To Enzyme Analogues by Lock and Key Chemistry with Crown Compounds. Part 1. Enantiomeric Differentiation by Configurationally Chiral Cryptands synthesised from L-Tartaric Acid and D-Mannitol

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The requirements of an enzyme analogue are discussed in terms of (i) binding, (ii) chirality, and (iii) functionality. The ability of 18-crown-6 derivatives to complex with primary alkylammonium cations indicates the potential of the 18-crown-6 constitution to provide the binding requirement of an enzyme analogue. Attention is drawn to the fact that carbohydrates provide not only functionality but also a relatively inexpensive source of chiral bismethylenedioxy units for incorporation into the 18-crown-6 framework. The optically pure configurationally chiral cryptands L-(14), LL-(15), LL-(16), LL-(17), DD-(17), LL-(18), DD-(28), D-(29), DDD-(30), DD-(31), DD-(32), and DD-(33) have been synthesised from L-tartaric acid and D-mannitol. The 18-crown-6 locks excluding the tetraol LL-(16) and the octaol DD-(31), have been shown by ^{1}H n.m.r. spectroscopy to form complexes in CD_2Cl_2 with primary alkylammonium salts. The stability constants for complexes formed in $CDCl_3$ solution between (i) t-butylammonium thiocyanate and (ii) benzylammonium thiocyanate and some of these 18-crown-6 locks have been determined by an ^{1}H n.m.r. spectroscopic method and compared with the complexing ability of 18-crown-6 (34). ^{1}H and ^{13}C N.m.r. spectroscopy has been used to demonstrate that the locks LL-(18) and DD-(28) exhibit enantiomeric differentiation in complexation equilibria towards (*RS*)-α-phenylethylammonium hexafluorophosphate [(*RS*)-(8),HPF_6]. The tetraol LL-(16) and the octaol DD-(31) have been shown by ^{1}H n.m.r. spectroscopy to form complexes in CD_3OD and D_2O with primary alkylammonium salts. The tetra-*O*-isopropylidene derivative DD-(28) forms strong complexes in methanolic solution with alkali metal cations.

HISTORY records [1] that serendipity played a crucial role in the discovery by Pedersen [2] of the so-called crown ethers. The accidental synthesis of dibenzo-18-crown-6 (1) led [1,2] directly to the appreciation that this compound exhibits intriguing properties. Perhaps most significant is the fact that it forms stable complexes, both in the crystalline state [3] and in solution,[1,2,4] with

[1] C. J. Pedersen, *Aldrichim. Acta*, 1971, **4**, 1.

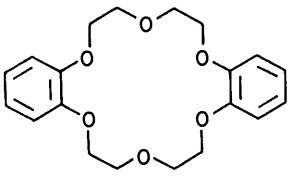
[2] C. J. Pedersen, *J. Amer. Chem. Soc.*, 1967, **89**, 2495, 7017; *Org. Synth.*, 1972, **52**, 66.

[3] M. R. Truter and C. J. Pedersen, *Endeavour*, 1971, **30**, 142; M. R. Truter, *Structure and Bonding*, 1973, **16**, 71.

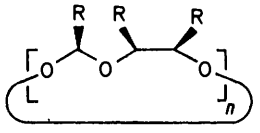
[4] C. J. Pedersen and H. K. Frensdorff, *Angew. Chem. Internat. Edn.*, 1972, **11**, 16.

metal (particularly the salts of the alkali and alkaline earth metals), ammonium, and primary alkylammonium salts.

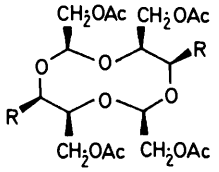
Our earlier interests in (i) the synthesis and conformational behaviour of the achiral macrocyclic polyacetals [5] (2) and (3) and the chiral 1,3,6,8-tetraoxacyclodecanes [6] (4) and (5) from carbohydrate precursors and (ii) the problem of assigning relative configurations to



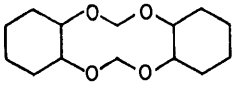
(1)



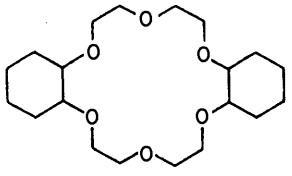
(2) R = CH_2OAc, n = 6
(3) R = CH_2OAc, n = 7



(4) R = H
(5) R = CH_3



(6)



(7)

the two di-*trans*-isomers of the bistetramethylene-1,3,6,8-tetraoxacyclodecane [7] (6) were revived in 1972 when we undertook the stereospecific synthesis of the two di-*trans*-isomers of dicyclohexyl-18-crown-6 (7) from (±)-cyclohexane-*trans*-1,2-diol. Initially, we had two objectives: (i) to resolve the confused situation [8] regarding the relative configurational assignments to two isomers—now known [9] to be the two di-*cis*-isomers—of dicyclohexyl-18-crown-6 (7) and (ii) to prepare the way for the synthesis of the pure enantiomers with the *trans,anti,trans*-configuration from (+)- and (−)-cyclohexane-*trans*-1,2-diols, respectively. In the event, objective (i) has been realised [8] and objective (ii) has not been pursued by us * because of the convincing demonstration by Cram and his associates [11] in 1973 that chiral crown ethers require a high degree of chirality associated with them in order to exhibit chiral recognition in molecular complexing.

The isolation [8] of crystalline 1 : 1 complexes of the *trans,syn,trans* isomer of dicyclohexyl-18-crown-6 (7) with methyl-, t-butyl-, and benzyl-ammonium thiocyanates illustrates the potential of the 18-crown-6 constitution for complexing with primary alkylammonium cations. This potential was first recognised by Pedersen [2] and has been further investigated, extended, and exploited by Cram [12,13] more recently. It has been suggested [12,13] that binding in the complex arises from hydrogen bonds involving the three hydrogen atoms on the RNH_3^+ cation with alternate oxygen atoms on the 18-crown-6 cycle. The lone pairs of electrons on the other three oxygen atoms probably lend some additional electrostatic stabilisation to the positively charged nitrogen of the RNH_3^+ cation. Inspection of molecular models employing an N–O distance of 2.88 Å for the three N^+–H · · · O hydrogen bonds [14] indicates that the complex is of a face-to-face type as shown in Figure 1. Although this three-point binding model [11-13] provides a useful working hypothesis for the structure of the complex, the model awaits some experimental justification in the form of a published crystal structure analysis of a suitable complex. Nonetheless, the principle is established that crown ethers of appropriate dimensions will form strong complexes with primary alkylammonium cations. Cram [12] has introduced the description ' Host–Guest Chemistry ' to refer to this type of complex formation and interrelated chemical phenomena. We recall Fischer's lock and key metaphor [15] to describe the match of an enzyme with its substrate in an enzyme–substrate complex and hence have decided to apply the description ' Lock and Key Chemistry ' to our investigations on complexation–decomplexation equilibria and catalysis with crown compounds. In the present context, the lock or host refers to the crown compound and the key or guest to the primary alkylammonium cation. Finally, on the

* Whitham and his associates [10] have prepared (+)-*trans,anti,trans*-dicyclohexyl-18-crown-6 and (+)-*trans*-cyclohexyl-18-crown-6 from (+)-cyclohexane-*trans*-1,2-diol.

[5] J. F. Stoddart, W. A. Szarek, and J. K. N. Jones, *Canad. J. Chem.*, 1969, **47**, 3213.

[6] J. F. Stoddart and W. A. Szarek, *Canad. J. Chem.*, 1968, **46**, 3061; R. G. S. Ritchie, J. F. Stoddart, D. M. Vyas, and W. A. Szarek, *Carbohydrate Res.*, 1974, **32**, 279.

[7] T. B. Grindley, J. F. Stoddart, and W. A. Szarek, *J. Amer. Chem. Soc.*, 1969, **91**, 4722.

[8] J. F. Stoddart and C. M. Wheatley, *J.C.S. Chem. Comm.*, 1974, 390; I. J. Burden, A. C. Coxon, J. F. Stoddart and C. M. Wheatley, *J.C.S. Perkin I*, 1977, 220.

[9] D. E. Fenton, M. Mercer, and M. R. Truter, *Biochem. Biophys. Res. Comm.*, 1972, **48**, 10; M. R. Mercer and M. R. Truter, *J.C.S. Dalton*, 1973, 2215; N. K. Dalley, D. E. Smith, R. M. Izatt, and J. J. Christensen, *J.C.S. Chem. Comm.*, 1972, 90; N. K. Dalley, J. S. Smith, S. B. Larson, J. J. Christensen, and R. M. Izatt, *J.C.S. Chem. Comm.*, 1975, 43; N. K. Dalley, J. S. Smith, S. B. Larson, K. L. Matheson, J. J. Christensen, and R. M. Izatt, *J.C.S. Chem. Comm.*, 1975, 84; R. M. Izatt, B. L. Haymore, J. S. Bradshaw, and J. J. Christensen, *Inorg. Chem.*, 1975, **14**, 3132.

[10] R. C. Hayward, C. H. Overton, and G. H. Whitham, *J.C.S. Perkin I*, 1976, 2413.

[11] E. P. Kyba, M. G. Siegel, L. R. Sousa, G. D. Y. Sogah, and D. J. Cram, *J. Amer. Chem. Soc.*, 1973, **95**, 2691.

[12] D. J. Cram and J. M. Cram, *Science*, 1974, **183**, 803.

[13] D. J. Cram, R. C. Helgeson, L. R. Sousa, J. M. Timko, M. Newcomb, P. Moreau, F. de Jong, G. W. Gokel, D. H. Hoffman, L. A. Domeier, S. C. Peacock, K. Madan, and L. Kaplan, *Pure Appl. Chem.*, 1975, **43**, 327.

[14] C. G. Pimentel and A. L. McCellan, ' The Hydrogen Bond,' Reinhold, New York, 1960, p. 289.

[15] E. Fischer, *Ber.*, 1894, **27**, 2985.

subject of nomenclature, Lehn [16] has suggested the use of the term ' cryptand ' to describe all types of cavity-containing ligands. On complex formation, such ligands become [17] ' cryptates.' The situation is summarised in Figure 1.

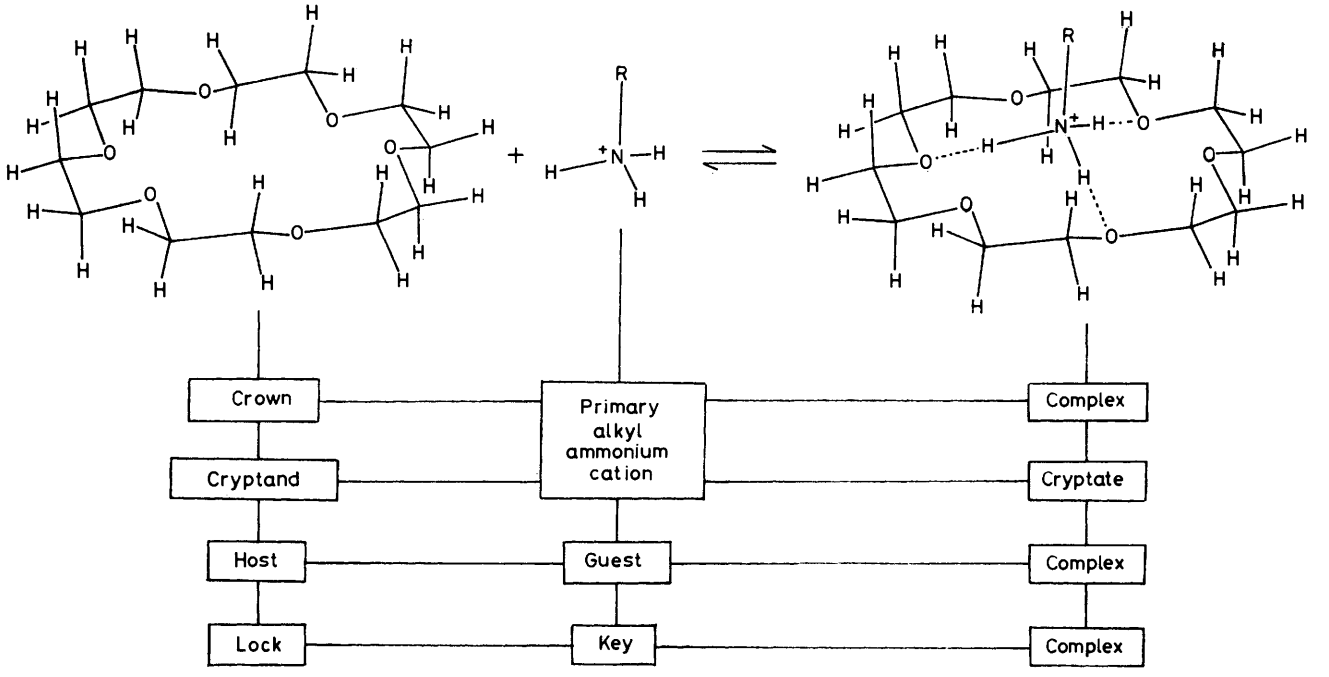


FIGURE 1 Complex formation and nomenclature

Our long-term objective is to build enzyme analogues around crown compounds as locks. The binding of primary alkylammonium cations as keys is only one requirement in the design of such enzyme analogues. It is also essential to incorporate chirality and functionality into the locks in order to achieve chiral recognition (i) as a ground-state phenomenon in complexation–decomplexation equilibria involving racemic keys (*i.e.* enantiomeric differentiation and ultimately resolution of racemic substrates) and (ii) as a transition-state phenomenon in chemical reactions involving both achiral and chiral substrates (*i.e.* stereoselective, and ultimately stereospecific, catalysis). Binding has been discussed already. Now let us consider how we have met the requirements for chirality and functionality in our locks. In fact, we have appealed to nature directly on both scores and in so doing have killed two birds with one stone. Not only are carbohydrates and their derivatives rich in substituted bismethylenedioxy units for incorporation into the 18-crown-6 constitution; they also provide a relatively inexpensive source of chirality and are usually well endowed with functionality. Our first thoughts, emanating from our interest [8] in cyclohexane-*trans*-1,2-diol as a precursor of crown compounds, were to utilise suitably substituted glucose, galactose, and mannose residues (*e.g.* the 4,6-*O*-benzylidene derivatives of their methyl α-glycosides) in the synthesis of chiral asymmetric 18-crown-6 locks. Indeed, this synthetic goal has been achieved and the results have been reported [18] briefly. However, the attractions of selecting carbohydrates with C_2 symmetry are considerable because of the relative ease this introduces into the syntheses of chiral symmetric 18-crown-6 locks. While both the tetritols and hexitols amongst the common alditols have the required constitutional symmetry, only threitol, mannitol, and iditol fulfil [19] the C_2 symmetry requirement. In this paper we describe the syntheses and evaluation of a range of chiral symmetric 18-crown-6 locks incorporating (i) L-threitol (which is derived from L-tartaric acid) and (ii) D-mannitol (which is readily available). This investigation has been the subject of two communications.[20] The incorporation of L-iditol, obtainable on reduction [21] of L-sorbose, into crown compounds has also been achieved recently and the results have been reported [22] briefly.

EXPERIMENTAL

The general methods have been described elsewhere.[8,23]

(4R,5R)-*Diethyl 2-Phenyl-1,3-dioxolan-4,5-dicarboxylate* (*Diethyl 2,3-O-benzylidene-L-tartrate*), L-(9).—Diethyl L-tartrate (250 g) was treated with benzaldehyde (250 g) and fused zinc chloride (250 g) at room temperature for 20 h. Extraction with chloroform afforded a yellowish oil

[16] B. Kaempf, S. Raynal, A. Collet, F. Schué, S. Boileau, and J.-M. Lehn, *Angew. Chem. Internat. Edn.*, 1974, **13**, 611.
[17] J.-M. Lehn, *Structure and Bonding*, 1973, **16**, 1.
[18] D. A. Laidler and J. F. Stoddart, *Carbohydrate Res.*, in the press.
[19] J. F. Stoddart, ' Stereochemistry of Carbohydrates,' Wiley–Interscience, New York, 1971, pp. 19—23.
[20] W. D. Curtis, D. A. Laidler, J. F. Stoddart, and G. H. Jones, *J.C.S. Chem. Comm.*, 1975, 833, 835.
[21] W. G. M. Jones and L. F. Wiggins, *J. Chem. Soc.*, 1944, 363.
[22] W. D. Curtis, D. A. Laidler, J. F. Stoddart, J. B. Wolstenholme, and G. H. Jones, *Carbohydrate Res.*, in the press.
[23] A. C. Coxon and J. F. Stoddart, *J.C.S. Chem. Comm.*, 1974, 537; *Carbohydrate Res.*, 1975, **44**, C1; *J.C.S. Perkin I*, 1977, 767.

which crystallised. Recrystallisation from ethanol–water gave diethyl 2,3-*O*-benzylidene-L-tartrate, L-(9) (122 g, 35%), m.p. 45° (lit.,[24] 48—49°), $[\alpha]_D$ −33.8° (*c* 1.5 in $CHCl_3$) [lit.,[24] −40.0° (*c* 1.0 in Et_2O)] (Found: C, 61.3; H, 6.3%; $M^{+\cdot}$, 294. Calc. for $C_{15}H_{18}O_6$: C, 61.2; H, 6.2%; *M*, 294), τ ($CDCl_3$) 2.32—2.80 (5 H, m, aromatic), 3.86 (1 H, s, PhC*H*), 5.09 and 5.19 (2 H, AB, J_{AB} 4 Hz, other CH), 5.70 and 5.76 (2 × 2 H, 2 × q, *J* 7.5 Hz each, 2 × $CO_2{\cdot}CH_2{\cdot}CH_3$), and 8.68 and 8.73 (2 × 3 H, 2 × t, *J* 7.5 Hz each, 2 × $CO_2{\cdot}CH_2{\cdot}CH_3$).

(4S,5S)-4,5-*Bishydroxymethyl*-2-*phenyl*-1,3-*dioxolan* (2,3-O-*Benzylidene*-L-*threitol*), L-(10).—The diester L-(9) (64 g), dissolved in ether (200 ml), was added dropwise with stirring to lithium aluminium hydride (16 g) in ether during 1 h. The mixture was heated under reflux for 1 h, then cooled, and the excess of hydride was destroyed by addition of aqueous 15% sodium hydroxide (60 ml). After filtration, the ethereal solution afforded a colourless oil (10.5 g) which crystallised. Soxhlet extraction of the inorganic residues with ether for 3 days yielded more (31.6 g) crystalline product (total yield 42.1 g, 92%). A small portion of the crude product was recrystallised from ether to afford 2,3-O-*benzylidene*-L-*threitol*, L-(10), m.p. 69—70°, $[\alpha]_D$ −11.4° (*c* 2.1 in CH_3OH) (Found: C, 62.7; H, 6.6%; $M^{+\cdot}$, 210. $C_{11}H_{14}O_4$ requires C, 62.9; H, 6.7%; *M*, 210), τ ($CDCl_3$) 2.50—2.85 (5 H, m, aromatic), 4.14 (1 H, s, PhC*H*), and 5.80—6.45 (8 H, m, CH_2, other CH, and OH).

(4S,5S)-4,5-*Bis*(*benzyloxymethyl*)-2-*phenyl*-1,3-*dioxolan* (1,4-*Di*-O-*benzyl*-2,3-O-*benzylidene*-L-*threitol*), L-(11).—The diol L-(10) (15 g) was treated with benzyl bromide (71.5 g) and potassium hydroxide (30 g) in dry toluene (150 ml) at 80 °C for 18 h. After cooling and washing with water, concentration of the toluene solution afforded a yellowish oil (26.8 g, 96%), $M^{+\cdot}$ 390, τ ($CDCl_3$) 3.32—2.74 (15 H, m, aromatic), 4.04 (1 H, s, PhC*H*), 5.40—5.45 (4 H, m, PhCH_2), 5.60—5.91 (2 H, m, other CH), and 6.10—6.50 (4 H, m, other CH_2), which was used in the next step without further purification.

(4S,5S)-4,5-*Dihydroxy*-1,8-*diphenyl*-2,7-*dioxaoctane* (1,4-*Di*-O-*benzyl*-L-*threitol*), L-(12).—The crude dibenzyl ether L-(11) (57 g) was heated under reflux in methanol–water (4 : 1; 250 ml) for 1 h in the presence of Zeo-Karb 325 resin (30 g) (H^+ form). The resin was then filtered off and the filtrate concentrated to give a brownish oil (45 g), which was chromatographed on silica gel (ether as eluant). The crude crystalline product was recrystallised from chloroform–light petroleum (b.p. 60—80 °C) to afford 1,4-*di*-O-*benzyl*-L-*threitol*, L-(12) (17.4 g, 38%), m.p. 66°, $[\alpha]_D$ −5.5° (*c* 5.0 in $CHCl_3$) (Found: C, 71.7; H, 7.4%; $M^{+\cdot}$, 302. $C_{18}H_{22}O_4$ requires C, 71.5; H, 7.3%; *M*, 302), τ ($CDCl_3$) 2.68 (10 H, s, aromatic), 5.46 (4 H, s, PhCH_2), 6.02—6.26 (2 H, m, CH), 6.30—6.48 (4 H, m, other CH_2), and 7.15br (2 H, s, OH).

2,2′-*Oxybis*(*ethyl tosylate*) (13).—Diethylene glycol (106 g) was tosylated with toluene-*p*-sulphonyl chloride (420 g) in dry pyridine (500 ml) as described previously [8,23] to afford the ditosylate (13) (202 g, 50%), m.p. 96° (lit.,[25] 98°).

(2S,3S)-2,3-*Bis*(*benzyloxymethyl*)-1,4,7-*trioxacyclononane* (1,4-*Di*-O-*benzyl*-2,3-*oxydiethylene*-L-*threitol*), L-(14), *and* (2S,3S,11S,12S)-2,3,11,12-*tetrakis*(*benzyloxymethyl*)-1,4,7,10,13,16-*hexaoxacyclo-octadecane* (1,1′,4,4′-*tetra*-O-*benzyl*-2,2′:3,3′-*bis*-O-*oxydiethylenedi*-L-*threitol*), LL-(15).—The diol L-(12) (2.0 g) was dissolved in dimethyl sulphoxide (25 ml) and sodium hydride (0.64 g) was added. The mixture was stirred under nitrogen at room temperature for 1 h before the temperature was raised to 40 °C. A solution of the ditosylate (13) (3.2 g) in dimethyl sulphoxide (25 ml) was added and the mixture was stirred under nitrogen for 60 h. On cooling, the excess of hydride was destroyed with water (50 ml). Extraction with chloroform yielded a crude oil (2.1 g), which was chromatographed on silica gel (100 g) (ethyl acetate as eluant) to afford a mixture of two compounds. These were separated by preparative t.l.c. on silica gel (ethyl acetate as eluant). The faster moving component was isolated as a colourless oil which crystallised to give the 9-crown-3 derivative L-(14) (81 mg, 3%), m.p. *ca.* 40°, $[\alpha]_D$ +19.3° (*c* 5.8 in $CHCl_3$), $M^{+\cdot}$ 372, τ ($CDCl_3$) 2.70 (10 H, s, aromatic), 5.46 and 5.60 (4 H, AB system, J_{AB} 11.5 Hz, PhCH_2), and 5.82—6.72 (14 H, m, other CH_2 and CH). The slower moving component was isolated as an oil and characterised as the 18-crown-6 derivative LL-(15) (274 mg, 11%), $[\alpha]_D$ +5.8° (*c* 3.5 in $CHCl_3$), $M^{+\cdot}$ 744, τ ($CDCl_3$) 2.70 (20 H, s, aromatic), 5.51 (8 H, s, PhCH_2), and 6.08—6.64 (28 H, m, other CH_2 and CH).

(2S,3S,11S,12S)-2,3,11,12-*Tetrakis*(*hydroxymethyl*)-1,4,7,10,13,16-*hexaoxacyclo-octadecane* (2,2′:3,3′-*Bis*-O-*oxydiethylenedi*-L-*threitol*), LL-(16).—The tetrabenzyl ether LL-(15) (660 mg) was hydrogenolysed at atmospheric pressure in methanol (30 ml) over 5% palladium–carbon (150 mg). After filtration, the methanolic solution was concentrated to give an oil (260 mg, 65%) which was the tetraol LL-(16), $M^{+\cdot}$ 384, τ [$CDCl_3$–$(CD_3)_2CO$] 5.90—6.50 (m, all protons).

(2S,3S,11S,12S)-2,3,11,12-*Tetrakis*(*acetoxymethyl*)-1,4,7,10,13,16-*hexaoxacyclo-octadecane* (1,1′,4,4′-*Tetra*-O-*acetyl*-2,2′:3,3′-*bis*-O-*oxydiethylenedi*-L-*threitol*, LL-(17).—The tetraol LL-(16) (250 mg) was acetylated with acetic anhydride (5 ml) and pyridine (20 ml) to give the *tetra-acetate* LL-(17) (322 mg, 89%), m.p. 81°, $[\alpha]_D$ −20.5° (*c* 5.0 in $CHCl_3$) (Found: C, 52.1; H, 7.1%; $M^{+\cdot}$, 552. $C_{24}H_{40}O_{14}$ requires C, 52.2; H, 7.3%; *M*, 552), τ ($CDCl_3$) 5.58—6.02 (8 H, m, AB of ABX, J_{AB} 11.5, J_{AX} 3.5, J_{BX} 5.5 Hz, 4 × CH_2·OAc), 6.04—6.48 (20 H, m including X of ABX, CH and other CH_2), and 7.94 (12 H, s, 4 × $CH_2{\cdot}OAc$).

(2S,3S,11S,12S)-2,3,11,12-*Tetrakis*(*triphenylmethoxymethyl*)-1,4,7,10,13,16-*hexaoxacyclo-octadecane* (1,1′,4,4′-*Tetra*-O-*triphenylmethyl*-2,2′:3,3′-*bis*-O-*oxydiethylenedi*-L-*threitol*), LL-(18).—A solution of trityl chloride (600 mg) in pyridine (2 ml) was added dropwise with stirring to the tetraol LL-(16) dissolved in pyridine (5 ml). The mixture was stirred under nitrogen for 3 days and then heated to 100 °C for 1 h. On cooling, the mixture was poured on to ice–water. Filtration removed trityl chloride and extraction of the filtrate with chloroform afforded the tetratrityl ether LL-(18) (510 mg, 73%), $M^{+\cdot}$ 1 352, τ ($CDCl_3$) 2.40—3.06 (60 H, m, aromatic) and 5.78—7.40 (28 H, m, CH_2 and CH).

1,2:5,6-*Di*-O-*isopropylidene*-D-*mannitol*, D-(23).—The reaction of D-mannitol (85 g) with dry acetone (675 ml) and zinc chloride (135 g) was carried out as described by Baer [26] to give di-*O*-isopropylidenemannitol, D-(23) (38.1 g, 31%), m.p. 118° (lit.,[26] 117—119°), τ ($CDCl_3$) 5.70—6.20 (6 H, m, 2 × H-1, H-2, H-5, and 2 × H-6), 6.27br (2 H, t, J_{HCOH} 6.0 Hz, H-3 and H-4, collapses to d after shaking with D_2O), 6.92 (2 H, d, J_{HCOH} 6.0 Hz, 2 × OH, disappears on shaking with D_2O), and 8.59 and 8.65 (2 × 6 H, 2 × s, 4 × CH_3).

[24] E. Ehrlenmeyer, *Biochem. Z.*, 1915, **68**, 351.
[25] J. Dale and P. O. Kristiansen, *Acta Chem. Scand.*, 1972, **26**, 1471.
[26] E. Baer, *J. Amer. Chem. Soc.* 1945, **67**, 338; see also G. Kohan and G. Just, *Synthesis*, 1974, 192.

3-O-*Allyl*-1,2:5,6-*di*-O-*isopropylidene*-D-*mannitol*, D-(24), *and* 3,4-*Di*-O-*allyl*-1,2:5,6-*di*-O-*isopropylidene*-D-*mannitol*, D-(25).—Di-*O*-isopropylidenemannitol, D-(23) (20 g), was stirred with powdered potassium hydroxide (18.6 g) and freshly distilled allyl bromide (26 ml) in dry toluene (450 ml) at 60—65 °C for 24 h. On cooling, the mixture was washed with water, dried (Na_2SO_4), and concentrated to give an oil which was shown by t.l.c. on silica gel (chloroform as eluant) to be a mixture of two components. Column chromatography on silica gel (800 g) and elution with chloroform afforded the faster moving component, the *diallyl ether* D-(25) (11.7 g, 45%), $[\alpha]_D$ +15° (*c* 3.0 in $CHCl_3$) (Found: C, 62.9; H, 8.8%; $M^{+\cdot}$, 342. $C_{18}H_{30}O_6$ requires C, 63.1; H, 8.8%; *M*, 342), τ ($CDCl_3$) 3.90—4.32 (2 H, m, 2 × $CH_2{\cdot}CH{:}CH_2$), 4.62—4.97 (4 H, m, 2 × $CH_2{\cdot}CH{:}CH_2$), 5.68—6.20 (10 H, m, 2 × H-1, H-2, H-5, 2 × H-6, and 2 × $CH_2{\cdot}CH{:}CH_2$), 6.40 (2 H, d, *J* 5 Hz, H-3 and H-4), and 8.61 and 8.67 (2 × 6 H, 2 × s, 4 × CH_3). This compound has been reported previously [27] but the only experimental data given was the b.p. (lit.,[27] 110—118° at 1 mmHg). The slower moving component, isolated as an oil as well, was the monoallyl ether D-(24) (8.8 g, 38%), $M^{+\cdot}$ 302, τ ($CDCl_3$) 3.86—4.29 (1 H, m, $CH_2{\cdot}CH{=}CH_2$), 4.60—4.98 (2 H, m, $CH_2{\cdot}CH{:}CH_2$), 5.60—6.32 (9 H, m, 2 × H-1, H-2, H-3, H-5, 2 × H-6, and $CH_2{\cdot}CH{:}CH_2$), 6.32—6.60br (1 H, m, H-4, sharpens upon shaking with D_2O), 7.63br (1 H, s, OH, disappears on shaking with D_2O), and 8.59 and 8.65 (2 × 6 H, 2 × s, 4 × CH_3).

3,4-*Di*-O-*allyl*-1,2:5,6-*di*-O-*isopropylidene*-D-*mannitol*, D-(25).—(*a*) The monoallyl ether D-(24) (4.86 g) was heated under reflux in dry toluene (100 ml) with potassium hydroxide (3.2 g) and allyl bromide (7.8 g) for 60 h. On cooling, the mixture was treated as described above to afford an oily product, the diallyl ether D-(25) (5.41 g, 98%).

(*b*) Di-*O*-isopropylidenemannitol, D-(23) (26 g), was heated overnight in dry toluene (250 ml) at 85—90 °C with potassium hydroxide (20 g) and allyl bromide (33.3 ml). On cooling, the mixture was treated as described above to afford a yellowish oil, the diallyl ether D-(25) (31.1 g, 91%).

3,4-*Bis*-O-(2-*hydroxyethyl*)-1,2:5,6-*di*-O-*isopropylidene*-D-*mannitol*, D-(26).—The diallyl ether D-(25) (29.5 g) was dissolved in methanol (600 ml) and stirred at −78 °C while ozone was passed through the solution until an aqueous potassium iodide trap became dark as a result of iodine formation in the presence of excess of ozone. Excess of ozone in the methanolic solution was removed by flushing with oxygen for 30 min. Then, a solution of sodium borohydride (13.6 g) in methanol–water (1 : 1, 200 ml) was added dropwise to the stirred mixture maintained below −21 °C. The mixture was stirred overnight at room temperature and concentrated to one-third of its original volume, and then water (100 ml) was added. The predominantly aqueous solution was extracted with chloroform several times and the combined extracts were dried ($MgSO_4$), filtered, and concentrated to give an oil. This was subjected to column chromatography on silica gel. Elution with ether removed impurities. Elution with ether–methanol (19 : 1) afforded a crystalline compound which was recrystallised from ether–light petroleum (b.p. 60—80 °C) to give the pure ' half-crown ' *diol* D-(26) (4.27 g, 14%), m.p. 76—77°, $[\alpha]_D$ +14.8° (*c* 2.1 in $CHCl_3$) (Found: C, 54.8; H, 8.6%; $M^{+\cdot}$ − 15, 335. $C_{16}H_{30}O_8$ requires C, 54.8; H, 8.6%; *M*, 350), τ ($CDCl_3$) 5.58—6.54 (16 H, m, all CH and CH_2), 6.74br (2 H, s, 2 × OH), and 8.58 and 8.65 (2 × 6 H, 2 × s, 4 × CH_3). In subsequent preparations the yield of D-(26) was increased to 82% by omission of the chromatographic step.

1,2:5,6-*Di*-O-*isopropylidene*-3,4-*bis*-O-(2-p-*tolylsulphonyloxyethyl*)-D-*mannitol*, D-(27).—The ' half-crown ' diol D-(26) (20 g) was stirred in dry pyridine (170 ml) cooled in an ice-bath. Toluene-*p*-sulphonyl chloride (24 g) was dissolved in dry pyridine (170 ml) and added to the diol solution during 2.5 h. The mixture was stirred overnight and then poured on to ice (600 g). A product precipitated from solution. It was filtered off, dried, and recrystallised from methanol to afford prisms of the ' half-crown ' *ditosylate* D-(27), m.p. 91—94°, $[\alpha]_D$ +12.1° (*c* 0.7 in $CHCl_3$) (Found: C, 54.8; H, 6.6%; $M^{+\cdot}$, 658. $C_{30}H_{42}O_{12}S_2$ requires C, 54.7; H, 6.6%; *M*, 658), τ ($CDCl_3$) 2.12—2.77 (8 H, 2 × AA'BB', aromatic), 5.79—6.32 (14 H, m, H-2, H-5, and all CH_2), 6.49 (2 H, d, *J* 5 Hz, H-3 and H-4), 7.58 (6 H, s 2 × $C_6H_4CH_3$), and 8.16 and 8.72 (2 × 6 H, 2 × s, 4 × CH_3).

1,2:1′,2′:5,6:5′,6′-*Tetra*-O-*isopropylidene*-3,3′:4,4′-*bis*-O-*oxydiethylenedi*-D-*mannitol*, DD-(28).—The ' half-crown ' diol D-(26) (2.0 g) was stirred in dimethyl sulphoxide (30 ml) under nitrogen, sodium hydride (0.55 g) was added, and the temperature was raised to 50 °C. A solution of the ' half-crown ' ditosylate D-(27) (4.16 g) in dimethyl sulphoxide (30 ml) was added dropwise. The mixture was stirred at 50 °C for 48 h then allowed to cool, and water was added carefully. The aqueous solution was extracted with chloroform (4 × 100 ml) and the combined extracts were washed with water, dried ($MgSO_4$), filtered, and concentrated to an oily residue which was chromatographed on silica gel. Elution with ether–methanol (24 : 1) gave the pure 18-*crown*-6 *derivative* DD-(28) (270 mg, 14%), $[\alpha]_D$ +7.6° (*c* 0.59 in chloroform) (Found: C, 57.8; H, 8.5%; $M^{+\cdot}$, 664. $C_{32}H_{56}O_{14}$ requires C, 58.3; H, 8.7%; *M*, 664), $\nu_{max.}$ (liquid) 2 990, 2 940, 2 890, 1 380, 1 370, 1 250, 1 220, 1 065, and 850 cm^{-1}, τ ($CDCl_3$) 5.60—6.60 (32 H, m, all CH and CH_2), and 8.61 and 8.66 (2 × 12 H, 2 × s, 8 × CH_3).

1,2:5,6-*Di*-O-*isopropylidene*-3,4-O-*oxydiethylene*-D-*mannitol*, D-(29), 1,2:1′,2′:5,6:5′,6′-*Tetra*-O-*isopropylidene*-3,3′:4,4′-*bis*-O-*oxydiethylenedi*-D-*mannitol*, DD-(28), *and* 1,2:1′,2′:1″,2″:5,6:5′,6′: 5″,6″-*Hexa*-O-*isopropylidene*-3,3′,3″:4,4′,4″-*tris*-O-*oxydiethylenetri*-D-*mannitol*, DDD-(30).—Di-isopropylidenemannitol, D-(23) (22 g), was stirred in dimethyl sulphoxide (370 ml), sodium hydride (8.0 g), and the ditosylate (13) (38 g) were added, and the temperature was raised to 50 °C. The mixture was stirred for 48 h, allowed to cool, and poured into water (1 l). The aqueous solution was extracted with chloroform and the combined extracts were washed with water, dried ($MgSO_4$), filtered, and concentrated to a brownish oil (33 g), which was chromatographed on alumina (1.5 kg; Laporte type H deactivated with 4% water). Elution with ether gave the pure 9-crown-3 derivative D-(29) (3.5 g, 13%) as an oil, $M^{+\cdot}$ 332. Further elution with ether gave the pure 18-crown-6 derivative DD-(28) (6.7 g, 24%) as an oil, and also the pure 27-crown-9 derivative DDD-(30) (2.7 g, 10%) as an oil, $M^{+\cdot}$ 996, $\nu_{max.}$ (liquid) 2 990, 2 940, 2 890, 1 380, 1 370, 1 250, 1 065, and 850 cm^{-1}.

3,3′:4,4′-*Bis*-O-*oxydiethylenedi*-D-*mannitol*, DD-(31).—The tetra-*O*-isopropylidene derivative DD-(28) (1.2 g) was dissolved in acetone–water (3 : 2; 150 ml) and refluxed with Zeo-Karb 325 resin (1.0 g) (H^+ form). The resin was filtered off after 24 h and the solution was concentrated to give an oil which crystallised to afford the *octaol* DD-(31)

[27] A. N. Wrigley and E. Yanovsky, *J. Amer. Chem. Soc.*, 1948, **70**, 2194.

(820 mg, 90%), m.p. 69—71°, $[\alpha]_D$ +24.5° (*c* 2.23 in CH_3OH) (Found: C, 48.0; H, 8.0%; $M^{+\cdot}$ + 1, 505. $C_{20}H_{40}O_{14}$ requires C, 47.6; H, 8.0%; *M*, 504), τ (CD_3OD) 5.90—6.62 (all protons, m with two sharp s evident at 6.21 and 6.37).

1,1′,2,2′,5,5′,6,6′-*Octa*-O-*acetyl*-3,3′:4,4′-*bis*-O-*oxydiethylenedi*-D-*mannitol*, DD-(32).—The octaol DD-(31) (460 mg) was acetylated with acetic anhydride (20 ml) in pyridine (50 ml) to give the *octa-acetate* DD-(32) (729 mg, 95%), $[\alpha]_D$ +48.4° (*c* 0.57 in $CHCl_3$) (Found: C, 51.3; H, 6.8%; $M^{+\cdot}$, 840. $C_{36}H_{56}O_{22}$ requires C, 51.4; H, 6.7%; *M*, 840), $\nu_{max.}$ (liquid) 2 920, 1 745, 1 375, 1 225, 1 100, and 1 045 cm^{-1}, τ ($CDCl_3$) 4.64—4.86 (4 H, m, X of ABX, 4 × AcO·C*H*), 5.28—5.82 (8 H, AB of ABX, J_{AB} 12.5, J_{AX} 3.0, J_{BX} 6.5 Hz, 4 × AcO·CH_2), 6.12—6.54 (20 H, m, other CH and CH_2), and 7.92 and 7.94 (2 × 12 H, 2 × s, 8 × Ac).

1,1′,2,2′,5,5′,6,6′-*Octa*-O-*methyl*-3,3′:4,4′-*bis*-O-*oxydiethylenedi*-D-*mannitol*, DD-(33).—The octaol DD-(31) (164 mg) was methylated with methyl iodide in 1,2-dimethoxyethane with sodium hydride as base to give the octamethyl ether DD-(33) (112.5 mg, 56%), $[\alpha]_D$ +4.7° (*c* 1.09 in $CHCl_3$), $M^{+\cdot}$ 616, τ ($CDCl_3$) 5.74—6.80 (all protons, m with two sharp s in evidence at 6.58 and 6.60 for 8 × OCH_3).

(2R,3R,11R,12R)-2,3 11,12-*Tetrakis*(*acetoxymethyl*)-1,4,7,10,13,16-*hexaoxacyclo-octadecane* (1,1′,4,4′-*Tetra*-O-*acetyl*-2,2′:3,3′-*bis*-O-*oxydiethylenedi*-D-*threitol*), DD-(17).—The octaol DD-(31) (2.23 g) was dissolved in water (100 ml) and sodium periodate (3.98 g) in water (100 ml) was added. The mixture was kept at room temperature for 20 h. After the excess of periodate and iodate had been precipitated with aqueous 10% barium chloride, sodium borohydride (2.0 g) was added to the filtered solution and the mixture was kept at room temperature for 5 h. The solution was then acidified with glacial acetic acid and concentrated. The residue which was acetylated with acetic anhydride (30 ml) in pyridine (124 ml) to yield a brownish oil (1.6 g). This was subjected to column chromatography on alumina (70 g; Laporte type H deactivated with 2.5% water). Elution with ether–methanol gave partially hydrolysed material. This was reacetylated to give the tetra-acetate DD-(17) (690 mg, 28%), $[\alpha]_D$ +20.2° (*c* 5.0 in $CHCl_3$), $M^{+\cdot}$ 552. The ^1H n.m.r. spectrum ($CDCl_3$) was identical with that obtained for the enantiomeric tetra-acetate LL-(17).

Primary Alkylammonium Thiocyanates.—Equimolar proportions of the primary alkylammonium chloride and sodium thiocyanate were dissolved in water. The aqueous solution was concentrated and the residue was extracted with ethanol to afford the crude thiocyanate. In most cases, the thiocyanates were crystalline and were recrystallised from appropriate solvents to give the pure *primary alkylammonium thiocyanates* (Table 1).

Stability Constant Measurements.—(a) *Metal cationic complexes*. The concentration stability constants for the formation of 1 : 1 polyether–cationic complexes of the lock DD-(28) with Na^+, K^+, and Rb^+ in methanolic solution were measured potentiometrically with ion selective electrodes [(i) a Corning NAS 11—18 (cat. no. 476210) sodium ion electrode for Na^+ and (ii) a Corning monovalent cation electrode (cat. no. 476220) for K^+ and Rb^+]. The stability constants, defined by the equilibrium constants (K'/l mol^{-1}) for complex formation according to equation (1), were obtained by a modification [8] of the method

$$L + M^+ n\text{MeOH} \overset{K'}{\rightleftharpoons} LM^+ + n\text{MeOH} \qquad (1)$$

described by Frensdorff,[28] assuming only 1 : 1 complex formation between the lock, L, and the metal cation, M^+.

(b) *Primary alkylammonium cationic complexes*. Stability constants, defined as equilibrium constants (K_a/l mol^{-1}) for the equilibrium (2), were measured in $CDCl_3$ by an ^1H n.m.r. spectroscopic method.[29] In a typical determination, a

$$RNH_3{}^+SCN^- + \text{lock} \overset{K_a}{\rightleftharpoons} RNH_3(\text{lock})^+SCN^- \qquad (2)$$

0.14M-solution of the lock in $CDCl_3$ (0.6 ml) was shaken at room temperature with a 1.0M-solution of the salt $RNH_3{}^+SCN^-$ in D_2O (0.3 ml). The layers were separated and the ^1H n.m.r. spectrum of the $CDCl_3$ layer was recorded. The relative concentrations of the key and lock were determined by integration of suitable signals.

Chiral Recognition.—An n.m.r. spectroscopic method [30,31] was used to identify the diastereoisomeric complexes and obtain their relative proportions at equilibrium in the $CDCl_3$ layer after partitioning of (+)-(*R*)-, (−)-(*S*)- and (±)-(*RS*)-α-phenylethylamine [(+)-(*R*)-(8), (−)-(*S*)-(8), and (±)-(*RS*)-(8)] hexafluorophosphate salts between D_2O and $CDCl_3$ in the presence of chiral locks. In all cases three experiments were performed in which the key was partitioned between D_2O and $CDCl_3$ in the presence of the chiral lock. In type (i) experiments, 0.126 mmol of lock dissolved in 0.7 ml of $CDCl_3$ was shaken for 1 min at room temperature with 0.8 ml of D_2O containing 0.745 mmol of (±)-(*RS*)-(8),HCl and 0.745 mmol of $LiPF_6$. The ^1H n.m.r. and/or broad-band decoupled ^{13}C n.m.r. spectrum were/was then recorded and integrated. In experiments (ii) and (iii), (+)-(*R*)-(8),HCl and (−)-(*S*)-(8),HCl, respectively, replaced (±)-(*RS*)-(8),HCl and thus permitted configurational assignments to be made to the diastereoisomeric complexes. Although diastereoisomeric complex formation is accompanied by significant changes in the n.m.r. spectra of the locks, it manifests itself most noticeably in small chemical shift differences between originally coincident signals arising from the previously enantiomeric keys. In type (i) experiments two doublets were observed in some cases in the ^1H n.m.r. spectra for the methyl groups of the keys in the diastereoisomeric complexes formed between the chiral locks and the enantiomeric keys. The molar ratios of key to lock were obtained directly from integration and the enantiomeric differentiations [*i.e.* (*R*) : (*S*) ratios] were deduced by (i) integration and (ii) line-shape analysis on expanded spectra (50 Hz sweep width) using a computer program suitable for exchange between two sites which experience independent coupling to two other sites.[32] On the assumption that no exchange occurs between the two sites (the rate constant for site exchange is set equal to zero), the chemical shifts, coupling constants, half-height peak widths, and relative populations are varied to give the best match with the experimental spectrum. The relative populations of the two sites give the (*R*) : (*S*) ratios.

[28] H. K. Frensdorff, *J. Amer. Chem. Soc.*, 1971, **93**, 600.
[29] J. M. Timko, R. C. Helgeson, M. Newcomb, G. W. Gokel, and D. J. Cram, *J. Amer. Chem. Soc.*, 1974, **96**, 7097.
[30] E. P. Kyba, K. Koga, L. R. Sousa, M. G. Siegel, and D. J. Cram, *J. Amer. Chem. Soc.*, 1973, **95**, 2692.
[31] C. M. Deber and E. R. Blout, *J. Amer. Chem. Soc.*, 1974, **96**, 7566; B. Bartman, C. M. Deber, and E. R. Blout, *ibid.*, 1977, **99**, 1028.
[32] I. O. Sutherland, *Ann. Rev. NMR Spectroscopy*, 1971, **4**, 71; G. Binsch, *Topics Stereochem.*, 1968, **3**, 97.

RESULTS AND DISCUSSION

Preparation of the Keys.—The primary alkylammonium thiocyanates listed in Table 1 were prepared by disproportionation of the corresponding chlorides with sodium thiocyanate. They were used (see Table 2) in an ^{1}H n.m.r. spectroscopic method [29] for measuring stability constants for complexation of primary alkylammonium keys with a range of 18-crown-6 locks.

TABLE 1

Primary alkylammonium thiocyanates

Salt	Recryst. solvent(s)	M.p. (°C)	Required (%) C	H	N	S	Found (%) C	H	N	S
$MeNH_3^+SCN^-$	EtOH–Et_2O	67—68	26.7	6.7	31.1	35.6	26.6	6.6	30.9	35.6
$Bu^tNH_3^+SCN^-$	EtOAc–LP [a]	122—123	45.4	9.2	21.2	24.3	45.3	9.3	21.3	24.2
$PhCH_2NH_3^+SCN^-$	EtOAc	97	57.8	6.1	16.9	19.3	58.0	6.2	17.2	19.0
(*R*)-$PhCHMeNH_3^+SCN^-$		(Oil) [b]								
(*S*)-$PhCHMeNH_3^+SCN^-$		65—66 [b]								
(*RS*)-$PhCHMeNH_3^+SCN^-$		50—53	60.0	6.7	15.5	17.8	59.8	6.9	15.3	17.8

[a] Light petroleum (b.p. 60—80 °C). [b] ^{1}H N.m.r. spectra in CD_3OD identical with that for (*RS*)-$PhCHMeNH_3^+SCN^-$ in CD_3OD.

TABLE 2

Stability constants (K_a/l mol^{-1}) and derived free energy differences ($\Delta G°$/kcal mol^{-1}) for complexation of primary alkylammonium keys with selected locks

Lock	Key	K_a [a]	$\Delta G°$
LL-(15)	$Bu^tNH_3^+SCN^-$	2.0×10^4	5.8
LL-(17)	$Bu^tNH_3^+SCN^-$	1.7×10^2	3.0
LL-(18)	$Bu^tNH_3^+SCN^-$	4.6×10^3	5.0
DD-(28)	$Bu^tNH_3^+SCN^-$	<30	<2.0
	$PhCH_2NH_3^+SCN^-$	2.1×10^5	7.3
DD-(32)	$Bu^tNH_3^+SCN^-$	<30	<2.0
(34) [b]	$Bu^tNH_3^+SCN^-$	7.5×10^5 [c]	8.0

[a] Determined at room temperature. [b] From ref. 29. [c] Determined at 24 °C.

The optically pure enantiomers and the racemic modification of α-phenylethylamine (8) were converted into the corresponding hydrochlorides for chiral recognition experiments (see Table 3) with selected chiral locks. This amine was chosen because it contains large (L), medium (M), and small (S) ligands attached to its chiral centre and hence the degree of chirality associated with its ammonium salts is high.

TABLE 3

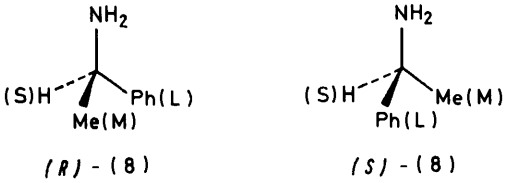
^{1}H N.m.r. spectroscopic data for the $CDCl_3$ layer in chiral recognition experiments on locks LL-(15), LL-(17), LL-(18), DD-(28), DD-(32), and DD-(33) with keys (*R*)-(8),HPF_6, (*S*)-(8),HPF_6, and (*RS*)-(8),HPF_6

Lock [a]	τ (*J*/Hz) (*R*)-Key-[Me]	τ (*J*/Hz) (*S*)-Key-[Me]	[Key]/[Lock] [b]	Enantiomeric differentiation (*R*)-Key : (*S*)-Key
LL-(15)	8.53 (6.8)	8.56 (6.8)	1.0	50 : 50 [d]
LL-(18) [c]	8.72 (6.6)	8.75 (6.6)	1.0	40 : 60 [d]
DD-(28)	8.38 (7.0)	8.33 (7.0)	1.3	62 : 38 [d]
DD-(33)	8.36 (7.0)	8.34 (7.0)	1.4	50 : 50 [d]

[a] Locks LL-(17) and DD-(32) exhibited insufficient splittings between the methyl doublets of the racemic keys to permit reliable calculations of the enantiomeric differentiation. [b] The key to lock ratios for LL-(17) and DD-(32) were 0.9 and 1.7 : 1, respectively. [c] ^{1}H N.m.r. spectrum recorded at 70 °C in a sealed tube in order to obtain better resolution. [d] Error of ±3.

Synthesis of the Locks.—We have utilised L-tartaric acid and D-mannitol separately as starting materials in two independent synthetic schemes to prepare chiral 18-crown-6 locks.

Diethyl L-tartrate was converted into its *O*-benzylidene derivative L-(9),[24] which was reduced to the diol L-(10) in good yield with lithium aluminium hydride. Subsequent benzylation of L-(10) afforded the dibenzyl ether L-(11) in almost quantitative yield. During acid-catalysed hydrolysis of the 1,3-dioxolan ring in L-(11) to give 1,4-di-*O*-benzyl-L-threitol, L-(12), some cleavage of the benzyl ether linkages also occurred and hence the yield of L-(12) was low (38%). Reaction of L-(12) with sodium hydride and the ditosylate (13) [25] in dimethyl sulphoxide afforded the 9-crown-3, L-(14), and 18-crown-6, LL-(15), derivatives in 3 and 11% yields, respectively. Catalytic hydrogenolysis of the tetrabenzyl ether LL-(15) gave the tetraol LL-(16), characterised as the crystalline tetra-acetate LL-(17) with a specific rotation of −20.5° in chloroform. Conversion of the tetraol LL-(16) into the tetratrityl ether LL-(18) was also carried out in order to increase the steric bulk of the substituent groupings attached to the four chiral centres in the 18-crown-6 lock. Recently, Lehn and his collaborators [33,34] have obtained the tetracarboxamide LL-(19) by thallium(I) ethoxide promoted condensation of the bis-(*NN*-dimethylamide) of L-tartaric acid with 1,5-di-iodo-3-oxapentane in *NN*-dimethylformamide. Acid-catalysed hydrolysis of LL-(19) gave the tetracarboxylic acid LL-(20), which was converted into the tetra-acid chloride LL-(21) for condensation with several amino-acid methyl esters to afford a range of tetracarbonyl[1]cryptands of the general type LL-(22).[34]



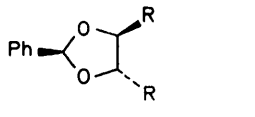
(*R*)-(8) (*S*)-(8)

In order to associate bulky substituents more intimately with the 18-crown-6 constitution, and at the same time double the number of chiral centres from four to eight, a synthetic scheme emanating from D-mannitol was devised and implemented. 1,2:5,6-Di-

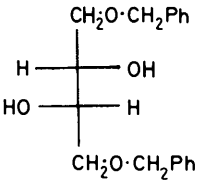
[33] J.-M. Girodeau, J.-M. Lehn, and J.-P. Sauvage, *Angew. Chem. Internat. Edn.*, 1975, **14**, 764.

[34] J.-P. Behr, J.-M. Lehn, and P. Vierling, *J.C.S. Chem. Comm.*, 1976, 621.

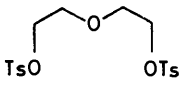
O-isopropylidene-D-mannitol D-(23) [26] was converted * into its diallyl ether D-(25),[27] which was subjected to ozonolysis followed by reduction with borohydride [10]



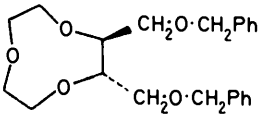
L-(9) R = CO_2Et
L-(10) R = CH_2OH
L-(11) R = $CH_2O{\cdot}CH_2Ph$



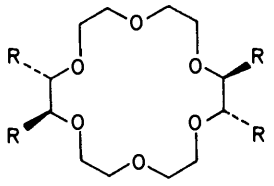
L-(12)



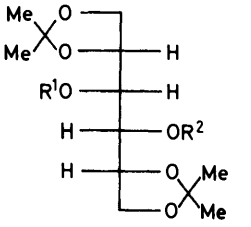
(13)



L-(14)



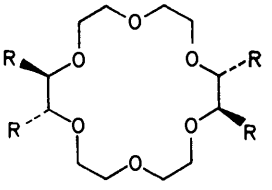
LL-(15) R = $CH_2O{\cdot}CH_2Ph$
LL-(16) R = CH_2OH
LL-(17) R = CH_2OAc
LL-(18) R = $CH_2O{\cdot}CPh_3$
LL-(19) R = $CO{\cdot}NMe_2$
LL-(20) R = CO_2H
LL-(21) R = COCl
LL-(22) R = $CO{\cdot}NHR'$
(34) R = H



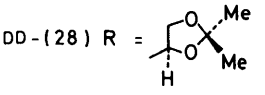
D-(23) R^1 = R^2 = H
D-(24) R^1 = $CH_2CH{:}CH_2$, R^2 = H
D-(25) R^1 = R^2 = $CH_2CH{:}CH_2$
D-(26) R^1 = R^2 = CH_2CH_2OH
D-(27) R^1 = R^2 = CH_2CH_2OTs

to give the 'half-crown' diol D-(26). Conversion of D-(26) into the 'half-crown' ditosylate D-(27) was followed by reaction of equimolar proportions of D-(26) and D-(27) with sodium hydride in dimethyl sulphoxide to afford the 18-crown-6 derivative DD-(28) in 14% yield. Subsequently, the tetra-*O*-isopropylidene derivative DD-(28) was isolated in 24% yield, together with some of the 9-crown-3, D-(29), and 27-crown-9, DDD-(30), derivatives, after chromatography on alumina of the products from sodium hydride promoted condensation of di-*O*-isopropylidenemannitol, D-(23), with the ditosylate (13) in dimethyl sulphoxide. This represents a two-step synthesis of a chiral 18-crown-6 lock from D-mannitol. Acid-catalysed hydrolysis of the four blocking *O*-isopropylidene groups in DD-(28) gave the octaol DD-(31), which was characterised as both its octa-acetate DD-(32) and its octamethyl ether DD-(33). Cleavage of the four vicinal glycol units in DD-(31) with periodate, followed by reduction with borohydride and acetylation, afforded the tetra-acetate DD-(17) with a specific rotation of +20.2° in chloroform. Thus, the enantiomerically related DD- and LL-tetra-acetates (17) have been obtained from D-mannitol and L-tartaric acid, respectively. This observation provides overwhelming evidence for the absence of any racemisation in the synthetic steps leading to either the DD- or the LL-lock.

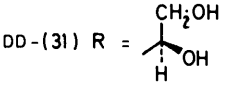
Complex Formation in Aprotic Solvents.—The 18-crown-6 derivatives LL-(15), LL-(17), DD-(17), LL-(18), DD-(28), and DD-(32) all solubilise primary alkylammonium thiocyanates in non-polar solvents. Moreover, the formation of complexes (*ca.* 1 : 1) with primary alkylammonium thiocyanates in CD_2Cl_2 is accompanied by significant changes in the ^1H n.m.r. spectral characteristics of the locks as well as by the emergence of additional signals arising from protons in the keys. The nature of



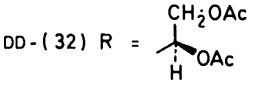
DD-(17) R = CH_2OAc
(34) R = H



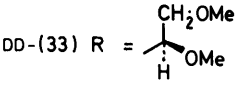
DD-(28) R =



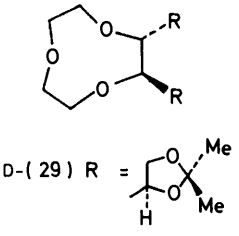
DD-(31) R =



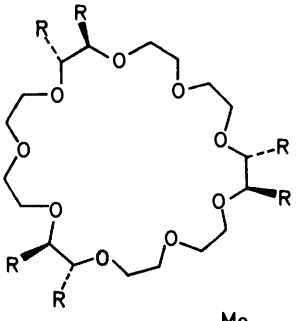
DD-(32) R =



DD-(33) R =



D-(29) R =



DDD-(30) R =

the anion is important in promoting complex formation involving primary alkylammonium cationic keys and 18-crown-6 locks in non-polar solvents. Soft anions, such as SCN^-, ClO_4^-, and PF_6^-, favour complex formation, whereas hard anions, such as OH^-, Cl^-, and Br^-, mitigate against the formation of a complex. The ^1H n.m.r. spectroscopic observations with the tetra-*O*-isopropylidene derivative DD-(28), summarised in Figure 2, exemplify the general situation. The ^1H n.m.r. spectrum of DD-(28) in CD_2Cl_2 was recorded [Figure 2(a)] and then

* The monoallyl ether D-(24) was also formed from di-*O*-isopropylidenemannitol, D-(23), when the alkylation conditions employed were relatively mild. The diallyl ether D-(25) was obtained from D-(24) on further allylation.

the solution was shaken with 1 mol. equiv. of benzylammonium bromide. The solid was filtered off and the spectrum was recorded again. There was no detectable

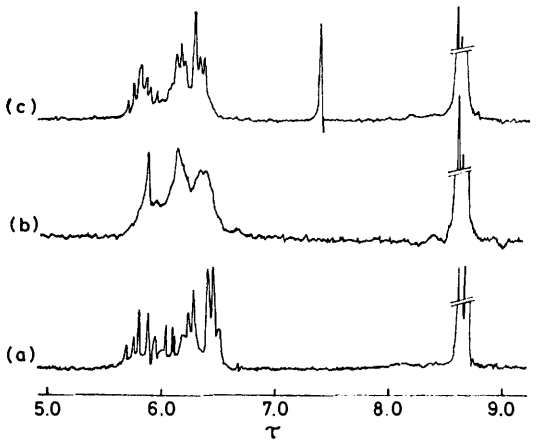


FIGURE 2 ^{1}H N.m.r. spectra of (a) the tetra-*O*-isopropylidene derivative DD-(28) in CD_2Cl_2, (b) the complex between lock DD-(28) and benzylammonium thiocyanate [key : lock 0.82 : 1] in CD_2Cl_2, and (*c*) the complex between lock DD-(28) and methylammonium thiocyanate [key : lock 0.72 : 1] in CD_2Cl_2

difference between the two spectra and this was taken as evidence that no complexation of the added salt had occurred. When the experiment was repeated with

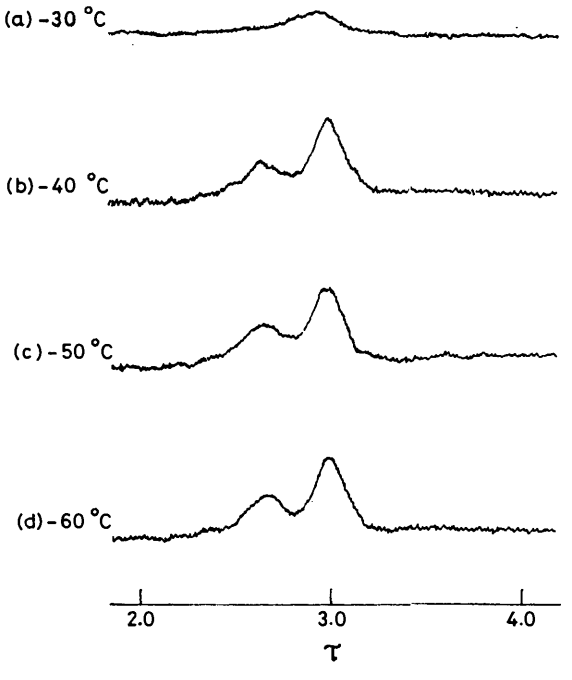


FIGURE 3 Temperature dependence of the ^{1}H n.m.r. signal for the ammonium protons in the complex between lock DD-(28) and methylammonium thiocyanate [key : lock 0.72 : 1] in CD_2Cl_2

1 mol. equiv. of benzylammonium thiocyanate instead of the bromide, changes occurred in the appearance of the lock signals together with a superimposition of signals for the benzylammonium cation [Figure 2(b)]. These chemical shift changes were taken as good evidence for complex formation in CD_2Cl_2 solution. The added thiocyanate did not dissolve completely and integration of appropriate lock and key signals gave a key : lock ratio of 0.82 : 1. Similarly, when 1 mol. equiv. of methylammonium thiocyanate was added to a solution of DD-(28) in CD_2Cl_2, there were significant chemical shift changes in the ^{1}H n.m.r. spectrum of the lock together with the appearance of a broad singlet at τ 2.90 for the ammonium protons and a sharp singlet at τ 7.39 for the methyl protons of the methylammonium cation [Figure 2(c)]. The key : lock ratio was found to be 0.72 : 1 by integration. On cooling the CD_2Cl_2 solution to −60 °C, the signal for the ammonium protons gradually separated (see Figure 3) into two peaks with relative intensities 1 : 2. This suggests that decomplexation is slow on the ^{1}H n.m.r. time scale at −60 °C, and that a situation exists where two of the protons attached to the nitrogen are in similar, or very similar, environments whereas the third proton is in a different environment. At least two models (see Figure 4) involving only oxygen atoms in the 18-crown-6 framework would satisfy the experimental facts: (i) a three-point binding model [Figure 4(a)] in which the

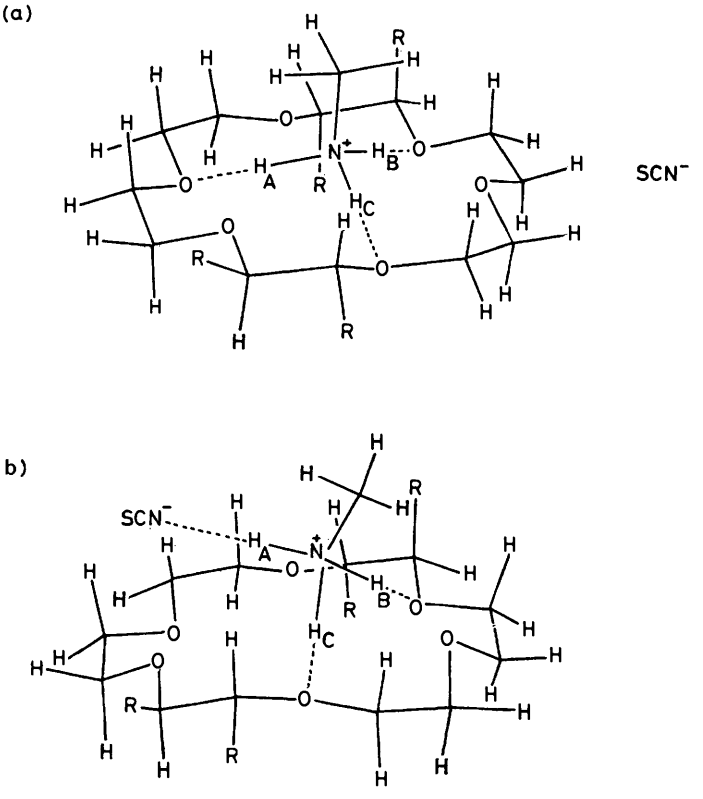


FIGURE 4 (*a*) Three-point binding model and (b) two-point binding model for the 1 : 1 complex between lock DD-(28) [R = 2,2-dimethyl-1,3-dioxolanyl] and methylammonium thiocyanate

environments of H_B and H_C are more similar to each other than to that of H_A or (ii) a two-point binding model [Figure 4(b)] in which H_B and H_C are hydrogen bonded to ether oxygen atoms in the lock and hence are located in similar environments, whereas H_A is hydrogen bonded to the nitrogen of the thiocyanate anion. Cram [35] ascribes the absence of chiral recognition of racemic primary alkylammonium thiocyanates towards chiral polyether locks, which are known to discriminate between enantiomeric primary alkylammonium hexafluorophosphates and perchlorates, to less ordered complexes in the case of the thiocyanates. Moreover, two-point binding has been observed [36] in the crystal structure of a complex between a macrocyclic diamine and benzylammonium thiocyanate where the ammonium group is attached by two hydrogen bonds to an oxygen and nitrogen in the lock leaving the third hydrogen to bond with the nitrogen of the thiocyanate anion.

Stability constants defined by equation (2) were measured by an ^1H n.m.r. spectroscopic method [29] in $CDCl_3$ after a two-phase equilibration procedure involving D_2O. Table 2 records stability constants and derived free energy differences for complexation of t-butylammonium, and in one case benzylammonium, thiocyanates with locks LL-(15), LL-(17), LL-(18), DD-(28), and DD-(32), as well as with 18-crown-6 (34). A number of features and trends in Table 2 merit special mention. (i) A factor of *ca.* 4 000 in K_a for the complexation of t-butylammonium thiocyanate is sacrificed on tetrasubstitution of 18-crown-6 (34) to give the tetra-acetate LL-(17), indicating that an appreciable steric effect is introduced by the presence of four acetoxymethyl groups. (ii) The very low value of K_a for the complexation of the octa-acetate DD-(32) with t-butylammonium thiocyanate shows an even greater steric effect when the bulk of the side chains is increased such that they contain two *O*-acetyl groups each. (iii) A factor of only *ca.* 40 in K_a for complexation of t-butylammonium thiocyanate is conceded on tetrasubstitution of 18-crown-6 (34) to give the tetrabenzyl ether LL-(15), indicating that the expected steric effect is probably largely offset by secondary attractive interactions between the hydrophobic benzyl groups in the lock and the hydrophobic t-butyl group in the key. (iv) The very similar values of K_a for the complexation of the tetrabenzyl ether LL-(15) and the tetratrityl ether LL-(18) by t-butylammonium thiocyanate support this suggestion that secondary attractive interactions can almost outweigh steric effects. (v) In common with the octa-acetate DD-(32), the tetra-*O*-isopropylidene derivative DD-(28) has an extremely low value of K_a for t-butylammonium thiocyanate indicating that the bulky 2,2-dimethyl-1,3-dioxolanyl groups attached to 18-crown-6 (34) give the lock the potential to be sterically selective towards an appropriate range of keys. This is confirmed apparently by the dramatic increase in K_a by a factor of *ca.* 10^5 for complexation by lock DD-(28) of a much less sterically demanding key salt, benzylammonium thiocyanate. However, it must be recognised that the strong complex formed between lock DD-(28) and benzylammonium thiocyanate may owe some of its origin to attractive π-lone pair interactions [37] involving the phenyl ring in the key and the oxygen atoms in the 2,2-dimethyl-1,3-dioxolanyl groups of the lock.

Chiral Recognition in Aprotic Solvents.—All the DD and LL locks have D_2 symmetry and consequently their two faces are homotopic. This means that complexation of achiral or optically pure chiral keys to either face affords identical complexes. However, complexation of enantiomeric keys to either face results in diastereoisomeric complexes. An n.m.r. spectroscopic method [30,31]

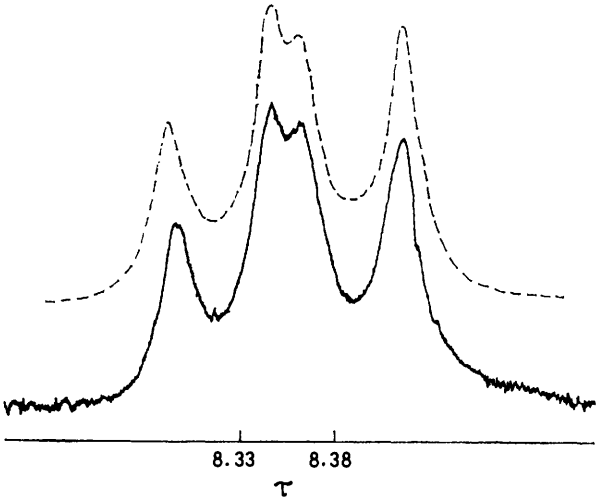


FIGURE 5 Observed (full line) and computed (broken line) ^1H n.m.r. spectral doublets for the methyl groups of the enantiomeric keys in the equilibrated complexes DD-(28)–(*R*)–(8),HPF_6 and DD-(28)–(*S*)–(8),HPF_6

was used to identify the diastereoisomeric complexes and obtain their relative proportions at equilibrium in the $CDCl_3$ layer after partitioning (*RS*)-α-phenylethylammonium hexafluorophosphate [(*RS*)-(8),HPF_6] between D_2O and $CDCl_3$ in the presence of the chiral locks.

Although diastereoisomeric complex formation is accompanied by significant changes in the ^1H n.m.r. spectra of the locks, it manifests itself most noticeably in anisochronous signals with small chemical shift differences arising from protons in the previously enantiomeric keys. The fact that no duplication of the signals for the locks is observed is a consequence of the fast exchange on the ^1H n.m.r. time-scale between the lock and the key at room temperature, which has already been discussed. In the case of the locks LL-(15), LL-(18), DD-(28), and DD-(33), two doublets were observed for the methyl group protons of the keys in the diastereoisomeric complexes formed between the locks and the racemic keys. Locks LL-(17) and DD-(32) exhibited insufficient separations between the methyl doublets of the racemic keys to permit reliable estimates of the enantiomeric

[35] D. J. Cram, personal communication, May 1976.
[36] L. C. Hodgkinson, S. J. Leigh, and I. O. Sutherland, *J.C.S. Chem. Comm.*, 1976, 639.
[37] J. E. Anderson, *Tetrahedron Letters*, 1965, 4713.

differentiation. Molar ratios of keys to locks were obtained directly from integration of appropriate key and lock signals. Key to lock ratios in excess of 1.0 : 1 indicate the presence of some 2 : 1 complex formation which could arise through hydrogen bonding of a second key, partially at least, to oxygen atoms in the side chains on the opposite face of the lock to that involved in 1 : 1 complex formation. Such a situation would correspond with a somewhat less ordered complex and consequently a possible diminution in the chiral recognition potential of the lock. The enantiomeric differentiations were deduced by (i) direct integration of the doublets for the methyl groups of the racemic keys and (ii) simulation of the experimental spectrum for the methyl groups of the racemic keys with a calculated spectrum. Method (ii) was generally considered to be more reliable than method (i) because of the overlapping nature of the doublets and consequent lack of base-line separations between peaks. For example, the (*R*) : (*S*) ratio for the tetra-*O*-isopropylidene derivative DD-(28) obtained by method (i) was 58 : 42, whereas the best match (see Figure 5) was obtained between experimental and calculated spectra when the (*R*) : (*S*) ratio was made equal to 62 : 38. The results for this and the other locks are summarised in Table 3.

The enantiomeric differentiation of 62 : 38 exhibited by the tetra-*O*-isopropylidene derivative DD-(28) towards (*RS*)-(8),HPF_6 in favour of the (*R*)-isomer was confirmed quantitatively in the broad-band decoupled ^{13}C n.m.r. spectrum (see Figures 6 and 7). The spectrum of the pure lock contained the expected eight resonances for the heterotopic carbon atoms and these could be assigned (see Table 4) partially after examination of the off-centre double resonance spectrum. As well as the eight peaks associated with the lock, the broad-band decoupled ^{13}C n.m.r. spectra of the diastereoisomeric complexes DD-(28)–(*R*)-(8),HPF_6 and DD-(28)–(*S*)-(8),HPF_6 each showed six additional peaks for the heterotopic carbon atoms in the previously enantiomeric keys. The methyl, methine, quaternary aromatic, and

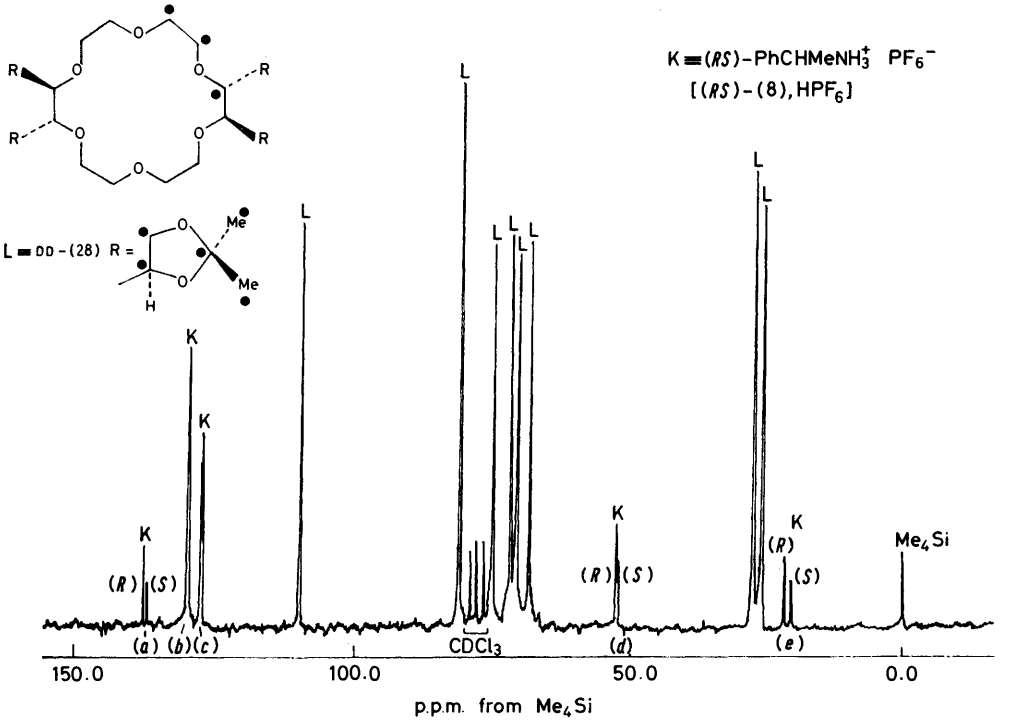


FIGURE 6 Broad-band decoupled ^{13}C n.m.r. spectrum of the equilibrated complexes DD-(28)–(*R*)–(8),HPF_6 and DD-(28)–(*S*)–(8),HPF_6 in $CDCl_3$; L indicates lock and K indicates key signals. Key signals are assigned from low field to high as (*a*) substituted carbons in the (*R*) and (*S*) phenyl rings, (*b*) *meta*- and *para*-carbons in the phenyl rings, (*c*) *ortho*-carbons in the (*S*) and (*R*) phenyl rings, (*d*) (*R*) and (*S*) methine carbons, and (*e*) (*R*) and (*S*) methyl carbons

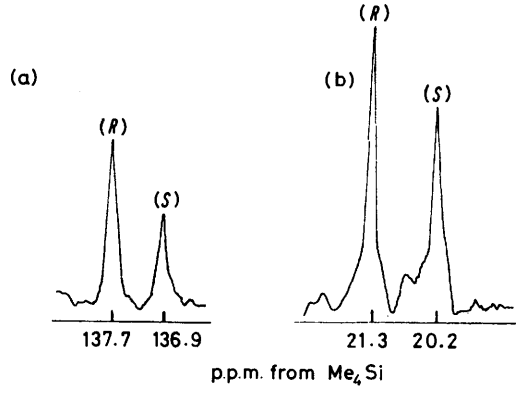


FIGURE 7 Partial broad-band decoupled ^{13}C n.m.r. spectrum of the equilibrated complexes DD-(28)–(*R*)–(8),HPF_6 and DD-(28)–(*S*)–(8),HPF_6 in $CDCl_3$ showing (a) the key quaternary aromatic resonances and (b) the key methyl carbon resonances

one of the tertiary aromatic carbon atoms associated with the diastereoisomeric complexes showed chemical shift non-equivalence (see Table 4 and Figure 6). Direct integration of the pairs of anisochronous quaternary aromatic and methyl carbon resonances (see Figure 7) gave (*R*) : (*S*) ratios of 64 : 36 and 60 : 40, respectively, for the equilibrated diastereoisomeric complexes. This result is in satisfying agreement with the computed value of 62 : 38 for the (*R*) : (*S*) ratio obtained by ^{1}H n.m.r. spectroscopy.

The results in Table 3 suggest that chiral recognition is observed when the substituent groups on the 18-crown-6 framework are bulky and somewhat lacking in flexibility. The absence of any chiral recognition by the tetrabenzyl ether LL-(15) and the octamethyl ether DD-(33) may be due to a combination of (i) a decrease in the bulk of the substituents as compared with the tetra-*O*-isopropylidene derivative DD-(28) and (ii) an increase in the flexibility of the substituents as a result of increased torsional freedom. In the case of the tetratrityl ether LL-(18), the complex LL-(18)–(*S*)-(8),HPF_6 is *ca.* 240 cal mol^{-1} more stable than the complex LL-(18)–(*R*)-(8),HPF_6. In the case of the tetra-*O*-isopropylidene derivative DD-(28), the complex DD-(28)–(*R*)-(8),HPF_6 is *ca.* 300 cal mol^{-1} more stable than the complex DD-(28)–(*S*)-(8),HPF_6. Although these free energy differences are small they are in accord with expectation arising out of examination of CPK space-filling molecular models. Assuming a three-point binding model for the 1 : 1 diastereoisomeric complexes (Figure 8) formed between lock DD-(28) and key (*R*)-(8),HPF_6, and lock DD-(28) and key (*S*)-(8),HPF_6, and selecting the Newman projection which places the phenyl group over the region of the 18-crown-6 cycle free of substituent groups, the methyl group in the key is seen to interact more severely with a 2,2-dimethyl-1,3-dioxolanyl group in the DD-(28)–(*S*)-(8),HPF_6 complex. Thus, one is led to the prediction that the DD-(28)–(*R*)-(8),HPF_6 complex will be the more stable, in accord with observation.

TABLE 4

Broad-band decoupled ^{13}C n.m.r. chemical shifts of the lock DD-(28), the DD-(28)–(*R*)-(8),HPF_6 complex, the DD-(28)–(*S*)-(8),HPF_6 complex, and the equilibrated DD-(28)–(*RS*)-(8),HPF_6 complex [a] in $CDCl_3$

		Chemical shifts (p.p.m. from Me_4Si)			
	Carbons	Lock DD-(28)	Complex DD-(28)–(*R*)-(8),HPF_6	Complex DD-(28)–(*S*)-(8),HPF_6	Complex [a] DD-(28)–(*RS*)-(8),HPF_6
Lock	Quaternary	108.6	109.4	109.3	109.3
	Methine	80.3	80.3	80.4	80.1
		75.7	74.1	74.3	74.1
	Methylene	71.9	71.0	70.9	70.9
		70.7	69.6	69.5	69.5
		66.7	67.5	67.4	67.4
	Methyl	26.8	26.8	26.8	26.8
		25.6	25.5	25.5	25.5
Key	Quaternary aromatic		137.7		137.7
				137.2	136.9
	Tertiary aromatic		129.5	129.7	129.5
			129.5	129.4	129.3
				127.3	127.3
			127.0		126.9
	Methine		52.1		51.9
				51.7	51.6
	Methyl		21.0		21.3
				20.3	20.2

In the equilibrated complex, the (*R*) : (*S*) ratio was 62 : 38.

CPK space-filling molecular models indicate that the lock DD-(28) with its eight chiral centres is topologically related to the lock (*SS*)-(35) with its two chiral axes (see Figure 9), which has been investigated in considerable detail by Cram and his associates.[11–13,30] Thus, it is hardly surprising that the two locks are on a par regarding their chiral recognition towards (*RS*)-α-phenylethylammonium hexafluorophosphate. We anticipate that

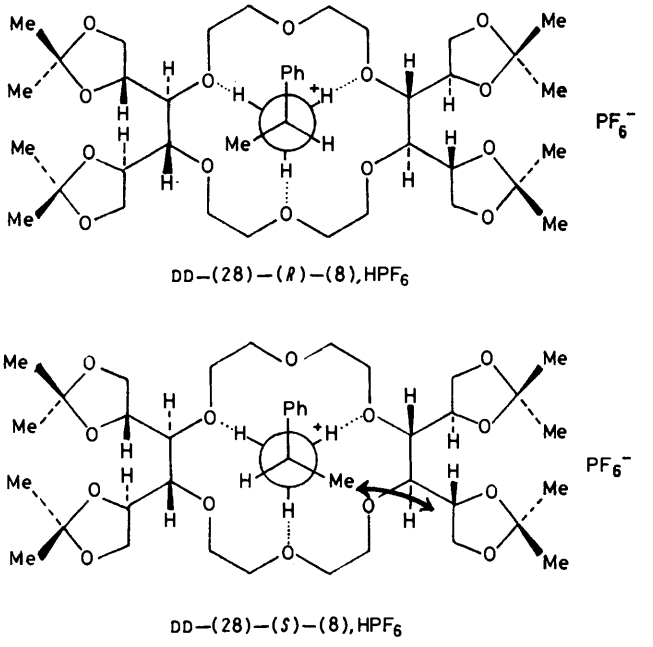


FIGURE 8 The diastereoisomeric complexes

modification of our carbohydrate-derived locks will lead to the same marked improvement in chiral recognition which has been observed [38] for chiral locks [*e.g.* (*RR*)-(36)] incorporating modified binaphthyl units.

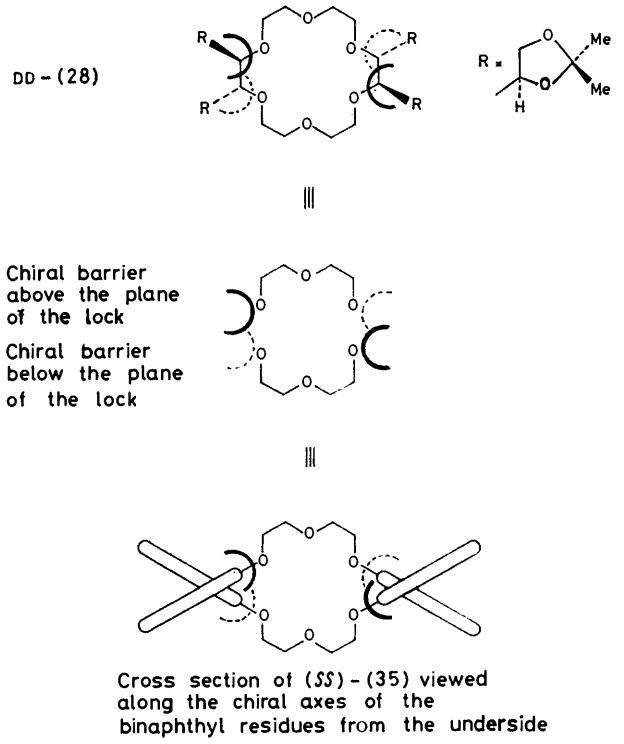
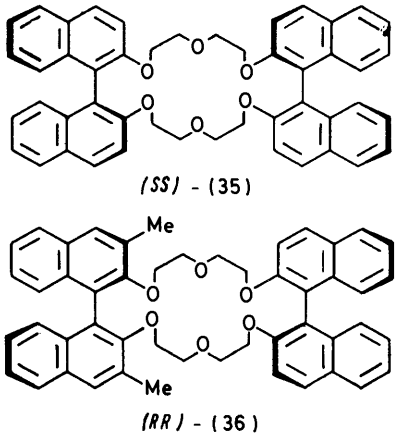


FIGURE 9 A comparison of the chiral barriers in locks DD-(28) and (*SS*)-(35)

Complex Formation in Protic Solvents.—The tetraol LL-(16) and the octaol DD-(31) are soluble in protic solvents, and so it was of interest to find out if they



form complexes with primary alkylammonium cations under such conditions.

Figure 10 summarises the ^{1}H n.m.r. spectroscopic evidence for complex formation by the octaol DD-(31) in CD_3OD with selected primary alkylammonium salts.

[38] S. C. Peacock and D. J. Cram, *J.C.S. Chem. Comm.*, 1976, 282.

The octaol DD-(31) was dissolved in CD_3OD and the ^{1}H n.m.r. spectrum of the solution was recorded [Figure 10(a)]. t-Butylammonium thiocyanate (1.0 mol. equiv.) was added to the CD_3OD solution and the ^{1}H n.m.r. spectrum was recorded again. Significant chemical shift changes were evident in the spectrum [Figure 10(b)] of the octaol DD-(31), and these were taken as an indication of complex formation. Similarly, when benzylammonium thiocyanate (1.0 mol. equiv.) was added to a solution of the octaol DD-(31) in CD_3OD, the ^{1}H n.m.r.

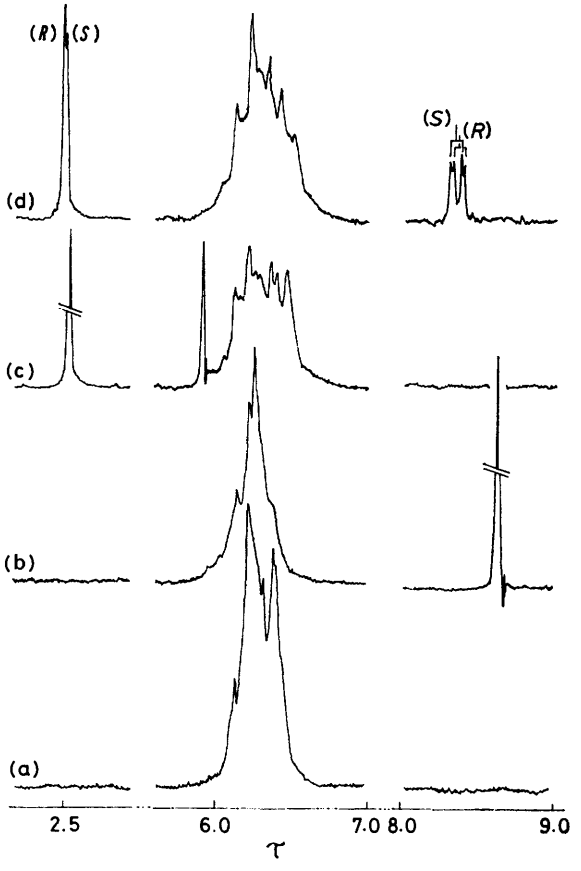


FIGURE 10 Partial ^{1}H n.m.r. spectra of (a) the octaol DD-(31) and its 1 : 1 complexes with (b) t-butylammonium thiocyanate, (c) benzylammonium thiocyanate, and (d) (*RS*)-α-phenylethylammonium thiocyanate in CD_3OD

spectrum [Figure 10(c)] of the lock showed significant chemical shift changes, which were associated with complex formation. Cooling of the CD_3OD solution indicated that complexation–decomplexation was fast on the ^{1}H n.m.r. time-scale even at −70 °C. When racemic α-phenylethylammonium thiocyanate (*RS*)-(8),HSCN (1.0 mol. equiv.) was added to a CD_3OD solution of the octaol DD-(31), not only did the ^{1}H n.m.r. spectrum of the lock exhibit significant chemical shift changes but the phenyl and methyl protons of the keys in the diastereoisomeric complexes also showed [Figure 10(d)] chemical shift nonequivalence. The experiment was repeated with (*R*)-(8),HSCN and (*S*)-(8),HSCN in order to establish the identity of the signals in the spectrum for the diastereoisomeric complexes. These

observations establish convincingly that the octaol DD-(31) forms complexes with primary alkylammonium thiocyanates in CD_3OD. ^1H N.m.r. spectroscopic evidence was also obtained for complex formation by the tetraol LL-(16) in CD_3OD.

Figure 11 summarises the ^1H n.m.r. spectroscopic evidence for complex formation by the octaol DD-(31) in D_2O with racemic α-phenylethylammonium thiocyanate (*RS*)-(8),HSCN. The octaol DD-(31) was dissolved in D_2O and the ^1H n.m.r. spectrum [Figure 11(a)] was recorded. When (*RS*)-(8),HSCN (1.0 mol. equiv.) was added to the D_2O solution, the ^1H n.m.r. spectrum of the lock exhibited [Figure 11(b)] chemical shift

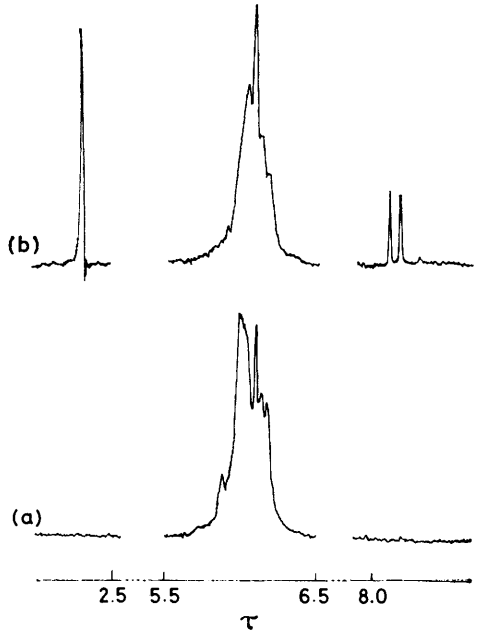


FIGURE 11 Partial ^1H n.m.r. spectra of (a) the octaol DD-(31) and (b) its 1 : 1 complex with (*RS*)-α-phenylethylammonium thiocyanate in D_2O

changes although on this occasion the signals for the non-equivalent methyl groups of the keys in the diastereoisomeric complexes were isochronous.

Chiral Recognition in Protic Solvents.—The ability of locks LL-(16) and DD-(31) to form complexes with primary alkylammonium salts in aqueous and methanolic solution is encouraging from the point of view of designing (*cf.* ref. 34) locks to (i) exhibit chiral recognition in protic solvents and (ii) perform catalysis when appropriate catalytic sites are associated with the lock in relation to a particular key. Although the potential of locks LL-(16) and DD-(31) to act as enzyme analogues in protic solvents has still to be investigated, an equilibration procedure has been devised to assess the chiral recognition properties of the octaol DD-(31) towards racemic α-phenylethylammonium perchlorate (*RS*)-(8),$HClO_4$ in D_2O. A solution of DD-(31), (*RS*)-(8),$HClO_4$ (2.0 mol. equiv.), and lithium perchlorate (2.0 mol. equiv.) in D_2O was shaken with a solution of 18-crown-6 (34) (1.0 mol. equiv.) in $CDCl_3$. The two layers were separated and the ^1H n.m.r. spectrum of the $CDCl_3$ layer was recorded. The $CDCl_3$ layer was found to contain (*RS*)-(8),$DClO_4$ and 18-crown-6 (34) in the molar ratio 1 : 1. The D_2O layer was concentrated and the residue was dissolved in CD_3OD. The ^1H n.m.r. spectrum of the CD_3OD solution showed the presence of diastereoisomeric complexes. Although the methyl doublet for the enantiomeric key cations were anisochronous as demonstrated previously, the two doublets were of equal intensity indicating that the octaol DD-(31) does not exhibit chiral recognition towards (*RS*)-(8),$HClO_4$ under these equilibration conditions. This result is not unexpected in view of the fact that neither the octa-acetate DD-(32) nor the octamethyl ether DD-(33) exhibited chiral recognition towards (*RS*)-(8),HPF_6 in $CDCl_3$ under equilibration conditions.

Complex Formation with Metal Cations.—The tetra-*O*-isopropylidene derivative DD-(28) was shown to complex alkali metal cations through its ability to effect dissolution of alkali metal *ortho*-nitrophenolates in chloroform. The stability constants defined by equation (1) for the formation of 1 : 1 complexes between crown DD-(28) and sodium, potassium, and rubidium chlorides in methanolic solution were measured potentiometrically [8,28] with ion-selective electrodes. The results are compared in Table 5 with those obtained by Frensdorff [28]

TABLE 5

Stability constants for 1 : 1 ligand–cation complexes based on K' in l mol^{-1}

	log K' [a]			
Ligand	Na^+	K^+	Rb^+	Cs^+
DD-(28)	3.6 [b]	4.5 [b]	4.7 [b]	
(34)	4.34 [b,c]	6.10 [b,c]	5.35 [b,c]	4.70 [b,c]
	4.32 [d,e]	6.10 [d,e]		

[a] Values obtained at room temperature unless otherwise stated for the chlorides. [b] Error of ±0.1. [c] Values from ref. 8. [d] Values from ref. 28 obtained at 25 °C. [e] Error of ±0.04.

for 18-crown-6 (34). The stability constants for crown DD-(28) are not as high as the corresponding values for 18-crown-6 (34). However, it is interesting that crown DD-(28) forms a slightly stronger complex with rubidium than with potassium ions, in contrast with the selectivity shown for potassium ions by 18-crown-6 (34). This may result from some additional stabilisation of the larger cation by the oxygen-containing 2,2-dimethyl-1,3-dioxolanyl substituents on the crown DD-(28).

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