Synthesis of Three Series of Diastereoisomeric Bicyclic Crown Ethers and their Stability Constants with Group 1A Cations

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The syntheses of a series of bridged crown ethers are described. Their binding strength to group 1A metals has been compared by determination of the stability constants. An explanation for the wide variation of the measured stability constants is given in terms of the influence of steric interactions on the conformation of the isomers and electrostatic effects occurring within the cavity.

The relationship between the molecular shape of the crown ethers and their ability to bind cations has created great interest since Pedersen [1] pointed out the correlation between the size of the hole in the crown ether and the diameter of the complexed cation. It soon became clear, however, that this relationship holds best for the smaller, relatively rigid host molecules. A larger and more flexible crown ether can fold to produce smaller cavities and then bind smaller cations; the formation of complexes between dibenzo-30-crown-10 and potassium salts is a good example of this property.[2] Although the most stable conformation of the host molecule existing in the free state may not be suitable for the complexation of a cation, a stable complex may be formed if a change in conformation can occur to give one in which the spatial distribution of the oxygen atoms can establish interactions with the cation. Whether this can occur depends largely on the balance between the increase in free energy on forming ion–dipole bonds with the cation and the energy required by the ligand to achieve an ideal conformation for complexation. If energetically unfavourable steric interactions are involved in the transformation to a complexing conformation then strong binding to a cation will not occur. Many papers have been published on the simple 'best fit' theory correlating cavity size to cation diameter, but relatively few have attempted to relate the stereochemistry of the crown ether with interactions with cations. Notably, Stoddart [3] has synthesised and examined the properties of the flexible isomeric dicyclohexano-18-crown-6 isomers, and other modified 18-crown-6 rings; he has stressed the importance of the effect of small conformational changes on the strength of binding to cations. The effect of small steric interactions occurring within the isomeric dicyclohexano-18-crown-6 on their binding to dimethylthallium has also been described.[4] The diastereoisomeric bicyclic crown ethers described in this paper are more rigid molecules, but the broad principles outlined still apply.

Three series of isomeric bicyclic crowns have now been synthesised, each series differing only in the configuration of the carbon atoms at the junction of the cyclohexyl and heterocyclic rings. The series of isomers, (**3a**—**c**), (**4a**—**c**), and (**5a**—**c**) were prepared by bridging the isomeric diols (**2a**—**c**) with the appropriate ditosyloxy compound. The series (**4a**—**c**) were also obtained from the products of the high pressure catalytic hydrogenation of the aromatic bicyclic crown (**7**)[5] previously described. The *in,in* and *out,out* abbreviated names refer to the direction in which the hydrogen atoms on the carbons at the cyclohexane–heterocyclic junctions are pointing relative to the molecular cavity.

The dicyclohexyl diols (**2**) were obtained by the high pressure hydrogenation of the diol (**1**)[6] over Ru–Al_2O_3 and separated by fractional crystallisation. The ditosyloxy compounds were prepared from the diols in the usual manner; *o*-bis(2-hydroxyethoxy)benzene was most conveniently prepared by the reaction of pyrocatechol in aqueous solution with an excess of ethylene oxide in the presence of a small amount of calcium chloride.[7] The bridging reaction was best carried out in dimethyl sulphoxide using sodium hydride, giving the bicyclic compounds in 20—40% yield. The bicyclic crowns having the highest stability constants were isolated from aqueous solution by separation of the insoluble complexes by the technique developed and described previously.[5] A preliminary account of the synthesis, formation constants, and crystal structures of compounds (**5a**—**c**) has been published.[8]

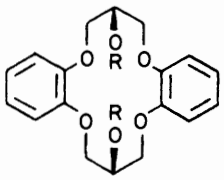
The aromatic bicyclic crown ether, dibenzo-223 (**6**), related to isomers (**3a**—**c**), has been prepared. From this reaction a product of low solubility, the dimer (**9**), was obtained in low yield. A similar dimer (**10**) was obtained with the *out,out*-dicyclohexano-223 (**3c**); the corresponding dimers were not isolated from the cyclisation reactions which gave (**3a**) and (**3b**). The smaller analogue (**8**), of (**9**) was obtained by a four-stage synthesis from the diol (**1**).

Experimental

Ether refers to diethyl ether throughout. Molecular weights were determined by mass spectrometry.

(1R,7S,12R,18S)-2,6,13,17,23,26,29,32-*Hexaoxatetracyclo*-[16.4.0.$10^{4,15}$.$0^{7,12}$]*dotriacontane* (**4b**) (in,in-*Dicyclohexano*-224).—The diol (**2b**) (2.05 g) in dimethyl sulphoxide (60 ml) was treated with sodium hydride (0.5 g) and stirred for 20 min, then 1,8-ditosyloxy-3,6-dioxaoctane (3.7 g) was added and the mixture warmed to 40 °C. After 5 h the product was poured into water, neutralised with dilute hydrochloric acid, and extracted with chloroform (2 × 100 ml). This extract, after being washed with water, was dried and subjected to column chromatography on neutral activated alumina, and the eluate ($CHCl_3$) was concentrated to yield a yellow oil (2.6 g). Attempted isolation of a complex with sodium or potassium perchlorate was not successful. The oil in ethyl acetate (25 ml) was rechromatographed through alumina (2 × 20 cm) and the first 200 ml (ethyl acetate) of the eluate collected and concentrated to an oil. Extraction of this oil with boiling cyclohexane (2 × 20 ml), then cooling, gave the product, recrystallisation of which from cyclohexane gave *prisms* (**4b**) (0.46 g), m.p. 135—137 °C (Found: C, 63.3; H, 9.3. $C_{24}H_{42}O_8$ requires C, 62.9; H, 9.2%).

(1S,7R,12S,18R)-2,6,13,17,23,26,29,32-*Hexaoxatetracyclo*-[16.4.0.$10^{4,15}$.$0^{7,12}$]*dotriacontane* (**4c**) (out,out-*Dicyclohexano*-224).—The diol (**2c**) (2.7 g) was treated with sodium hydride (0.6 g) and then with 1,8-ditosyloxy-3,6-dioxaoctane (3.9 g), as for (**4b**). The product was shaken with water (300 ml) at 50 °C, then filtered. Sodium perchlorate (4 g) was added to the aqueous solution and it was kept at 3 °C for 16 h. The crystalline sodium perchlorate complex was collected, washed with water, and



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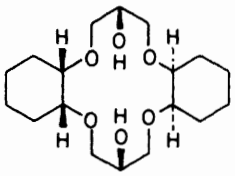
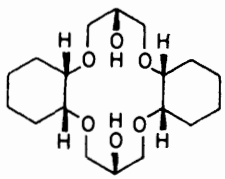
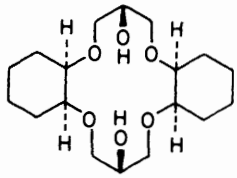


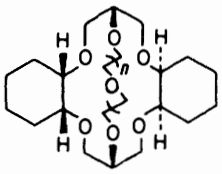
(2a)



(2b)



(2c)



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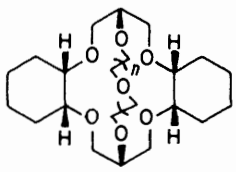
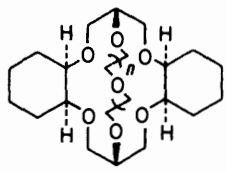
(4a) $n = 2$



(3b) $n = 1$
(4b) $n = 2$



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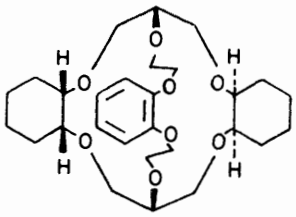
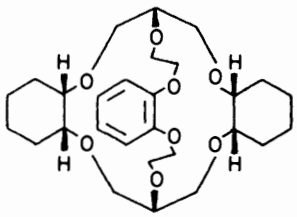
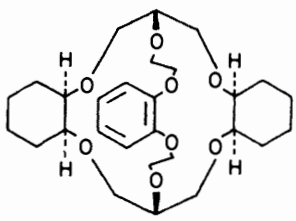


(5a)



(5b)

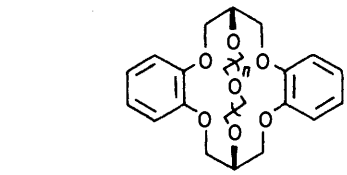


(5c)

dissolved in hot 50% aqueous methanol. This solution was washed through an Amberlite IRA 400 F^- column with 50% aqueous methanol (1 l). Concentration of the eluate gave the buff sodium fluoride complex which was heated under reflux in toluene (50 ml) for 20 min. The solution was filtered through a pad of alumina to remove the sodium fluoride and concentrated to give a pale yellow oil; this crystallised on standing. Recrystallisation from light petroleum (b.p. 80—100 °C) (10 ml) gave *prisms* (**4c**) (0.38 g), m.p. 85 °C (Found: C, 62.8; H, 6.95. $C_{24}H_{42}O_8$ requires C, 62.9; H, 9.2%).

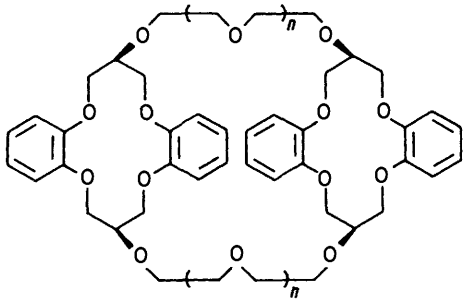
(1R,7R,12S,18R)-2,6,13,17,23,26,29,32-*Hexaoxatetracyclo*-[16.4.0.0^{4,15}.0^{7,12}]*dotriacontane* (**4a**) (in,out-*Dicyclohexano*-224).—The diol (**2a**) (1.81 g) in dimethyl sulphoxide (50 ml) was treated with sodium hydride (0.5 g) and then with 1,8-ditosyloxy-3,6-dioxaoctane (2.8 g) in the same manner as (**2b**). Isolation of the product using a similar technique of chromatography through alumina gave *microneedles* (**4a**) [from light petroleum (b.p. 80—100 °C)] (0.25 g), m.p. 102—104 °C (Found: C, 63.0; H, 9.5. $C_{24}H_{42}O_8$ requires C, 62.9; H, 9.2%).

Hydrogenation of 7,8,16,17-*Tetrahydro*-6H,15H-5,9,14,18,19,-22,25,28-*octaoxa*-7,16-*decanodibenzo*[a,h]*cyclotetradecene* (**7**) (*Dibenzo*-224).—A mixture of dibenzo-224 (**7**) (4.8 g) and potassium chloride (3.0 g) in water (800 ml) was stirred for 4 h at 100 °C in the presence of 5% Ru–Al_2O_3 (750 mg) at 100 atm. Absorption of hydrogen was rapid above 90 °C and almost complete after 30 min. The solution was filtered and the catalyst washed with a little methanol; measurement of the u.v. spectrum confirmed that hydrogenation of the aromatic rings was complete. Concentration of the solution gave an oil which was dissolved in cyclohexane and filtered to remove the potassium chloride. The oil, in ethyl acetate (25 ml), was then eluted through neutral activated alumina (25 cm × 2 cm) with ethyl acetate (300 ml). Concentration, and dissolution of the product in ether–light petroleum (60:40; 30 ml) gave, on standing at 3 °C, a crystalline precipitate which was recrystallised from ether (needles) (0.49 g), m.p. 132—136 °C, having an i.r. spectrum identical with the *in,in*-dicyclohexano-224 (**4b**). Concentration of the mother-liquor gave, after standing overnight, impure material (0.55 g), m.p. 96—102 °C; recrystallisation from light petroleum (80—100 °C) gave thick needles (0.38 g), m.p. 102—104 °C, identical with the *in,out*-isomer (**4a**). The mother-liquor from the second isomer failed to produce any further crystalline product on standing. This solution was reconcentrated, dissolved in ethyl acetate, and rechromatographed (ethyl acetate; 100 ml) through basic activated alumina (1 cm × 20 cm) and the eluate concentrated. After several weeks the oily material partially solidified, the oily material was dissolved in cyclohexane–ether, and the solid



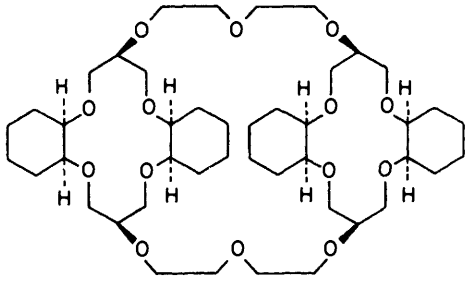
(6) $n = 1$

(7) $n = 2$



(8) $n = 0$

(9) $n = 1$



(10)

collected. Recrystallisation from a small amount of light petroleum yielded the pure *out,out*-isomer (**4c**) (0.13 g), m.p. 85 °C.

(1S,7R,12S,18R)-4r,15r-2,6,13,17,23,26,29-*Heptaoxatetracyclo*[16.4.0.$7^{4,15}$.$0^{7,12}$]*nonacosane* (**3b**) (in,in-*Dicyclohexano*-223).—The diol (**2b**) (3.0 g), in dimethyl sulphoxide (75 ml) treated with sodium hydride (0.6 g), and 1,5-ditosyloxy-3-oxapentane (4.2 g) were allowed to react at 30—50 °C for 3 h. The product was poured into water and extracted with chloroform (4 × 100 ml), washed with water, and concentrated to an oil. This oil was dissolved in light petroleum and filtered through a short neutral activated alumina column to yield a colourless solution. After concentration the oil obtained was dissolved in ethyl acetate (15 ml) and treated with sodium thiocyanate (100 mg). The complex slowly crystallised at 3 °C and was collected after 3 days to give the hydrated *complex* (**3b**)·NaNCS (0.45 g), m.p. 110—112 °C (Found: C, 53.6; H, 7.8; N, 2.7. $C_{22}H_{38}O_7$·NaNCS·H_2O requires C, 53.8; H, 7.9; N, 2.7%). This was shaken with chloroform–water and the chloroform phase was separated, washed with water, and concentrated to an oil which crystallised on standing; recrystallisation from cyclohexane gave colourless *needles* (**3b**) (0.284 g), m.p. 87 °C (Found: C, 63.9; H, 9.4. $C_{22}H_{38}O_7$ requires C, 63.7; H, 9.2%).

(1S,7S,12R,18R)-2,6,13,17,23,26,29-*Heptaoxatetracyclo*[16.4.0.$7^{4,15}$.$0^{7,12}$]*nonacosane* (**3a**) (in,out-*Dicyclohexano*-223).—The diol (**2a**) (2.7 g) in dimethyl sulphoxide (60 ml) was treated with sodium hydride (0.5 g) and allowed to react with 1,5-ditosyloxy-3-oxapentane (3.8 g) for 4 h at 40 °C. The product was poured into water (300 ml) and heated to 60 °C. After filtration, lithium perchlorate (5 g) was added and the solution cooled to 3 °C for 16 h. The *lithium perchlorate complex* (0.5 g) was collected (Found: C, 50.0; H, 7.4; Cl, 6.5. $C_{22}H_{38}O_7$·$LiClO_4$·1/2H_2O requires C, 49.9; H, 7.4; Cl, 6.7%). The complex was boiled under reflux in toluene, filtered through alumina, concentrated to an oil, and the free ligand obtained was crystallised from light petroleum (20 ml). The product was washed with ether–light petroleum to give *flakes* (**3a**), m.p. 104 °C (0.235 g) (Found: C, 63.9; H, 9.35. $C_{22}H_{38}O_7$ requires C, 63.7; H, 9.2%).

(1R,7S,12R,18S)-4s,15s-2,6,13,17,23,26,29-*Heptaoxatetracyclo*[16.4.0.$17^{4,15}$.$0^{17,12}$]*nonacosane*(**3c**)(out,out-*Dicyclohexano*-223) *and* (1R,15R,20S,34S,41S,46R,51S,56R)-4s,12r,23r,31s-2,5,8,11,14,21,24,27,30,33,40,47,50,57-*Tetradecaoxaheptacyclo*[32.4.0.$10^{4,31}$.$10^{12,23}$.$0^{41,46}$.$0^{51,56}$]*octapentacontane* (**10**).—The diol (**2c**) (3.0 g) in dimethyl sulphoxide (100 ml) was treated with sodium hydride (0.6 g) and then with 1,5-ditosyloxy-3-oxapentane (4.2 g) and heated at 40 °C with stirring for 4 h. The mixture was poured into water (500 ml), neutralised with dilute hydrochloric acid and the oily product extracted with chloroform (2 × 100 ml) to remove the dimer (**10**). The aqueous solution was treated with sodium perchlorate (5 g) and kept at 3 °C for 16 h. The crystalline sodium perchlorate complex of (**3c**) (anhydrous; m.p. 250 °C) which separated was collected and converted into the sodium fluoride complex by passing a methanolic solution through Amberlite IRA 400 F^- resin. Dissociation of the sodium fluoride complex by heating it in toluene under reflux gave, after filtration and concentration, the product (**3c**). Crystallisation from light petroleum (80—100 °C) gave pure material (0.55 g), m.p. 95 °C (Found: *M*, 414; C, 63.9; H, 9.1. $C_{22}H_{38}O_7$ requires *M*, 414; C, 63.7; H, 9.2%). A complex with magnesium perchlorate was obtained from methanol [Found: C, 40.3; H, 6.2; Cl, 10.7. Calc. for $C_{22}H_{38}O_7$·$Mg(ClO_4)_2$·H_2O: C, 40.3; H, 6.2; Cl, 10.8%]. (For crystal structure, see ref. 9.)

The chloroform extract containing the dimer (**10**) was concentrated to yield a brown oil and then dissolved in methanol. On standing an amorphous precipitate was obtained; this was collected and recrystallised from butanol, yielding fine *needles* (0.18 g), m.p. 172° C (Found: *M*; 828 C, 64.0; H, 9.4. $C_{44}H_{76}O_{14}$ requires *M*, 828; C, 63.7; H, 9.2%).

7,8,16,17-*Tetrahydro*-6H,5H-3,9,14,18,19,22,25-*heptaoxa*-7,16-*heptanodibenzo*[a,h]*cyclotetradecene* (**6**) (*Dibenzo*-223) *and* 3,3′:14,14′-*Bis*[*ethylenedioxybis*(*ethyleneoxy*)]*bis*(1,5,12,16-*tetraoxa*[5.5]*orthocyclophane* (**9**) (*Dibenzo*-223 *Dimer*).—The diol (**1**) (10.0 g) in dimethyl sulphoxide (100 ml) was treated with sodium hydride (2.0 g) and then with 1,5-ditosyloxy-3-oxapentane (12.5 g). This mixture was stirred for 5 h at 40 °C. The product was poured into water (1 l), warmed to 60 °C, and the aqueous phase decanted, the organic part being washed with more hot water (500 ml). The combined aqueous solutions containing the monomer were filtered and treated with lithium perchlorate (20 g); the precipitated complex was collected (4.3 g) after 16 h at 3 °C. This precipitate in aqueous methanol (20:80, v/v) was washed through an Amberlite 400 F^- column, and the eluate concentrated to give the lithium fluoride complex. Dissociation of the complex was achieved by heating it under reflux in toluene; the solution was filtered hot and concentrated to give the crystalline product, recrystallisation of which from methanol gave needles (**6**) (2.35 g), m.p. 125 °C (Found: *M*, 402; C, 65.7; H, 6.5. Calc. for $C_{22}H_{26}O_7$: *M*, 402; 65.7; H, 6.5%). (For crystal structure see ref. 10.)

The oily organic phase was dissolved in ethyl acetate (100 ml) and eluted from neutral activated alumina (30 × 1.5 cm) with

ethyl acetate. After concentration the pale yellow oil obtained was dissolved in hot methanol (50 ml) and the amorphous material which separated on standing was collected. Recrystallisation from butanol gave *microneedles* of the dimer (**9**) (0.41 g), m.p. 187 °C (Found: *M*, 804; C, 65.5; H, 6.6. $C_{44}H_{52}O_{14}$ requires *M*, 804; C, 65.7; H, 6.5%).

o-*Bis*(2-*tosyloxyethoxy*)*benzene*.—Pyrocatechol (50 g) dissolved in water (250 ml) was treated with calcium chloride (5 g) and cooled to 10 °C; cold ethylene oxide (100 ml) was added while the mixture was well-cooled in an ice-bath, and it was then gradually warmed to 40 °C, and stirred at room temperature for 48 h. Finally, the product was warmed to 80—90 °C for 2 h to expel the unchanged ethylene oxide. The resulting brown solution was concentrated to an oil, extracted with ethyl acetate (3 × 150 ml), and chromatographed through activated alumina with ethyl acetate; concentration under reduced pressure gave the crystalline product *o*-bis(2-hydroxyethoxy)benzene in three crops (total yield 65 g), m.p. 80—82 °C.

This diol (40 g) in pyridine (150 ml) was treated with tosyl chloride (100 g) at 20—25 °C. Work-up and crystallisation from propan-2-ol (800 ml) gave *o*-bis(2-tosyloxyethoxy)benzene as fine needles (80.5 g), m.p. 94 °C.

(4aR,9aR,13aS,18aS)-1,2,3,4,4a,7,8,9a,10,11,12,13,13a,16,17,-18a-*Hexadecahydro*-7,16-[o-*phenylenedioxybis*(*ethyleneoxy*)]-6H,15H-5,9,14,18-*tetraoxadibenzo*[a,h]*cyclotetradecane* (**5a**) (in,out-*Dicyclohexanobenzo*-224).—The diol (**2a**) (2.7 g) in dimethyl sulphoxide (100 ml) was treated with sodium hydride (1.0 g) and stirred for 30 min at 40 °C. After it had been cooled to 25 °C, *o*-bis(2-tosyloxyethoxy)benzene (5.0 g) was added and the mixture stirred in the absence of air for 1 h at 30—40 °C, then overnight at room temperature. The product was poured into water (800 ml) and the aqueous solution warmed to 40 °C and filtered. The oily part remaining was washed with warm dilute sodium chloride solution and the filtrates combined. Sodium perchlorate (10.0 g) was added and the mixture cooled to 3 °C overnight. The anhydrous complex was collected and washed with cold water, redissolved in methanol (25 ml), filtered, and diluted with water (25 ml). After concentration to about half-volume, the solution was allowed to crystallise slowly at room temperature, giving the sodium perchlorate complex in large *rhombs* (1.8 g) (Found: C, 53.1; H, 7.0; Cl, 5.6. $C_{28}H_{42}O_8 \cdot NaClO_4$ requires C, 53.5; H, 6.7; Cl, 5.6%); m.p. 135—140 °C. The complex was dissolved in aqueous methanol, washed through a mixed-bed ion exchange resin with aqueous methanol, and the eluate concentrated to yield an oil; crystallisation occurred on standing. Recrystallisation from cyclohexane gave colourless *needles* (**5a**) (0.94 g), m.p. 133—135 °C (Found: C, 66.7; H, 8.4. $C_{28}H_{42}O_8$ requires C, 66.4; H, 8.4%).

The (21S,26R,29S,34R)-*Isomer* (**5c**) (out,out-*Dicyclohexanobenzo*-224).—The diol (**2c**) (3.1 g) in dimethyl sulphoxide (100 ml) was treated with sodium hydride (1.0 g) and stirred for 30 min; *o*-bis(2-tosyloxyethoxy)benzene (6.0 g) was added in one portion and the mixture stirred at room temperature for 30 min, then after being stirred for 2 h at 45—50 °C allowed to cool to room temperature overnight. The product was poured into cold water (800 ml) and the aqueous solution filtered. The oil remaining was re-extracted with potassium chloride solution (5 g/l) and combined with the initial filtrate. The filtrate (1.5 l) was treated with potassium perchlorate (20 g) and stirred for 20 min. The flocculent potassium perchlorate complex was collected and washed with a little water. This complex, suspended in 50% aqueous methanol (10 ml), was washed through an Amberlite IR 400 F^- column (30 cm × 2 cm) with 50% methanol (1 l). The eluate was concentrated under reduced pressure and the residue dissociated on being heated under *reflux* in toluene; filtration and concentration yielded a pale yellow oil which rapidly crystallised. This product was dissolved in hot cyclohexane (50 ml), filtered through alumina to give a colourless solution, and allowed to crystallise as fine needles (1.51 g), m.p. 133 °C; a second crop (0.14 g) was obtained after concentration (Found: C, 66.7; H, 8.5. Calc. for $C_{28}H_{42}O_8$: C, 66.4; H, 8.4%). A sample of the potassium perchlorate complex, recrystallised from water, gave the following analysis (Found: C, 52.2; H, 6.7; Cl, 5.6. $C_{28}H_{42}O_8 \cdot KClO_4$ requires C, 52.1; H, 6.6; Cl, 5.5%). (For crystal structure, see ref. 11.)

The (21R,26S,29R,34S)-*Isomer* (**5b**) (in,in-*Dicyclohexanobenzo*-224).—The diol (**2b**) (2.9 g) in dry dimethyl sulphoxide (75 ml) was converted into its sodium salt and treated with *o*-bis(2-tosyloxyethoxy)benzene in the manner described for the isomer (**5c**). The crude reaction products in water (800 ml) were extracted with dichloromethane (3 × 150 ml), concentrated to a yellow oil, and washed with water. The oil in ethyl acetate, after drying, was passed through neutral activated alumina (20 × 1.5 cm) and the fraction containing the bicyclic compound was re-extracted with hot cyclohexane and passed again through neutral alumina (20 × 1.5 cm), being eluted with cyclohexane (400 ml). The product obtained after concentration gave an oil which crystallised on standing; this was recrystallised from cyclohexane (15 ml) giving a pure sample (1.3 g), m.p. 133 °C (Found: C, 66.7; H, 8.1. $C_{28}H_{42}O_8$ requires C, 66.4; H, 8.4%). Crystallisation from methanol yielded a tightly bound methanolate characterised by a sharp non-hydrogen bonded –OH stretch at 3 555 cm^{-1} (Found: C, 64.7; H, 8.7. $C_{28}H_{42}O_8 \cdot CH_3OH$ requires C, 64.7; H, 8.6%). (For crystal structure, see ref. 12.)

7,16-*Bis*(*methoxycarbonylmethoxy*)-7,8,16,17-*tetrahydro*-6H,-15H-5,9,14,18-*tetraoxadibenzo*[b,i]*cyclotetradecene*.—A solution of the diol (**1**) (5.0 g) in tetrahydrofuran (65 ml) containing sodium hydride (1.0 g) was stirred for 20 min, treated with methyl chloroacetate (6.0 g), and stirred at room temperature for 40 h. The product was poured into water, extracted with chloroform (3 × 50 ml), washed with water, and concentrated to an oil. This oil was extracted with benzene, treated with charcoal, and filtered. The product obtained on evaporation of the benzene partially crystallised. This material was then subjected to chromatography through activated neutral alumina, eluting with methanol–chloroform. Concentration of the eluate afforded the crude diester which was recrystallised from methanol (50 ml) to give colourless *needles* of the title bis(methoxycarbonylmethoxy)cyclotetradecene (3.2 g), m.p. 118 °C (Found: C, 60.4; H, 5.9. $C_{24}H_{28}O_{10}$ requires C, 60.5; H, 5.9%).

7,16-*Bis*(1-*hydroxyethoxy*)-7,8,16,17-*tetrahydro*-6H,15H-5,9,14,18-*tetraoxadibenzo*[b,i]*cyclotetradecene*.—The above bis(methoxycarbonylmethoxy)cyclotetradecene (4.0 g) was added to a suspension in lithium aluminium hydride (1.0 g) in tetrahydrofuran (30 ml) and stirred first at room temperature and then heated under reflux for 2 h. The excess of lithium aluminium hydride was destroyed with a few drops of water, the solution evaporated to dryness, and the product extracted with hot toluene. This solution was washed with a little water, concentrated to an oil, and crystallised from toluene giving the title *diol* (3.1 g), m.p. 122 °C (Found: C, 62.5; H, 6.7. $C_{22}H_{28}O_8$ requires C, 62.8; H, 6.7%).

3,3′:14,14′-*Bis*[*oxybis*(*ethyleneoxy*)]*bis*(1,5,12,16-*tetraoxa*-[5.5]*orthocyclophane* (**8**).—The above diol (4.0 g) in pyridine (15 ml) was treated with tosyl chloride (10 g) and stirred at 20 °C

Table. Stability constants [log (K_e^{-1})] in methanol[a] (values ±0.05)

Crown ether	Metal salt NaX	KX	RbX	CsX
(**6**)	6.08[c]	3.17 (3.60)[b]		
(**3b**)	5.57	1.99		
(**3a**)	5.50	2.01		
(**3c**)	6.60	3.74		
(**7**)	7.61	7.48	6.21	4.64
(**4b**)	4.78	4.82[c]	2.73	2.80
(**4a**)	5.95	6.78[c]	4.89	3.56
(**4c**)	7.80	8.50[c]	6.88	4.77
Tribenzo-224	7.72[c]	8.75[c]	5.69[c]	4.25
(**5b**)	4.13	4.65	2.42[c]	1.85[c,8]
(**5a**)	5.86	6.50	4.62[c]	3.58[c,8]
(**5c**)	7.86	8.18	7.16[c]	5.01[c,8]

[a] Approx. 2×10^{-3}M (concentration of 1:1 mixture). [b] K_e 2:1. [c] X = Cl; otherwise X = Br.

for 4 h. Crude 7,16-bis(2-tosyloxyethoxy)-7,8,16,17-tetrahydro-6*H*,15*H*-5,9,14,18-tetraoxadibenzo[*b*,*i*]cyclotetradecene (6.1 g) was isolated as a glassy solid, and was used without further purification. The diol (**1**) (2.0 g) in dimethyl sulphoxide (30 ml) was treated with sodium hydride (0.5 g) and then with a solution of the above ditosyloxy compound (4.5 g) in dimethyl sulphoxide, added dropwise during 30 min. After being stirred for 1.5 h, the product was poured into water, acidified with dilute hydrochloric acid, and extracted with chloroform. Concentration to an oil and trituration with methanol gave an insoluble amorphous material. This was washed with methanol and recrystallised from dioxane and then from dimethyl formamide, giving *microneedles* (**8**) (1.1 g), m.p. 310 °C (Found: *M*, 716; C, 66.9; H, 6.3. $C_{40}H_{44}O_{12}$ requires *M*, 716; C, 67.0; H, 6.2%). A strongly hydrated *complex* with rubidium bromide crystallised from ethanol (Found: C, 50.4; H, 5.3. $C_{40}H_{44}O_{12}$·RbBr·4H_2O requires C, 50.4; H, 5.5%). After being dried, this complex rapidly adsorbed atmospheric water.

Stability Constant Measurements.—Stability constants were measured in methanol at 25 °C using glass ion-selective electrodes by methods described previously,[13,14] and calculated according to the equation

$$K_e = [M^+L]/[M^+][L] \text{ mol}^{-1}$$

where $[M^+L]$ is the concentration of the complex and $[M^+]$ and [L] are the concentrations of the metal ion and the crown, respectively. A methanolic solution of the metal halide (5.0×10^{-3}M; 10 ml) at 25 °C was titrated with a 3—10×10^{-3}M-crown ether solution in methanol, the concentration used depending on the solubility of the crown. The cell consisted of an ion-selective electrode in combination with an Ag/AgCl reference electrode in saturated methanolic sodium chloride in contact with the solution through a fritted alumina plug. After each addition the mixture was stirred for a few seconds then allowed to stand until a steady E.M.F. was reached. No corrections were made for the change in ionic strength which occurs during the titration or for the junction potentials produced by the reference electrodes. Our own work had shown the effect of loading the solution with t-butylammonium bromide to be very small compared with the p*K* values found; also the calibration and dilution curves obtained by titration in the absence of crown ether indicated a near Nernstian response. The stability constant was calculated for 1:1 complexation after each addition. Normally it was found that the 1:1 complexation values gradually increased until a constant value was reached when the ratio of added crown ether and salt concentration reached unity, *i.e.* showing the formation of a 1:1 complex; these values were taken as the true stability constants and are given in the Table. When the data were processed using the Miniquad[15] program the values obtained for 1:1 complexation were in good agreement with the constant value; 2:1 complexation was rejected except in the case of dibenzo-223 where values of pK 3.17 (1:1) and pK_2 3.60 (2:1) were found. The reason for the apparent lowering of the stability constants at high cation to crown ether ratios is not clear. This may be a result of the method used since the free ligand concentration is determined as the difference between the initial concentration of the salt and the free salt concentration at each titration point (for 1:1 complexation); thus, in the initial stages of the titration when the free ligand concentration is very low, small errors in the cation concentration will lead to large errors in the ligand concentration. However, since the calculated ligand concentration nearly always appears to be too high—thus giving an apparently low stability constant—it is possible that the 1:1 complexation is not occurring in the presence of a large excess of the cation, and instead the simultaneous competition of several cations for the receptor site is preventing the formation of the 'ideal' complexing conformation of the crown ether.

Discussion

The wide differences found in the stability constants for each set of diastereoisomers with a particular cation is much greater than that found for the monocyclic dicyclohexano-18-crown-6 *cis syn cis* and *cis anti cis* isomers, the differences being particularly marked for the 224 series where sodium, potassium, or rubidium ions are able to enter the molecular cavity. Molecular models (C.P.K.) had shown very little difference in the size and shape of the molecular cavity for each series of diastereoisomers and suggested that a cation situated in the cavity would have fairly close contacts with all the oxygen atoms. The principal difference in predicted conformations between the *in,in*-isomers where the junction hydrogen atoms were on the same side of the 14-crown-4 ring as the bridge, and the *out,out*-isomers where these hydrogen atoms were on the opposite side to the bridge, was the relative disposition of the four oxygen atoms of the 14-crown-4 ring. The relationship between the positions of the oxygen atoms and the cation has been examined[16,17] for a number of complexes where the ligands have a high flexibility and could therefore assume the positions of maximum binding. The strongest binding appears to occur along the bisector of the C–O–C plane and somewhere within the angle subtended between the tetrahedral lone pair directions, the precise direction depending on the nature of the ligand and the size of the cation. The smaller cations Li and Na tend to bind in a trigonal lone pair direction. In the case of the *in,in*-isomers (the cyclohexane rings being in the chair form) the oxygen atoms are not directed towards the centre of the cavity, but somewhat away and at an angle greater than that between the lone-pair electrons. This conformation has been found[12] to exist for crystalline *in,in*-benzodicyclohexano-224 (**5b**). With the *out,out*-isomers, the chair conformations of the cyclohexane rings cause the four oxygen atoms to be pushed towards the cavity and directed inwards, and to lie within the angle subtended by the lone pair electrons. It appears that, although the cation could approach close to the oxygen atoms in both the *in,in*- and the *out,out* pairs of isomers, only in the latter are the oxygen atoms 'pointing' at the cation without being shielded by adjacent atoms. In order that the *in,in*-isomers might achieve a conformation in which the four oxygen atoms of the 14-crown-

4 ring are directed towards the centre of the cavity, a change from the chair to the boat conformation of the cyclohexane ring would be required. The energy required to convert the chair–chair form of the *in,in*-isomers (**3b**), (**4b**), and (**5b**) into the boat–boat conformation would be expected to be at least twice the energy difference between the chair and boat forms of cyclohexane, which is estimated to be in the region of 7 kcal/mol;[18,*] this is probably much larger than the binding energy derived from the formation of the ion–dipole bonds on complexation.

With the isomers (**4b**) and (**5b**) which have the *in,in* hydrogen atoms in the region close to the molecular cavity, an extra contribution to the destabilisation of the complex could occur. The increase in the polarisation of the O–C–H bonds caused by the extra negative charge on the oxygen atoms on complexation with the cation results in an increase in the positive charge on the corresponding hydrogen atoms. If these particular hydrogen atoms are close to the cavity where complexation is occurring, then the stability of the complex would be reduced because of the reduced negative charge environment.

A good correlation exists relating the configuration of the 224 diastereoisomers and the stability constants found with sodium and potassium salts. If, as is possible with the *out,out* isomers (**4c**) and (**5c**), all eight oxygen atoms can be involved in bonding, and this is found in the crystal structure[11] for (**5b**)·$KClO_4$, then the pK values are *ca.* 8. Note the small reduction in the pK value found for (**5c**)·$KClO_4$ (8.18 compared with 8.78 found for tribenzo-224), may be related to one long K–O bond which is found in the crystal structure.[11] If only six oxygen atoms are available for binding, as in the *in,out*-isomers (**4a**) and (**5a**) the pK value falls by 2; it falls further, to *ca* pK 4, for the *in,in*-isomers (**4**) and (**5b**) where only four oxygen atoms are readily available for complexation.

In the dicyclohexano-223 series, the cavity is too small to allow a potassium ion to enter and also, being a more rigid molecule, there is less possibility of conformational change than in the 224 series. The K_e values for potassium are much lower than the 224 series; however, the *out,out*-isomer (**3c**) shows the highest value, 3.74, suggesting five oxygen atoms are probably involved, complexing the potassium as a sandwich in the same way as benzo-15-crown-5. There is very little difference in the K_e values for sodium salts with the 223-isomers; the fairly high values in the range pK 5.5—6.5 suggest that the sodium ion is close to the centre of the cavity bound most strongly to the three oxygen atoms of the bridge, the four oxygen atoms of the 14-crown-4 ring playing a smaller part in the binding.

* 1 kcal is 4.184 kJ.

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