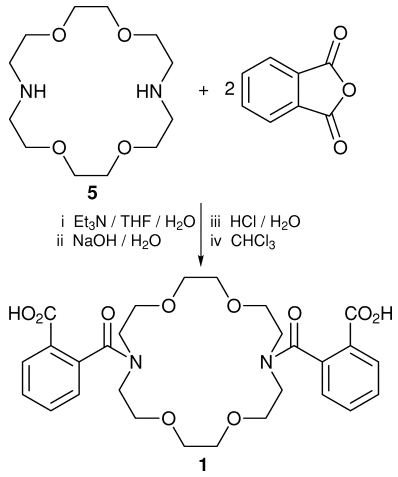


2 R = $[CH_2]_2CO_2H$
3 R = $[CH_2]_3CO_2H$
4 R = $CH_2OCH_2CO_2H$

Fig. 1 Dicarboxylic acid functionalised crown ethers

Our chosen methodology for the synthesis of the novel crown ethers **1**–**4** involved the reaction of 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane **5** with a series of dicarboxylic acid anhydrides.[9,10] Nucleophilic ring opening of an anhydride by the secondary amine of the crown ether brought about pendant arm attachment *via* amide bond formation and the simultaneous liberation of the desired carboxylic acid moiety.

Two sets of reaction conditions were established for the preparation of our target molecules. The first utilised a base-catalysed nucleophilic attack upon the chosen anhydride[11] followed by an extraction and acidification work-up (Method A). For example, crown ether **1** was synthesized by reaction of 2 equivalents of phthalic anhydride with 1 equivalent of aza-crown ether **5** in the presence of a stoichiometric quantity of triethylamine for 1 h at room temperature (Scheme 1).[12] Following extraction with sodium hydroxide solution, reacidification and isolation using chloroform, a spectroscopically pure product was obtained in 77% yield without the need for recrystallisation.



Scheme 1 Base-catalysed preparation of dicarboxylic acid functionalised crown ethers (Method A)

A second, simplified procedure without the need for a catalyst but requiring a much extended reaction time was also developed (Method B). Stirring a mixture of acid anhydride and aza-crown ether in dichloromethane for up to 3 d gave high yields of the desired dicarboxylic acid functionalised crown ethers. For example, the room temperature reaction of 2 equivalents of succinic anhydride with 1 equivalent of aza-crown ether **5** over 3 d gave a spectroscopically pure precipitate of **3** in 93% yield (Scheme 2). Clearly, the utility of this reaction is somewhat dependent upon the product solubility. We found dichloromethane to be by far the best candidate for the reaction solvent, since **5** and our series of anhydrides were easily dissolved and in all cases precipitates of the difunctionalised crown ethers have been isolated in good yields. On occasions, the most

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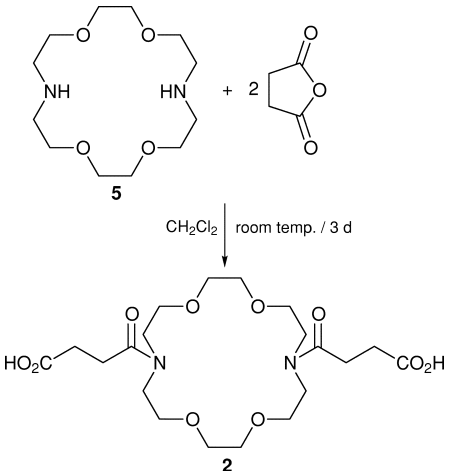

Scheme 2 Uncatalysed preparation of dicarboxylic acid functionalised crown ethers

aliphatic products formed as viscous oils but solidified upon tituration with diethyl ether.

We have shown here two methods for the production of carboxylic acid functionalised aza-crown ethers, one that leads to pure products within 1–2 h, the other allowing the generation of novel species with minimum experimental effort. It is now our aim to study the complexation abilities of the new receptors, both in their anionic and protonated forms, with a range of metal ions and assess their suitability for incorporation within cation selective solid phase extraction systems.

Experimental

Typical Procedure for Method A: Dicarboxylic Acid Crown Ether **1**.—A solution of aza-crown ether **5** (0.52 g, 1.98 mmol) and triethylamine (0.2 g) in water (2 mL) was added dropwise to a solution of phthalic anhydride (0.60 g, 4.05 mmol) in THF (6 mL). During stirring at room temperature for 1 h a further portion of triethylamine (0.2 g) was added. The aqueous phase was separated and the organic phase extracted with 30% NaOH solution (5 mL). The combined aqueous layers were washed with diethyl ether (3×10 mL) and acidified with concentrated HCl to pH 2. The oily residue was extracted with $CHCl_3$ (3×15 mL), dried ($MgSO_4$), filtered and the volume reduced to *ca.* 10 mL. On stirring overnight a fine white precipitate formed that was collected by filtration and dried to give spectroscopically pure **1**.

Typical Procedure for Method B: Dicarboxylic Acid Crown Ether **2**.—Succinic anhydride (0.42 g, 4.20 mmol) and aza-crown ether **5** (0.50 g, 1.91 mmol) were dissolved in CH_2Cl_2 (10 mL) and stirred at room temperature for 3 d. During this time a white precipitate formed which was collected by filtration, washed with cold CH_2Cl_2 and dried to give spectroscopically pure **2**.

Compound **1**.—Yield 77% (method A), mp 121–123 °C. MS: $C_{28}H_{34}N_2O_{10}$ requires *m/z* 558; Found $[M + H]^+$ *m/z* 559, $[M + Na]^+$ 581 (FAB). ^{1}H NMR (270 MHz, d_6-DMSO); δ 13.22 (2 H, br s, CO_2H), 7.93 (2 H, d, $J = 6.7$, Ar-H), 7.62 (2 H, t, $J = 7.3$, Ar-H), 7.50 (2 H, t, $J = 7.3$, Ar-H), 7.29 (2H, d, $J = 6.7$ Hz, Ar-H), 3.78–3.09 (24 H, m, OCH_2 and NCH_2). ^{13}C NMR (67.5 MHz, d_6-DMSO); δ 170.2, 166.8 (C=O), 138.8, 132.4, 130.1, 128.6, 128.0, 126.9 (Ar-C), 69.9, 69.7, 68.9, 68.2 (OCH_2), 48.6, 44.9 (NCH_2).

Compound **2**.—Yield 93% (method B), mp 131–133 °C. MS: $C_{20}H_{34}N_2O_{10}$ requires *m/z* 462; Found $[M + H]^+$ *m/z* 463, $[M + Na]^+$ 485 (FAB). ^{1}H NMR (270 MHz, d_6-DMSO); δ 13.58 (2 H, br s, CO_2H), 3.57–3.34 (24 H, m, OCH_2 and NCH_2), 2.50–2.40 (4 H, br d, CH_2CH_2), 2.39–2.28 (4 H, br d, CH_2CH_2). ^{13}C NMR (67.5 MHz, d_6-DMSO): δ 174.0, 171.1 (C=O), 70.0, 69.9, 69.4, 48.9 (OCH_2), 48.0, 46.5 (NCH_2), 29.1, 27.5 (CH_2CH_2).

Compound **3**.—Yield 88% (method B), mp 80–82 °C. MS: $C_{22}H_{38}N_2O_{10}$ requires *m/z* 490; Found $[M + H]^+$ *m/z* 491, $[M + Na]^+$ 513 (FAB). ^{1}H NMR (270 MHz, d_6-DMSO); δ 13.30 (2 H, br s, CO_2H), 3.65–3.41 (24 H, m, OCH_2 and NCH_2), 2.32 (4 H, t, $J = 4.5$, CH_2C=O), 2.21 (4 H, t, $J = 4.5$ Hz, CH_2C=O), 1.79–1.61 (4 H, m, $CH_2CH_2CH_2$). ^{13}C NMR (67.5 MHz, d_6-DMSO): δ 174.4, 171.7 (C=O), 70.0, 69.4, 68.9 (OCH_2), 48.0, 46.3 (NCH_2), 33.0, 31.3 (CH_2C=O), 20.3 ($CH_2CH_2CH_2$).

Compound **4**.—Yield 86% (method B), mp 129–131 °C. MS: $C_{20}H_{34}N_2O_{12}$ requires *m/z* 494; Found $[M + H]^+$ *m/z* 493, $[M + Na]^+$ 517 (FAB). ^{1}H NMR (270 MHz, d_6-DMSO): δ 13.65 (2 H, br s, CO_2H), 4.26 4 H, s, CH_2CO_2H), 4.08 (4 H, s, CH_2CON), 3.62–3.42 (24 H, m, OCH_2 and NCH_2). ^{13}C NMR (67.5 MHz, d_6-DMSO): δ 171.3, 168.9 (C=O), 69.9, 69.4, 68.8, 68.5, 67.7 (OCH_2), 47.3, 46.5 (NCH_2).

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