Synthesis of crown ethers based on a spiro acetal framework

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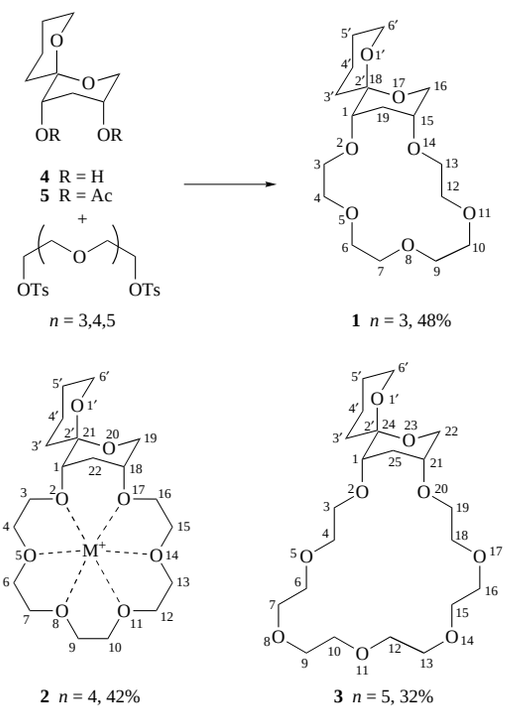
A novel class of crown ether derivatives incorporating a 1,7-dioxaspiro[5.5]undecane ring system have been prepared *via* alkylation of 3,5-diaxial diol 4 with polyethylene glycol ditosylates [di(toluene-*p*-sulfonates)]. The complexing properties of these crown ethers with alkali metal cations and ammonium ion have been evaluated using Cram's picrate extraction method. Crown ethers 1, 2 show a higher affinity for potassium ion than 18-crown-6 exhibits.

The synthesis of crown ethers has had a significant impact on the study of host–guest interactions and separation science.[1–5] A major impetus in this area stems from the chemist's ability to modify the useful features of crown ethers by altering various structural parameters. Thus the cation-binding ability and selectivity of a given crown ether can be related to the cavity size, electron density, softness, spatial arrangement and presence of any additional binding sites in the molecule. Modification of the shape and cavity of crown ethers has been achieved by incorporation of a crown ether into a variety of scaffolds including carbohydrates[6–9] and cage structures.[10] Despite the presence of spiro acetals in a range of naturally occuring ionophores and the many methods available to synthesise them[11–13] it is somewhat surprising that spiro acetal based crown ethers have not been synthesised. We therefore report herein the synthesis and binding constants for the first series of crown ethers **1**–**3** in which the crown ether functionality is incorporated onto a spiro acetal ring system.

In designing our spiro acetal based crown ethers we were conscious of the fact that crown ether synthesis is facilitated by preorganisation and the use of template assisted synthesis. With these factors in mind we were attracted to the use of diaxial 3,5-diol **4** as the spiro acetal framework for incorporation into a crown ether (Scheme 1). Diol **4** has been previously synthesised by our research group *via* base induced ring opening of an epoxy spiro acetal.[14] The X-ray structure[15] of the derived diacetate **5** established that the two tetrahydropyran rings adopt chair conformations with the oxygen atoms of the tetrahydrofuran rings adopting positions axial with respect to the C–O bond of the adjacent ring thereby gaining maximum stability from the anomeric effect.[16] The 1,3-diaxial orientation of the acetate groups in **5** and hence the hydroxy groups in diol **4** therefore offered the potential to prepare crown ether derivatives of diol **4** due to the well-defined position of the hydroxy groups for further functionalisation.

Several methods for the synthesis of crown ethers were evaluated including those by Ouchi *et al.*[17] and Casnati *et al.*,[18] however, the best method was found to be that described by Gokel.[1] Treatment of 3,5-diaxial diol **4** with potassium hydride (2.5 equiv.) followed by the slow addition of a solution of tetraethylene glycol di(toluene-*p*-sulfonate) [di(tosylate)], pentaethylene glycol ditosylate or hexaethylene glycol ditosylate (1.1 equiv.)† in tetrahydrofuran afforded crown ethers **1**–**3** in 48, 42 and 32% yield respectively after heating for 24 h under reflux followed by purification by flash chromatography (Scheme 1). The crown ether was established to adopt axial positions on the



Scheme 1 *Reagents and conditions*: KH (2.5 equiv.), THF, N_2 atmosphere, reflux, 0.5 h then ditosylate (1.1 equiv.) in THF over 3 h, reflux 24 h

spiro acetal ring from the resonances assigned to the CHO protons in the ^{1}H NMR spectra. Thus, for crown ether **1**, 1-H resonated as a triplet at δ_H 3.10, $J_{1,19}$ 4.1 Hz, establishing that 1-H adopts a pseudoequatorial position. 15-H Resonated as a double double double doublet at δ_H 3.40, $J_{16eq,16ax}$ 3.0, $J_{15eq,16eq}$ 3.0, $J_{15eq,19ax}$ 3.0 and $J_{15eq,19eq}$ 3.0 Hz, establishing that 15-H also resided in a pseudoequatorial orientation.

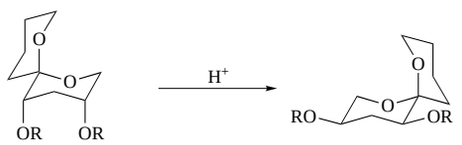
In the ^{1}H NMR spectrum for crown ether **2**, 1-H resonated as a triplet at δ_H 3.06, $J_{1,22}$ 4.0 Hz, establishing that 1-H adopts a pseudoequatorial position. 22ax-H Resonated as a double double doublet at δ_H 1.96, J_{gem} 13.6, $J_{22ax,1}$ 4.0 and $J_{22ax,18}$ 4.0 Hz, establishing that 18-H also adopted a pseudoequatorial position. This latter assignment was further confirmed by the double double double doublet at δ_H 3.39, $J_{18eq,22ax}$ 4.0, $J_{18eq,22eq}$ 4.0, $J_{18eq,19ax}$ 4.0 and $J_{18eq,19eq}$ 4.0 Hz, assigned to 18-H which established that 18-H also resided in a pseudoequatorial orientation.

In the ^{1}H NMR spectrum for crown ether **3**, 1-H resonated as a triplet at δ_H 3.09, $J_{1,25}$ 3.9 Hz, establishing that 1-H adopts a pseudoequatorial position whilst 25ax-H resonated as a double double doublet at δ_H 1.93, J_{gem} 14.6, $J_{25ax,1}$ 3.9 and $J_{25ax,21}$ 3.9

† The IUPAC nomenclature system for compounds of this type has not been used for the sake of clarity. For example the IUPAC name for pentaethylene glycol ditosylate is 3,6,9,12-tetraoxatetradecane-1,14-diyl di(toluene-*p*-sulfonate).

Hz, establishing that 21-H also adopted a pseudoequatorial orientation. 25eq-H Resonated as a multiplet together with 3′eq-H at δ_H 2.08–2.15 obscuring the coupling constants for this proton, however, 21-H resonated as a double double double doublet at δ_H 3.39, $J_{21eq,25ax}$ 3.9, $J_{21eq,25eq}$ 3.9, $J_{21eq,22ax}$ 3.9 and $J_{21eq,22eq}$ 3.9 Hz, providing further evidence that 21-H adopted a pseudoequatorial position.

Spiro acetals **1**–**4** which bear alkoxy substituents in a 1,3-diaxial arrangement can undergo acid catalysed ring opening followed by reclosure of the ring with the substituents adopting more favourable equatorial positions (Scheme 2). Crown ethers

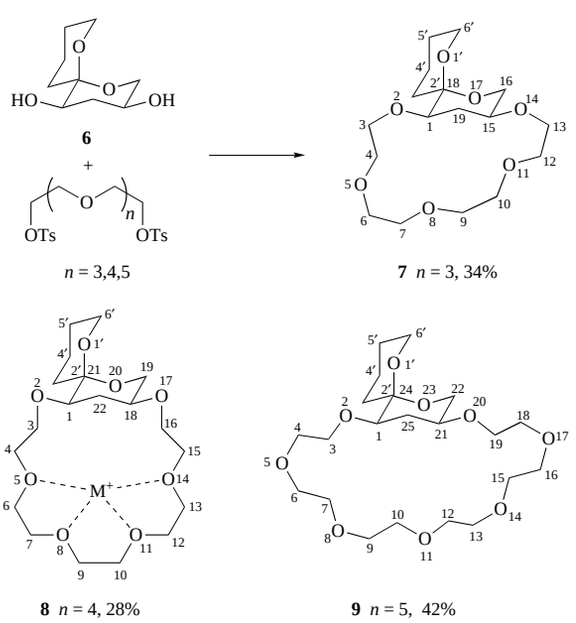


1–4 R = H or $-CH_2CH_2OCH_2(CH_2OCH_2)_nCH_2$ (n = 2,3,4)

6–9

Scheme 2

1–**3** may therefore show variable binding ability towards cations depending upon the pH of the environment. Having synthesised the axial crown ethers **1**–**3**, our attention next focused on the synthesis of the equatorial crown ethers **7**–**9** (Scheme 3).



Scheme 3 *Reagents and conditions*: KH (2.5 equiv.), THF, N_2 atmosphere, reflux, 0.5 h then ditosylate (1.1 equiv.) in THF over 3 h, reflux 24 h

Having successfully prepared crown ethers **1**–**3** where the alkoxy substituents adopt pseudoaxial orientations, the preparation of crown ethers **7**–**9** where the alkoxy substituents adopt pseudoequatorial positions was undertaken. It was envisaged that crown ethers **7**–**9** could be synthesised from 3,5-diequatorial diol **6** in an analogous manner to crown ethers **1**–**3**. Diol **6** was prepared by treatment of a solution of diaxial 3,5-diol **4** in dichloromethane with camphorsulfonic acid (0.5 equiv.) at room temperature, affording diaxial 3,5-diol **4** and diequatorial 3,5-diol **6** in 23 and 66% yield respectively, after purification by flash chromatography.

In the ^{1}H NMR spectrum recorded for diol **6**, 5-H resonated at δ_H 3.53–3.80 together with signals for 2eq-H and 8-CH_2, thereby precluding direct assignment of the orientation for 5-H. The stereochemistry at C-5 was subsequently confirmed upon conversion of **6** to the crown ether derivatives **7**–**9** (*vide infra*). 3-H Resonated as a multiplet at δ_H 4.08–4.18, however, the stereochemistry for 3-H could be assigned from the clean coupling constants obtained for 2ax-H. 2ax-H resonated as a double doublet at δ_H 3.27, J_{gem} 10.1 and $J_{2ax,3ax}$ 10.1 Hz, establishing that 3-H adopted an axial position. The ^{13}C NMR spectrum exhibited resonances at δ_C 65.2 and 70.8 assigned to C-3 and C-5 respectively with a characteristic quaternary resonance at δ_C 96.3 confirming that the spiro acetal ring was intact.

Conversion of diol **6** to the equatorial crown ethers **7**–**9** proceeded in a similar fashion to the axial crown ethers (Scheme 3). Treatment of a solution of diequatorial 3,5-diol **6** in dry tetrahydrofuran with potassium hydride (2.5 equiv.) followed by the slow addition of a solution of tetraethylene glycol ditosylate (1.1 equiv.) in dry tetrahydrofuran afforded crown ether **7** in 34% yield after heating for 24 h under reflux followed by purification by flash chromatography.

In the ^{1}H NMR spectrum recorded for crown ether **7**, 1-H resonated as a double doublet at δ_H 3.30, $J_{1,19ax}$ 12.0 and $J_{1,19eq}$ 4.6 Hz, establishing that 1-H adopts a pseudoaxial position. 19-H Resonated as a multiplet together with 3′eq-H at δ_H 2.09–2.20 and 15-H resonated as a multiplet at δ_H 3.50–3.72 together with 6′-CH_2, 16eq-H and 8 × CH_2O precluding direct assignment of the stereochemistry for 15-H. The stereochemistry for 15-H, however, could be assigned from the clean coupling constants obtained for 16ax-H. 16ax-H Resonated as a double doublet at δ_H 3.73, J_{gem} 10.1 and $J_{16ax,15ax}$ 10.1 Hz, thereby establishing that 15-H adopts an axial position. Resonances at δ_C 68.5 and 70.5 were assigned to C-15 and C-1 respectively and a quaternary resonance at δ_C 96.3 characteristic of a spiro acetal carbon was assigned to C-18.

With crown ether **7** in hand, attention shifted to the synthesis of the larger 19-crown-6 spiro acetal analogue **8**. Thus, treatment of a solution of diequatorial 3,5-diol **6** in dry tetrahydrofuran with potassium hydride (2.5 equiv.) followed by the slow addition of a solution of pentaethylene glycol ditosylate (1.1 equiv.) in dry tetrahydrofuran afforded crown ether **8** in 28% yield after heating for 24 h under reflux followed by purification by flash chromatography. In the ^{1}H NMR spectrum recorded for crown ether **8**, 1-H resonated as a double doublet at δ_H 3.14, $J_{1,22ax}$ 11.6 and $J_{1,22eq}$ 3.2 Hz, establishing that 1-H adopts a pseudoaxial position. 18-H Resonated as a multiplet at δ_H 3.53–3.78 together with 6′-CH_2, 19eq-H and 8 × CH_2O thereby precluding direct assignment of stereochemistry for 18-H. The stereochemistry for 18-H, however, was assigned from the clean coupling constants obtained for 19ax-H. Thus, 19ax-H resonated as a double doublet at δ_H 3.28, J_{gem} 10.3 and $J_{19ax,18ax}$ 10.3 Hz, establishing that 18-H adopted an axial position.

With crown ether **8** in hand, attention focused on the synthesis of the remaining crown ether **9**. Thus, treatment of a solution of diequatorial 3,5-diol **6** in dry tetrahydrofuran with potassium hydride (2.5 equiv.) followed by the slow addition of a solution of hexaethylene glycol ditosylate (1.1 equiv.) in dry tetrahydrofuran afforded crown ether **9** in 42% yield after heating for 24 h under reflux followed by purification by flash chromatography. In the ^{1}H NMR spectrum recorded for crown ether **9**, 1-H resonated as a double doublet at δ_H 3.11, $J_{1,25ax}$ 11.8 and $J_{1,25eq}$ 3.6 Hz, establishing that 1-H adopted a pseudoaxial orientation. The stereochemistry for 21-H was assigned from the clean coupling constants obtained for 22ax-H. Thus, 22ax-H resonated as a double doublet at δ_H 3.28, J_{gem} 10.2 and $J_{22ax,21ax}$ 10.2 Hz, clearly establishing that 21-H was in an axial position.

Having successfully synthesised crown ethers **1**–**3** and **7**–**9** attention then focused on their binding affinity for various metal ions and the ammonium ion using lithium, sodium, potassium, caesium and ammonium picrate salts. The relative extraction efficiencies of crown ethers **1**–**3** and **7**–**9** toward alkali metal picrates were compared to 18-crown-6 at the same concentration using the method described by Cram and co-workers.[19–21] The association constants (K_a) and binding free

Table 1 Association constants (K_a) and binding free energies ($-\Delta G°$) of complexes of hosts with alkali and ammonium picrates in $CHCl_3$ at 22 °C

Host	Cation	$K_a/10^{-3}$ M^{-1}	$\Delta G°$/kJ mol^{-1}
1	Li^+	155.81	−29.33
	Na^+	23 314.18	−41.61
	K^+	19 660.60	−41.19
	NH_4^+	1 632.73	−35.09
	Cs^+	683.21	−32.95
2	Li^+	130.10	−28.88
	Na^+	7 063.31	−38.68
	K^+	16 343.40	−40.74
	NH_4^+	9 453.28	−39.39
	Cs^+	553.68	−32.43
3	Li^+	108.91	−28.45
	Na^+	371.22	−31.46
	K^+	1 596.62	−35.03
	NH_4^+	1 715.78	−35.21
	Cs^+	2 382.14	−36.01
18-crown-6	Li^+	26.32	−24.96
	Na^+	426.65	−31.79
	K^+	6 813.39	−38.59
	NH_4^+	373.01	−31.47
	Cs^+	4 288.32	−37.45
7	Li^+	2.31	−18.99
	Na^+	5.05	−20.91
	K^+	27.81	−25.09
	NH_4^+	3.17	−26.27
	Cs^+	44.81	−19.78
8	Li^+	1.15	−17.29
	Na^+	4.41	−20.58
	K^+	83.58	−27.79
	NH_4^+	4.54	−26.37
	Cs^+	46.73	−20.66
9	Li^+	3.08	−19.70
	Na^+	10.19	−22.64
	K^+	91.94	−28.03
	NH_4^+	17.52	−25.15
	Cs^+	28.42	−23.97

energies ($\Delta G°$) for crown ethers **1**–**3**, **7**–**9** and 18-crown-6 as a standard are summarised in Table 1. Association constants were determined using the ultraviolet spectroscopic method developed by Cram.[19–21]

A comparison of the association constants for the axial crown ethers **1**–**3** and the equatorial crown ethers **7**–**9** show that the axial crown ethers **1**–**3** exhibit over 1000 fold superior complexing ability to the alkali metal cations sodium and potassium compared to the equatorial crown ethers **7**–**9**. Crown ether **1** exhibits a strong binding affinity for the sodium cation, however, **1** shows only moderate selectivity for the sodium ion over the potassium ion. Crown ether **2** exhibits moderate selectivity for the potassium ion over the sodium ion. Surprisingly both **1** and **2** exhibit a higher binding affinity for the potassium ion than does 18-crown-6. The equatorial crown ethers **7**–**9** all show selectivity for the potassium ion.

Crown ethers **1**–**3** show selectivity for Na^+, K^+ and Cs^+ respectively, as expected due to the corresponding increase in cavity size of the crown ether. This is in accordance with the size match hypothesis expounded by Hancock.[22] Crown ether **2** is more selective for K^+ over Cs^+ ions than both crown ether **3** or 18-crown-6 with a difference of 8.31 kJ mol^{-1} in binding free energy compared to 0.98 and 1.14 kJ mol^{-1} for **3** and 18-crown-6 respectively. This may reflect unfavourable interactions between the larger Cs^+ ion and the spiro acetal ring.

The large difference in binding between the axial crown ethers **1**–**3** and the equatorial crown ethers **7**–**9** may be attributed to the loss of binding interactions between the two oxygen atoms directly attached to the spiro acetal ring since the lone pairs on these atoms are now directed away from the metal ion. All of the equatorial crown ethers **7**–**9** display selectivity for the K^+ ions which may well be accounted for by their similar cavity size.

With such a large difference in the complexing ability between the axial crown ethers and the equatorial crown ethers it is suggested that the axial spiro acetal crown ethers may function as pH dependent ionophores thereby having the ability to complex cations and transport them across a phase boundary. Subsequent treatment with acid could possibly equilibrate the axial crown ethers to their respective equatorial counterparts thereby lowering their complexing ability and releasing the metal cation. This theory however, requires measurement of the association constants for crown ethers **1**–**3** at different pH, which is an avenue for further investigation.

Experimental

Mps were determined on a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 200 (200.13 MHz), Bruker AM 200 (200.13 MHz), Bruker AMX 400 (400.13 MHz), Bruker DRX 400 (400.12 MHz) or a Bruker AMX 600 (600.13 MHz) spectrometer at ambient temperature. All J values are given in Hz. ^{13}C NMR spectra were recorded on a Bruker AC 200 (50.3 MHz), Bruker AM 400 (100.6 MHz), Bruker AMX 400 (100.4 MHz), Bruker DRX 400 (100.51 MHz) or a Bruker AMX 600 (150.7 MHz) spectrometer at ambient temperature with complete proton decoupling. Data are expressed in parts per million downfield from tetramethylsilane as an internal standard and reported as position (δ_C), multiplicity (aided by DEPT 135 and DEPT 90 experiments) and assignment (aided by COSY and HETCOR experiments). Low resolution mass spectra were recorded on a VG70-250S, a VG70-SD or an AEI model MS902 double focusing magnetic sector mass spectrometer operating with an ionisation potential of 70 eV (EI, DEI, CI and DCI). High resolution mass spectra were recorded at nominal resolution of 5000 or 10 000 as appropriate. Major fragments are given as percentages relative to the base peak and assigned where possible. Ionisation methods employed were (i) electron impact (EI), (ii) desorption electron impact (DEI), (iii) chemical ionisation with ammonia as reagent gas (CI) and (iv) desorption chemical ionisation (DCI) with ammonia as reagent gas. Low resolution chemical ionisation mass spectra were also recorded on a Hewlett Packard 5989A mass spectrometer using ammonia as reagent gas with the sample dissolved in methanol. Flash chromatography was performed using Merck Kieselgel 60 or Riedel-de Haen Kieselgel (both 230–400 mesh) with the indicated solvents. Thin layer chromatography (TLC) was performed using 0.2 mm thick precoated silica gel plates (Merck Kieselgel 60 F_{254} or Riedel-de Haen Kieselgel S F_{254}). Compounds were visualised by ultraviolet fluorescence or by staining with iodine or vanillin in methanolic sulfuric acid. Spiro acetal **4** was prepared as reported previously.[14]

Pentaethylene glycol ditosylate †

Pentaethylene glycol ditosylate was prepared from pentaethylene glycol (10 g, 41.9 mmol) and sodium hydroxide (6.0 g, 147 mmol) in tetrahydrofuran (25 ml)–water (25 ml) and toluene-*p*-sulfonyl chloride (18.0 g, 92 mmol) in tetrahydrofuran (38 ml) using the procedure described by Ouchi *et al.*[17] as a colourless viscous oil (19.5 g, 85%). The ^{1}H NMR spectrum was in agreement with the published data.[17]

Hexaethylene glycol ditosylate

Hexaethylene glycol ditosylate was prepared from hexaethylene glycol (10 g, 35.4 mmol) and sodium hydroxide (5 g, 125 mmol) in tetrahydrofuran (25 ml)–water (25 ml) and toluene-*p*-sulfonyl chloride (14.8 g, 78 mmol) in tetrahydrofuran (38 ml) using the procedure described by Ouchi *et al.*[17] as a colourless viscous oil (16.5 g, 80%).

(1*S**,15*R**,18*S**)-Spiro[2,5,8,11,14,17-hexaoxabicyclo[13.3.1]-nonadecane-18,2′-tetrahydropyran] 1

To a solution of (3*R**,5*S**,6*S**)-1,7-dioxaspiro[5.5]undecane-

3,5-diol **4** (214 mg, 1.1 mmol) in dry tetrahydrofuran (100 ml) under a nitrogen atmosphere was added potassium hydride (105 mg, 2.6 mmol) and the resulting solution heated under reflux for 0.5 h. A solution of tetraethylene glycol di(toluene-*p*-sulfonate) (670 mg, 1.3 mmol) in dry tetrahydrofuran (50 ml) was added dropwise over 3 h, and the reaction mixture heated under reflux for a further 24 h. After this time a brown precipitate had formed. After filtration through a short Celite pad, the solvent was removed at reduced pressure to give a tan oil, which was purified by flash chromatography using methanol–dichloromethane (5:95) as eluent to afford the title compound **1** (182 mg, 48%) as a colourless oil [Found (DEI): M^+, 346.198 50. $C_{17}H_{30}O_7$ requires M^+, 346.199 15]; ν_{max}(film)/cm^{-1} 2930, 2860 (s, C-H) and 1120, 1041, 1003 (s, C-O); δ_H(600 MHz, $CDCl_3$) 1.40 (1 H, ddd, $J_{3'ax,3'eq}$ 13.4, $J_{3'ax,3'ax}$ 13.4 and $J_{3'ax,4'eq}$ 4.1, 3′ax-H), 1.46–1.57 (4 H, m, 4′-CH_2 and 5′-CH_2), 2.07–2.14 (3 H, m, 19-CH_2 and 3′eq-H), 3.10 (1 H, t, $J_{1,19}$ 4.1, 1-H), 3.40 (1 H, dddd, $J_{16eq,16ax}$ 3.0, $J_{15eq,16eq}$ 3.0, $J_{15eq,19ax}$ 3.0 and $J_{15eq,19eq}$ 3.0, 15-H) and 3.57–3.81 (20 H, m, 16-CH_2, 6′-CH_2 and 8 × CH_2O); δ_C(100 MHz, $CDCl_3$) 17.9, 25.2, 27.1, 29.2 (CH_2, C-19, C-3′, C-4′ and C-5′), 60.9, 62.4 (CH_2, C-16 and C-6′), 68.5, 70.1 (CH, C-15 and C-1), 70.2, 70.7, 72.1, 77.6 (CH_2, OCH_2) and 96.9 (quat, C-18); *m*/*z* (CI, NH_3) 347 (M^+H, 25%), 219 (14), 195 (75), 153 (100).

(1*S**,18*R**,21*S**)-Spiro[2,5,8,11,14,17,20-heptaoxabicyclo-[16.3.1]docosane-21,2′-tetrahydropyran] 2

The title compound **2** was prepared from diol **4** (200 mg, 1.1 mmol), potassium hydride (104 mg, 2.6 mmol) and pentaethylene glycol ditosylate (714 mg, 1.3 mmol) using a similar procedure to that described above for crown ether **1**. The crude product, a tan oil, was purified by flash chromatography using methanol–dichloromethane (5:95) as eluent to afford the title compound **2** (180 mg, 42%) as a colourless oil [Found (EI): M^+, 390.2295. $C_{19}H_{34}O_8$ requires M^+, 390.2253]; ν_{max}(film)/cm^{-1} 2933, 2840 (s, C-H) and 1116, 1039, 1007 (s, C-O); δ_H(600 MHz, $CDCl_3$) 1.30 (1 H, ddd, $J_{3'ax,3'eq}$ 13.3, $J_{3'ax,4'ax}$ 13.3 and $J_{3'ax,4'eq}$ 4.1, 3′ax-H), 1.44–1.55 (4 H, m, 5′-CH_2 and 4′-CH_2), 1.96 (1 H, ddd, $J_{22ax,22eq}$ 13.6, $J_{22ax,1}$ 4.0 and $J_{22ax,18}$ 4.0, 22ax-H), 2.04–2.20 (2 H, m, 3′eq-H and 22eq-H), 3.06 (1 H, t, $J_{1,22}$ 4.0, 1-H), 3.39 (1 H, dddd, $J_{18eq,22ax}$ 4.0, $J_{18eq,22eq}$ 4.0, $J_{18eq,19ax}$ 4.0 and $J_{18eq,19eq}$ 4.0, 18-H) and 3.51–3.75 (24 H, m, 19-CH_2, 6′-CH_2 and 10 × CH_2O); δ_C(150 MHz, $CDCl_3$) 17.9, 25.1, 26.3, 29.4 (CH_2, C-22, C-5′, C-4′ and C-3′), 60.9, 62.4 (CH_2, C-19 and C-6′), 68.2, 69.9 (CH, C-18 and C-1), 70.6, 71.7, 72.1, 77.6 (CH_2, CH_2O) and 96.7 (quat, C-21); *m*/*z* (CI, NH_3) 391 (M^+H, 100%), 263 (8), 239 (80) and 153 (60).

(1*S**,21*R**,24*S**)-Spiro[2,5,8,11,14,17,20,23-octaoxabicyclo-[19.3.1]pentacosane-24,2′-tetrahydropyran] 3

The title compound **3** was prepared from diol **4** (219 mg, 1.2 mmol), potassium hydride (110 mg, 2.7 mmol) and hexaethylene glycol ditosylate (823 mg, 1.4 mmol) using a similar procedure to that described above for crown ether **1**. The crude product, a tan oil, was purified by flash chromatography using methanol–dichloromethane (5:95) as eluent to afford the title compound **3** (141 mg, 32%) as a colourless oil [Found (DEI): M^+, 434.251 28. $C_{21}H_{38}O_9$ requires M^+, 434.251 58]; ν_{max}(film)/cm^{-1} 2938, 2900 (s, C-H) and 1123, 1040, 1010 (s, C-O); δ_H(600 MHz, $CDCl_3$) 1.32 (1 H, ddd, $J_{3'ax,3'eq}$ 13.2, $J_{3'ax,4'ax}$ 13.2 and $J_{3'ax,4'eq}$ 4.1, 3′ax-H), 1.47–1.57 (4 H, m, 4′-CH_2 and 5′-CH_2), 1.93 (1 H, ddd, $J_{25ax,25eq}$ 14.6, $J_{25ax,1}$ 3.9 and $J_{25ax,21}$ 3.9, 25ax-H), 2.08–2.15 (2 H, m, 3′eq-H and 25eq-H), 3.09 (1 H, t, $J_{1,25}$ 3.9, 1-H), 3.39 (1 H, dddd, $J_{21eq,25ax}$ 3.9, $J_{21eq,25eq}$ 3.9, $J_{21eq,22ax}$ 3.9 and $J_{21eq,22eq}$ 3.9, 21-H) and 3.57–3.77 (28 H, m, 22-CH_2, 6′-CH_2 and 12 × CH_2O); δ_C(150 MHz, $CDCl_3$) 17.9, 25.2, 26.3, 29.6 (CH_2, C-25, C-3′, C-4′ and C-5′), 60.9, 62.4 (CH_2, C-22 and C-6′), 68.4, 69.9 (CH, C-22 and C-1), 70.7, 71.7, 72.1, 77.6 (CH_2, CH_2O) and 96.8 (quat, C-24); *m*/*z* (CI, NH_3) 435 (M^+H, 100%), 283 (100) and 153 (50).

Equilibration of (3*S**,5*R**,6*S**)-1,7-dioxaspiro[5.5]undecane-3,5-diol 4

To a solution of (3*R**,5*S**,6*S**)-1,7-dioxaspiro[5.5]undecane-3,5-diol **4** (520 mg, 2.8 mmol) in dichloromethane (20 ml), was added (1*S*)-(+)-10-camphorsulfonic acid (320 mg, 1.38 mmol), and the resultant solution allowed to stand at room temperature for 48 h. Removal of the solvent under reduced pressure afforded a tan oil, that was purified by flash chromatography using hexane–ethyl acetate (1:1) as eluent to afford (i) recovered (3*R**,5*S**,6*S**)-1,7-dioxaspiro[5.5]undecane-3,5-diol **4** (119 mg, 23%); (ii) (3*S**,5*R**,6*S**)-1,7-dioxaspiro[5.5]-undecane-3,5-diol **6** (345 mg, 66%) as a colourless oil [Found (CI, NH_3): M^+H, 189.1138. $C_9H_{16}O_4$ requires M^+H, 189.1127]; ν_{max}(film)/cm^{-1} 3770–3150 (br s, OH), 2944, 2817 (s, C-H) and 1114, 1050 (m, C-O); δ_H(200 MHz, $CDCl_3$) 1.37–1.94 (6 H, m, 9-CH_2, 10-CH_2, 11ax-H and 4eq-H), 2.06–2.14 (2 H, m, 4ax-H and 11eq-H), 2.45 (1 H, br s, 3-OH), 2.89 (1 H, br s, 5-OH), 3.27 (1 H, dd, J_{gem} 10.1 and $J_{2ax,3ax}$ 10.1, 2ax-H), 3.53–3.80 (4 H, m, 2eq-H, 8-CH_2 and 5-H) and 4.08–4.18 (1 H, m, 3-H); δ_C(50 MHz, $CDCl_3$) 18.1, 24.8, 29.6, 37.1 (CH_2, C-4, C-9, C-10 and C-11), 60.9 (CH_2, C-8), 63.9 (CH_2, C-2), 65.2 (CH, C-3), 70.8 (CH, C-5) and 96.3 (quat, C-6); *m*/*z* (EI) 188 (M^+, 18%), 157 (53), 144 (14), 114 (10), 101 (100), 83 (25), 55 (59) and 43 (34).

(1*R**,15*S**,18*S**)-Spiro[2,5,8,11,14,17-hexaoxabicyclo[13.3.1]-nonadecane-18,2′-tetrahydropyran] 7

To a solution of (3*R**,5*S**,6*S**)-1,7-dioxaspiro[5.5]undecane-3,5-diol **6** (65 mg, 0.34 mmol) in dry tetrahydrofuran (100 ml) under a nitrogen atmosphere was added potassium hydride (37 mg, 0.9 mmol) and the resulting solution heated under reflux for 0.5 h. A solution of tetraethylene glycol ditosylate (191 mg, 0.37 mmol) in dry tetrahydrofuran (50 ml) was added dropwise over 3 h, and the reaction mixture heated under reflux for a further 24 h. After this time a brown precipitate had formed. After filtration through a short Celite pad, the solvent was removed at reduced pressure to give a tan oil, which was purified by flash chromatography using methanol–dichloromethane (5:95) as eluent to afford the title compound **7** (40 mg, 34%) as a colourless oil [Found (DEI): M^+, 346.198 86. $C_{17}H_{30}O_7$ requires M^+, 346.199 15]; ν_{max}(film)/cm^{-1} 2934, 2851 (s, C-H) and 1127, 1052, 1011 (s, C-O); δ_H(200 MHz, $CDCl_3$) 1.39–1.88 (5 H, m, 4″-CH_2, 5′-CH_2 and 3′ax-H), 2.09–2.20 (3 H, m, 19-CH_2 and 3′eq-H), 3.30 (1 H, dd, $J_{1,19ax}$ 12.0 and $J_{1,19eq}$ 4.6, 1-H), 3.50–3.72 (20 H, m, 16eq-H, 15-H, 6′-CH_2 and 8 × CH_2O) and 3.73 (1 H, dd, J_{gem} 10.1 and $J_{16ax,15ax}$ 10.1, 16ax-H); δ_C(50 MHz, $CDCl_3$) 18.2, 24.9, 29.6, 37.2 (CH_2, C-19, C-3′, C-4′ and C-5′), 60.9, 64.1 (CH_2, C-16 and C-6′), 68.5, 70.5 (CH, C-15 and C-1), 70.9 (CH_2, OCH_2) and 96.3 (quat, C-18); *m*/*z* (CI, NH_3) 347 (M^+H, 47%), 280 (6), 195 (78) and 153 (100).

(1*R**,18*S**,21*S**)-Spiro[2,5,8,11,14,17,20-heptaoxabicyclo-[16.3.1]docosane-21,2′-tetrahydropyran] 8

The title compound **8** was prepared from diol **6** (130 mg, 0.69 mmol), potassium hydride (33 mg, 0.83 mmol) and hexaethylene glycol ditosylate (503 mg, 0.92 mmol) using a similar procedure to that described above for crown ether **7**. The crude product, a tan oil, was purified by flash chromatography using methanol–dichloromethane (5:95) as eluent to afford the title compound **8** (74 mg, 28%) as a colourless oil [Found (EI): M^+, 390.2261. $C_{19}H_{34}O_8$ requires M^+, 390.2253]; ν_{max}(film)/cm^{-1} 2941, 2837 (s, C-H) and 1126, 1028, 1012 (s, C-O); δ_H(200 MHz, $CDCl_3$) 1.31–1.85 (5 H, m, 4′-CH_2 and 5′-CH_2 and 3′ax-H), 1.94–2.30 (3 H, m, 22-CH_2 and 3′eq-H), 3.14 (1 H, dd, $J_{1,22ax}$ 11.6 and $J_{1,22eq}$ 3.2, 1-H), 3.28 (1 H, dd, J_{gem} 10.3 and $J_{19ax,18ax}$ 10.3, 18ax-H) and 3.53–3.78 (24 H, m, 19eq-H, 18-H, 6′-CH_2 and 10 × CH_2O); δ_C(50 MHz, $CDCl_3$) 18.0, 24.4, 29.7, 30.7 (CH_2, C-22, C-3′, C-4′ and C-5′), 60.3, 61.3 (CH_2, C-19 and C-6′), 67.9, 70.2 (CH, C-18 and C-1), 70.8, 71.8, 72.9, 73.1 (CH_2, CH_2O) and 95.4 (quat, C-21); *m*/*z* (CI, NH_3) 391 (M^+H, 100%), 263 (8), 239 (80), 153 (60).

(1*R,21*S**,24*S**)-Spiro[2,5,8,11,14,17,20,23-octaoxabicyclo-[19.3.1]pentacosane-24,2′-tetrahydropyran] 9**

The title compound **9** was prepared from diol **6** (200 mg, 1.1 mmol), potassium hydride (104 mg, 2.6 mmol) and pentaethylene glycol ditosylate (714 mg, 1.3 mmol) using a similar procedure to that described above for crown ether **7**. The crude product, a tan oil, was purified by flash chromatography using methanol–dichloromethane (5:95) as eluent to afford the title compound **9** (180 mg, 42%) as a colourless oil [Found (DEI): M^+, 434.251 35. $C_{21}H_{38}O_9$ requires M^+, 434.251 58]; ν_{max}(film)/cm^{-1} 2946, 2918 (s, C-H) and 1128, 1056, 1021 (s, C-O); δ_H(200 MHz, $CDCl_3$) 1.38–1.91 (5 H, m, 4′-CH_2 and 5′-CH_2, and 3′ax-H), 2.10–2.24 (3 H, m, 25-CH_2 and 3′eq-H), 3.11 (1 H, dd, $J_{1,25ax}$ 11.8 and $J_{1,25eq}$ 3.6, 5-H), 3.28 (1 H, dd, J_{gem} 10.2 and $J_{22ax,21ax}$ 10.2, 2ax-H) and 3.50–3.79 (28 H, m, 22eq-H, 21-H, 6′-CH_2 and 12 × CH_2O); δ_C(50 MHz, $CDCl_3$) 18.1, 24.8, 29.6, 37.2 (CH_2, C-25, C-4′, C-5′ and C-3′), 60.9, 64.1 (CH_2, C-22 and C-6′), 65.3, 68.1 (CH, C-21 and C-1), 70.5, 70.8 (CH_2, CH_2O) and 96.2 (quat, C-24); *m*/*z* (CI, NH_3) 435 (M^+H, 84%), 283 (100) and 153 (58).

Determination of the association constants

Lithium, sodium, potassium, caesium and ammonium picrates were prepared from picric acid. Lithium carbonate, sodium carbonate, potassium carbonate, caesium carbonate and ammonium hydroxide were prepared in distilled water according to the procedure of Silberrad *et al.*[23] The picrates were recrystallised twice from distilled water then dried at room temperature at 0.1 mmHg for 48 h.

Association constants were determined using the ultraviolet spectroscopic method developed by Cram *et al.*[19] Solutions of the picrate salts were prepared in distilled water at a concentration of 0.015 mol l^{-1}. Solutions of the hosts were prepared in 2.0 ml volumetric flasks as 0.075 mol l^{-1} solutions in chloroform. All volume transfers were carried out using a Gilson P1000 pipetman at 22 °C.

The extraction studies were performed using the following procedure. A solution of the host (0.20 ml) was added to a 2 ml centrifuge tube containing the picrate solution (0.5 ml). A blank solution consisting of the host solution (0.20 ml) and water (0.5 ml) was also prepared in each study. The tubes were immediately stoppered, shaken for 2 min and centrifuged for 2 min. An aliquot of the chloroform layer (0.15 ml) was transferred to a volumetric flask (50 ml) and diluted to the mark with acetonitrile. An appropriate blank was also prepared from the chloroform layer of the blank solution. All ultraviolet measurements were obtained at 380 nm at 22 °C. Calculations were based on the Beer's law relationship $a = \varepsilon bc$ where a is the absorbance, ε is the extinction coefficient, b the path length of the cell (cm) and c the concentration of the measured species. From Beer's law the millimoles of the picrate salts extracted into the chloroform layer could be determined. The millimoles of the host could be calculated from the original concentration and the aliquot volume and thus the guest to host ratio (R), was given by the millimoles of picrate salt divided by the millimoles of host. Using the experimentally determined values for R, the extraction constant, K_e, could be calculated from eqn. (1),

$$K_e = \frac{R}{(1 - R)\{[\text{Guest}]_i - R[\text{Host}]_i(V_{org}/V_{aq})\}^2} \quad (1)$$

where R = the molar ratio of guest to host in the chloroform layer as determined by UV spectroscopy, $[\text{Guest}]_i$ = the initial concentration of the guest in the aqueous layer, $[\text{Host}]_i$ = the initial concentration of the host in the chloroform layer, and V_{org} and V_{aq} are the volumes of the organic and aqueous phases respectively. The association constant (K_a) is defined by eqn. (2), and the distribution (K_d) constant by eqn. (3).

$$[\text{Host}]_{aq} + [\text{Guest}]_{aq} \overset{K_a}{\underset{CDCl_3}{\rightleftharpoons}} [\text{Host–Guest Complex}]_{org} \quad (2)$$

$$[\text{Guest}]_{aq} \overset{K_d}{\rightleftharpoons} [\text{Guest}]_{org} \quad (3)$$

K_a is then related to K_e and K_d by eqn. (4).

$$K_a = K_e/K_d \quad (4)$$

The K_d values used were those obtained in acetonitrile by *Cram et al.*[19] The Gibbs free energy of the system could then be calculated from eqn. (5).

$$\Delta G = -RT \ln(K_a) \quad (5)$$

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