# The *trans,anti,trans*- and *trans,syn,trans*-Isomers of Dicyclohexyl-18-crown-6 and their Complexes

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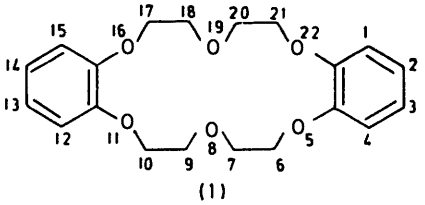
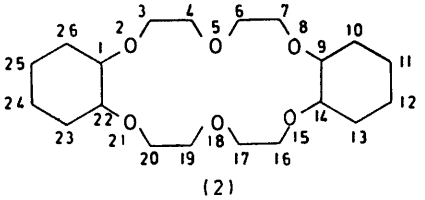
The stereospecific synthesis of the *trans,anti,trans*- (2a) and *trans,syn,trans*-(2b) isomers of dicyclohexyl-18-crown-6 (2) from the diastereoisomeric (±)- (6a) and *meso*- (6b) 2,2'-methylenedioxydicyclohexanols has been achieved. A one-step synthesis of the di-*trans*-isomers (2a and b) from (±)-cyclohexane-*trans*-1,2-diol (3) is accompanied by the formation of some *trans*-cyclohexyl-9-crown-3 (10). *trans,syn,trans*-Dicyclohexyl-18-crown-6 (2b) forms crystalline complexes with alkali metal, ammonium, and primary alkylammonium salts. In methanolic solutions, the stability constants for the complexes with sodium, potassium, and caesium chlorides are greater for the *cis,anti,-cis*- (2c) and *cis,syn,cis*- (2d) isomers than they are for either of the di-*trans*-isomers (2a and b). Also, within each pair of isomers, the *syn*-isomers (2b and d) form stronger complexes than the *anti*-isomers (2a and c). All four isomers exhibit selectivity for binding potassium ions.

MACROCYCLIC polyethers [1-9] have attracted considerable attention because of their ability to form reasonably stable complexes with many metal, ammonium, and primary alkylammonium cations. Consequently, they serve as model compounds for investigating ion transport phenomena in biological systems,[10] as reagent modifiers in synthetic organic chemistry,[11] and as enzyme analogues for chiral recognition of racemic primary alkylammonium salts.[8,9,12,13] Of the many so-called [1-3] crown compounds which are known, dibenzo-18-crown-6 (1) [1,14] and dicyclohexyl-18-crown-6 † (2) [1,14] are amongst the most widely investigated to date.

There are five possible configurational diastereoisomers (2a—e) of dicyclohexyl-18-crown-6 (2) (Figure). Catalytic hydrogenation [1,3,14] of dibenzo-18-crown-6 (1), followed by column chromatography of the product on alumina,[14-17] yielded two of these isomers as crystalline compounds. These have been designated [14-17] as Isomer-A (m.p. 61—62.5°) and Isomer-B (m.p. 69—70°).



(1)



(2)

Isomer-B exists [16,17] in a second form, B', with m.p. 83—84°. Recently, a ready separation of Isomers-A and -B' has been reported [18] which takes advantage of

† I.U.P.A.C. names for structures (1) and (2) are 6,7,9,10,17,18,20,21-octahydrodibenzo[*b*,*k*][1,4,7,10,13,16]hexaoxacyclooctadecin and 2,5,8,15,18,21-hexaoxatricyclo[20.4.0.0$^{9,14}$]hexacosane, respectively.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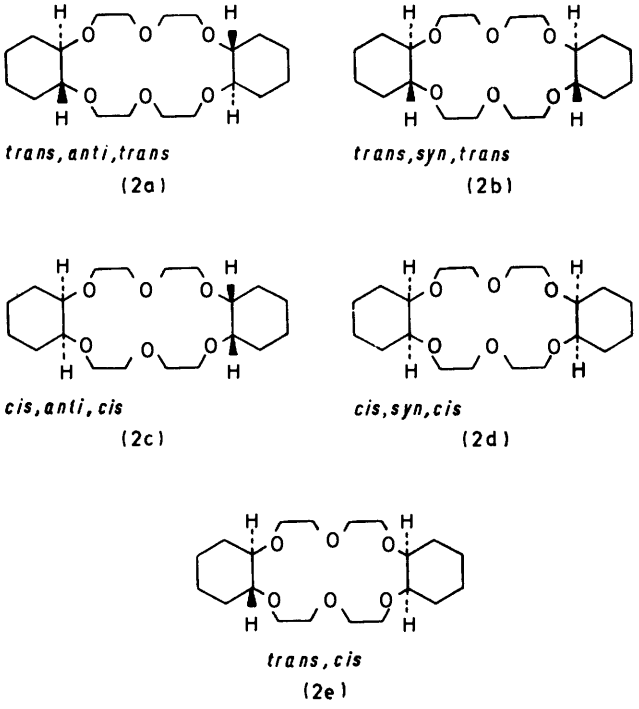
the large differences in solubility in water between the lead and oxonium perchlorate complexes of the two isomers. Forms B and B′ are identical [17] in solution.‡




The five possible configurational diastereoisomers of dicyclohexyl-18-crown-6 (2): (2a) with $D_2$ symmetry, (2b) and (2c) each with $C_{2h}$ symmetry, (2d) with $C_{2v}$ symmetry, and (2e) with $C_1$ symmetry

Initially, it was claimed [19] on the basis of their $^1H$ n.m.r. spectra that the ring junctions in Isomers-A and B (B′) were *trans* [*i.e.* the two isomers could be assigned structures (2a and b)]. This claim appeared to gain support from a suggestion,[20] which was subsequently revised [21] (see below), that the *X*-ray structural investigation of Isomer-B as its sodium bromide dihydrate complex indicated that Isomer-B had a ' centrosymmetric *trans* conformation.' By contrast, $^{13}C$ n.m.r. spectroscopy indicated [22,23] that the ring junctions in both isomers were *cis* [*i.e.* the two isomers could be assigned structures (2c and d)]. The combined n.m.r. spectroscopic evidence [19,22,24] excluded the possibility that either Isomer-A or -B (B′) was the *trans,cis*-isomer (2e). Eventually, an *X*-ray crystal structure analysis of the barium thiocyanate complex of Isomer-A indicated [23] that it was the *cis,syn,cis*-isomer (2d). Also, when detailed information on the *X*-ray crystal structure of the sodium bromide dihydrate complex of Isomer-B became available,[21] it transpired that it was the *cis*-isomer (2c), which has the *cis,anti,cis*-configuration. Much more recently, *X*-ray crystallographic data on the uncomplexed ligands have confirmed [25] that Isomer-A is the *cis,syn,cis*-isomer (2d) and that Isomer-B′ is also the *cis,anti,cis*-isomer (2c).‡

Initially the present investigation had two main objectives: (i) to resolve the confusion concerning the disparate configurational assignments to Isomers-A, -B, and -B′ of dicyclohexyl-18-crown-6 (2), and (ii) to prepare the way for the synthesis of chiral 18-crown-6 derivatives from (+)- and (−)-cyclohexane-*trans*-1,2-diols. In the event, this second objective has been realised by incorporating L-tartaric acid [13,26] and D-mannitol [13] into the 18-crown-6 constitution.

The stereospecific synthesis of the *trans,anti,trans*-(2a) and *trans,syn,trans*- (2b) isomers of dicyclohexyl-18-crown-6 has been the subject of a preliminary communication.[27]

## EXPERIMENTAL

M.p.s were determined with a Reichert hot-stage apparatus. Microanalyses were carried out by the University of Sheffield microanalytical service. T.l.c. was carried out on glass plates (20 × 5 cm) coated with either Merck silica gel G or Merck aluminium oxide G (type 60/E). Developed plates were air-dried and either exposed to iodine vapour or sprayed with a cerium(IV) sulphate–sulphuric acid reagent, and heated at about 110 °C. Hopkin and Williams silica gel (M.F.C. grade) and Laporte (type H) alumina were used as chromatographic media for column separations. Low resolution mass spectra were determined with an A.E.I. MS12 spectrometer. I.r. spectra were recorded for Nujol mulls with a Perkin-Elmer 137 sodium chloride spectrophotometer, calibrated with reference to polystyrene (1 603 $cm^{-1}$). $^1H$ N.m.r. spectra were recorded with a Varian HA 100 spectrometer (tetramethylsilane as ' lock ' and internal standard).

rel-(1R,2R)-2-*Hydroxycyclohexyl Acetate* (4).—(±)-Cyclohexane-*trans*-1,2-diol (3) (50 g) was acetylated with acetic anhydride (17.5 ml) in dry pyridine (125 ml) to give a crude product shown by t.l.c. to contain some diacetate and diol in addition to the required monoacetate.[28] Column chromatography, on alumina [ether–methanol (93 : 7) as eluant] yielded an oil, characterised as the monoacetate (4) (18 g, 26%), τ ($CDCl_3$) 5.26—5.56 (1 H, m, H-1), 6.30—

‡ Although Isomer-B and Isomer-B′ are generally believed [17,18] to be polymorphs the possibility does exist that they are *conformational isomers* differing in the relative conformations of the cyclohexane rings fused to the 18-crown-6 rings. This problem could be solved if the crystal structures of both B and B′ were available for comparison. It is known [25] that Isomer-B′ [the *cis,anti,cis*-isomer (2c)] is centrosymmetric in the crystal with O(2) and O(15) axial and O(8) and O(21) equatorial. It is possible that O(2) and O(8) are axial, and O(15) and O(21) equatorial, in Isomer-B.

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6.60 (1 H, m, H-2), 7.62br (1 H, s, OH), 7.94 (3 H, s, Ac), and 7.80—8.90 (8 H, m, $CH_2$).

rel-(1R,1'R,2R,2'R)-2,2'-*Methylenedioxydicyclohexanol* (6a) *and* rel-(1R,1'S,2R,2'S)-2,2'-*Methylenedioxydicyclohexanol* (6b).—The monoacetate (4) (11 g) was dissolved in dry dimethyl sulphoxide (165 ml) and freshly recrystallised *N*-bromosuccinimide (28 g) was added.[29] The mixture was stirred at 50 °C for 26 h. After neutralising with sodium hydrogen carbonate solution, the mixture was extracted with ether (3 × 300 ml). The extracts were washed with water (300 ml), dried ($MgSO_4$), and evaporated under reduced pressure to afford an orange-coloured oil (9.4 g). This product was dissolved in methanol (200 ml) and sodium (600 mg) was added. Deacetylation was followed by t.l.c. and the methanol was removed under reduced pressure when the reaction was complete (24 h). Sodium carbonate (2 g) in water (50 ml) was added to the residue and the aqueous solution was steam-distilled for 1 h to remove volatile products. Chloroform extraction of the aqueous residue afforded a crude product which was shown to contain two major components, $R_F$ 0.4 and 0.5 on t.l.c. on silica gel with ether as eluant. Column chromatography on silica gel (ether as eluánt) afforded two crystalline compounds. Recrystallisation of the faster moving component from light petroleum (b.p. 60—80 °C) afforded prisms of *meso*-2,2'-methylenedioxydicyclohexanol (6b) (735 mg), m.p. 80—82° (lit.,[30,31] 81—82° for isomer-B), τ ($CDCl_3$) 4.97 and 5.20 (2 H, AB system, $J_{AB}$ 6.9 Hz, O·$CH_2$·O), 6.30br (2 H, s, 2 × OH), 6.40—6.90 (4 H, m, H-1, -2, -1', and -2'), and 7.80—9.00 (16 H, m, other $CH_2$). Recrystallisation of the slower moving component from light petroleum (b.p. 60—80 °C) afforded needles of (±)-2,2'-methylenedioxydicyclohexanol (6a) (1.0 g), m.p. 102.5—103.5° (lit.,[30,31] 104—105° for isomer-A), τ ($CDCl_3$) 5.18 (2 H, s, O·$CH_2$·O), 5.99br (2 H, s, 2 × OH), 6.41—6.81 (4 H, m, H-1, -2, -1', and -2'), and 7.80—9.00 (16 H, m, other $CH_2$).

2,2'-*Oxybis*(*ethyl tosylate*) (9).—Diethylene glycol (9.4 g) was dissolved in dry pyridine (80 ml) and solid toluene-*p*-sulphonyl chloride (38.5 g) was added in portions during 2 h to the stirred solution cooled in an ice-bath. Stirring was continued for a further 4 h at *ca.* 0 °C. The mixture was then left overnight at room temperature, poured on to ice (100 g), and diluted by addition of water (50 ml). The precipitate was filtered off and washed with ice-cold water (160 ml). Recrystallisation from ethanol (200 ml) afforded the pure ditosylate (9) (26.9 g, 65%), m.p. 85.5—87.0° (lit.,[32] 98°) (Found: C, 52.3; H, 5.6; S, 15.2%; $M^+$, 414. Calc. for $C_{18}H_{22}O_7S_2$: C, 52.2; H, 5.35; S, 15.5%; *M*, 414), τ ($CDCl_3$) 2.16—2.80 (8 H, AA'BB' system, aromatic), 5.86—6.52 (8 H, AA'BB' system, $CH_2$), and 7.59 (6 H, s, 2 × Me).

rel-(1R,5R,10R,18R)-2,4,11,14,17-*Pentaoxatricyclo*-[16.4.0.0$^{5,10}$]*docosane* (7a).—The (±)-modification (6a) (1.22 g) was dissolved in 1,2-dimethoxyethane (30 ml) and dimethyl sulphoxide (10 ml), and sodium hydride (500 mg) was added. The ditosylate (9) (2.28 g) was added and the mixture was heated at 50—55 °C with stirring. After 24 h t.l.c. on silica gel [ethyl acetate–light petroleum (b.p. 60—80°) (1 : 1) as eluant] indicated that although all the ditosylate had been consumed some of the diol remained. Consequently, more ditosylate (1.14 g) was added, and heating and stirring were continued. After a further 24 h, t.l.c. indicated that the reaction was complete. The excess of sodium hydride was destroyed by careful addition of water. The mixture was then poured into water (100 ml) and extracted with ether (4 × 50 ml). The combined extracts were dried ($MgSO_4$) and evaporated to leave a crude oil. Column chromatography on silica gel (ether as eluant) gave the (±)-*cyclic acetal* (7a) as an oil (899 mg, 57%) (Found: C, 65.0; H, 9.6%; $M^+$, 314. $C_{17}H_{30}O_5$ requires C, 64.9; H, 9.6%, *M*, 314), τ ($CDCl_3$) 5.23 (2 H, s, O·$CH_2$·O), 6.08—6.66 (12 H, m, CH and other O·$CH_2$), and 7.80—8.90 (16 H, m, other $CH_2$).

rel-(1R,5S,10S,18R)-2,4,11,14,17-*Pentaoxatricyclo*-[6.4.0.0$^{5,10}$]*docosane* (7b).—The *meso*-isomer (6b) (1.04 g) was dissolved in 1,2-dimethoxyethane (30 ml) and dimethyl sulphoxide (10 ml), and sodium hydride (400 mg) was added. By the procedure already described for the (±)-modification (6a), reaction with the ditosylate (9) (1.94 g + 0.97 g) gave a product which crystallised after chromatography on silica gel. Recrystallisation from ether–light petroleum (b.p. 60—80 °C) afforded prisms of the meso-*cyclic acetal* (7b) (275 mg, 21%), m.p. 62—63° (Found: C, 65.1; H, 9.6%; $M^+$, 314. $C_{17}H_{30}O_5$ requires C, 64.9; H, 9.6%; *M*, 314), τ ($CDCl_3$) 4.99 and 5.13 (2 H, AB system, $J_{AB}$ 4.0 Hz, O·$CH_2$·O), 6.06—6.96 (12 H, m, CH and other O·$CH_2$), and 7.90—9.00 (16 H, m, other $CH_2$).

rel-(1R,1'R,2R,2'R)-2,2'-[*Oxybis*(*ethyleneoxy*)]*dicyclohexanol* (8a).—The (±)-cyclic acetal (7a) (861 mg) was refluxed in N-sulphuric acid (40 ml) and acetone (10 ml) for 30 min. On cooling, the aqueous mixture was extracted with chloroform (3 × 25 ml). Evaporation of the combined extracts afforded an oily product which was homogeneous by t.l.c. on silica gel (ether as eluant) and was characterised as the (±)-*modification* (8a) (835 mg, 99%), $M^+$ 302, τ ($CDCl_3$) 5.40br (2 H, s, 2 × OH), 6.00—7.20 (12 H, m, CH and O·$CH_2$), and 7.80—9.10 (16 H, m, other $CH_2$).

rel-(1R,1'S,2R,2'S)-2,2'-[*Oxybis*(*ethyleneoxy*)]*dicyclohexanol* (8b).—Acid-catalysed hydrolysis of the *meso*-cyclic acetal (7b) (225 mg) by the procedure described above afforded an oily product which was characterised as the meso-*isomer* (8b) (210 mg, 97%), $M^+$ 302, τ ($CDCl_3$) 4.98br (2 H, s, 2 × OH), 5.90—7.10 (12 H, m, CH and O·$CH_2$), and 7.80—9.00 (16 H, m, other $CH_2$).

rel-(1R,9R,14R,22R)-2,5,8,15,18,21-*Hexaoxatricyclo*-[20.4.0.0$^{9,14}$]*hexacosane* (2a).—The (±)-diol (8a) (822 mg) was dissolved in 1,2-dimethoxyethane (30 ml) and dimethyl sulphoxide (10 ml), and sodium hydride (400 mg) and the ditosylate (9) (1.30 g) were added. The mixture was stirred at 50—55 °C. After 16 h, t.l.c. on silica gel (ether as eluant) indicated that reaction was complete. Water (150 ml) was added to destroy the excess of sodium hydride and the aqueous solution was extracted with ether (3 × 50 ml). Evaporation of the combined extracts afforded an oil which was extracted with hexane to give a crystalline product. T.l.c. indicated that this material was impure, so it was subjected to column chromatography on silica gel to give needles of trans,anti,trans-*dicyclohexyl*-18-*crown*-6 (2a) (251 mg, 25%), m.p. 77—80° (Found: C, 64.1; H, 9.6%; $M^+$, 372. $C_{20}H_{36}O_6$ requires C, 64.5; H,

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9.75%; *M*, 372), τ ($CDCl_3$) 5.84—6.44 (16 H, m, O·$CH_2$), 6.70—6.95 (4 H, m, H-1, -9, -14, and -22), and 7.80—9.00 (16 H, m, other $CH_2$).

rel-(1R,9S,14S,22R)-2,5,8,15,18,21-*Hexaoxatricyclo*-[20.4.0.0$^{9,14}$]*hexacosane* (2b).—The *meso*-diol (8b) (200 mg) was dissolved in 1,2-dimethoxyethane (15 ml) and dimethyl sulphoxide (5 ml), and sodium hydride (200 mg) and the ditosylate (9) (350 mg) were added. The above procedure for the reaction of the (±)-diol (8a) with the ditosylate (9) resulted in isolation of prisms of trans,syn,trans-*dicyclohexyl*-18-*crown*-6 (2b) (74 mg, 30%), m.p. 120—121° (from methanol) (Found: C, 64.6; H, 9.8%; $M^+$, 372. $C_{20}H_{36}O_6$ requires C, 64.5; H, 9.75%; *M*, 372), τ ($CDCl_3$) 6.10—6.41 (16 H, m, O·$CH_2$), 6.66—6.93 (4 H, m, H-1, -9, -14, and -22), and 7.80—9.00 (16 H, m, other $CH_2$).

*Reaction of* (±)-*Cyclohexane*-trans-1,2-*diol* (3) *with the Ditosylate* (9).—The diol (3) (21.05 g) and the ditosylate (9) (80.10 g) were added to a suspension of sodium hydride (9.0 g) in dimethyl sulphoxide (450 ml), and the mixture was stirred at 45 °C for 72 h. Water (450 ml) was then cautiously added to the cooled mixture, after which it was extracted with chloroform (3 × 200 ml). The combined extracts were washed with water (3 × 200 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to leave a heterogeneous mixture (30.3 g) of crystalline material in a pale brown oil. When acetonitrile (25 ml) was added, the oil dissolved and allowed the crystalline product to be filtered off. When the filtrate was left overnight at −10 °C, more crystals were obtained. The crystalline product was trans,syn,trans-*dicyclohexyl*-18-*crown*-6 (2b) (2.84 g, 12%), m.p. 120—121° (from methanol). The mother liquors from the acetonitrile crystallisation were subjected to column chromatography on alumina (1 500 g) deactivated with water (5%) (ether as eluant). One major fraction was obtained as an oil, shown to contain two components by t.l.c. on alumina (ether as eluant). On addition of hexane this fraction yielded crystals of rel-(1R,9R)-2,5,8-*trioxabicyclo*[7.4.0]*tridecane* (trans-*cyclohexyl*-9-*crown*-3) (10) (2.10 g, 6%), m.p. 29—30° (Found: C, 64.7; H, 9.92%; $M^+$, 186. $C_{10}H_{18}O_6$ requires C, 64.5; H, 9.74%; *M*, 186), τ ($CDCl_3$) 6.00—6.73 (8 H, m, O·$CH_2$), 6.73—7.15 (2 H, m, H-1 and -9), and 7.80—9.00 (8 H, m, other $CH_2$). The mother liquors from the hexane crystallisation were concentrated under vacuum to afford an oil, which, on vacuum sublimation (0.1 mmHg) at 50 °C for 6 h, yielded more *trans*-cyclohexyl-9-crown-3 (10) (980 mg, 3%). The viscous oily residue (2.58 g) from the sublimation crystallised from hexane to give needles of trans,anti,trans-*dicyclohexyl*-18-*crown*-6 (2a) (860 mg, 4%), m.p. 63—66°.

T.l.c. of isomers (2a and b) on alumina by use of a double development technique with chloroform as eluant indicated that the *trans,syn,trans*-isomer (2b) migrated sufficiently slower than the *trans,anti,trans*-isomer (2a) to permit the homogeneity of both isomers isolated from the above preparation to be established.

*Preparation of Crystalline Complexes between Selected Salts and* rel-(1R,9S,14S,22R)-2,5,8,15,18,21-*Hexaoxatricyclo*[20.4.0.0$^{9,14}$]*hexacosane* (trans,syn,trans-*Dicyclohexyl*-18-*crown*-6) (2b).—(a) *Complexes* (I)—(VI), (VIII), *and* (X). Equimolar proportions of the crown ether (2b) and the appropriate alkali metal salt were dissolved in dry methanol. The methanol was allowed to evaporate off at room temperature and the residue was finally dried at 0.1 mmHg and room temperature for 48 h to give crystals of the appropriate *complex* (see Table 1).

(b) *Ammonium thiocyanate complex* (VII). The crown ether (2b) (93 mg) and ammonium thiocyanate (19 mg) were dissolved in dry methanol (2 ml) and the solution was cooled to −10 °C overnight. Needles formed and were filtered off and dried at 0.1 mmHg and room temperature for 48 h, giving the *ammonium thiocyanate complex* (VII) (see Table 1).

(c) *Methylammonium thiocyanate complex* (IX). The crown ether (2b) (62 mg) and methylammonium thiocyanate (15 mg) were dissolved in chloroform (3 ml) and dry methanol (1 ml). The solution was filtered and evaporated to dryness at room temperature and finally at 0.1 mmHg for 48 h to afford crystals of the *methylammonium thiocyanate complex* (IX) (see Table 1).

*Stability Constant Measurements*.—The activity of the uncomplexed cation in methanolic solution was measured potentiometrically with ion selective electrodes [(i) a Corning NAS 11—18 (Cat. No. 476210) sodium ion electrode for $Na^+$ ions and (ii) a Corning monovalent cation electrode (Cat. No. 476220) for $K^+$, $Rb^+$, and $Cs^+$ ions] as described by Frensdorff.[15]

In the calculations of stability constants for 1 : 1 complexes the assumption was made that *only* 1 : 1 complexation occurred. The thermodynamic stability constant, *K*, for a 1 : 1 complex is defined by equation (1), where

$$K = f_{ML}[ML^+]/(f_M[M^+]f_L[L]) \quad (1)$$

$[ML^+]$, $[M^+]$, and [L] are the molar concentrations of complexed cation, uncomplexed cation, and uncomplexed polyether respectively, and $f_{ML}$, $f_M$, and $f_L$ are the corresponding activity coefficients. Since $f_{ML}$ and $f_M$ are unknown, the concentration stability constant, *K'*, is given by equation (2), where $f_L$ has been taken as unity.

$$K' = Kf_M/f_{ML} = [ML^+]/([M^+][L]) \quad (2)$$

When *m* ml of $M_0$ molar cation solution are mixed with *c* ml of $C_0$ molar polyether solution, *K'* is given by equation (3), where the dilution factor $D = m/(m + c)$ and *u* is the

$$K' = (1 - u)/\{uD[cC_0/m - M_0(1 - u)]\} \quad (3)$$

fraction of the cation left uncomplexed. Dilution by the titrant was taken into account in obtaining the molar ratio *u* from the concentration ratio. For the Corning Ag/AgCl reference electrode (Cat. No. 476029), equation (4) applies,

$$u = (10^{-\Delta V/59.16})/D^2 \quad (4)$$

where $\Delta V$ is the difference between the e.m.f. of the salt solution and that of the salt–polyether solution in mV measured with a Radiometer Copenhagen 26 pH meter to within ±0.2 mV.

The stability constant, *K'*, was calculated directly for each value of *u* by using equation (3) and the results were then averaged.

## RESULTS AND DISCUSSION

Acid-catalysed methylation of (±)-cyclohexane-*trans*-1,2-diol (3) with formaldehyde yields, amongst other products, the diastereoisomeric (±)- (6a) and *meso*- (6b) 2,2'-methylenedioxydicyclohexanols, which may be separated[30] by fractional crystallisation from light petroleum. Configurational assignments can be made[31] to these compounds on the basis of the O·$CH_2$·O signals

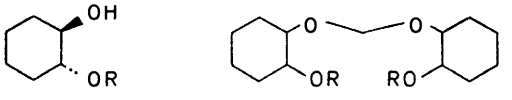
in their $^1H$ n.m.r. spectra. The enantiomers of the (±)-modification (6a) have $C_2$ symmetry and homotopic dioxymethylene protons. The *meso*-isomer (6b) has $C_s$ symmetry and diastereotopic dioxymethylene protons. Thus, the compound with m.p. 102.5—103.5°, which gave a two-proton singlet for these protons, was assigned [31] the (±)-structure (6a), and the compound with m.p. 80—82°, which gave an AB system, was assigned [31] the *meso*-structure (6b).

*Stereospecific Synthesis.*—The acyclic acetals (6a and b) were obtained by (i) methylenation of the mono-acetate (4) with dimethyl sulphoxide in the presence of 2 mol. equiv. of *N*-bromosuccinimide,[29] followed by (ii) de-*O*-acetylation of the diastereoisomeric diacetates (5) to give the diastereoisomeric diols (6), which were separated chromatographically.

The stereospecific synthesis of the *trans,anti,trans*- (2a) and *trans,syn,trans*- (2b) isomers of dicyclohexyl-18-crown-6 was accomplished as illustrated in the Scheme, in which the diastereoisomeric acyclic acetals (6a and b) were the key compounds. Treatment of (6a) and (6b) in turn with sodium hydride and 2,2′-oxybis(ethyl tosylate) (9) in 1,2-dimethoxyethane–dimethyl sulphoxide (3 : 1) afforded the cyclic acetals (7a and b) in 21 and 57% yield respectively. Acid-catalysed hydrolysis of the acetal groups in (7a and b) proceeded quantitatively in each case to give the non-crystalline diols (8a and b). Reactions of (8a) and (8b) in turn with the ditosylate (9) under similar conditions to those described above for insertion of the first $CH_2{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2$ units afforded the *trans,anti,trans*- (2a) and *trans,syn,trans*- (2b) isomers, respectively.

Recently, Bailey and Chidlow [33] have determined the *X*-ray crystal structures of these two isomers. Their results will be published elsewhere.

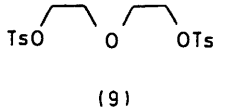
*One-step Synthesis.*—Subsequently, a one-step synthesis of (2a and b), together with some *trans*-cyclohexyl-9-crown-3 (10), was accomplished by treating (±)-cyclohexane-*trans*-1,2-diol (3) and the ditosylate



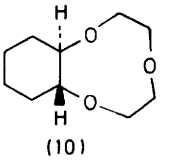
(3) R : H
(4) R : Ac



(5) R : Ac
(6) R : H



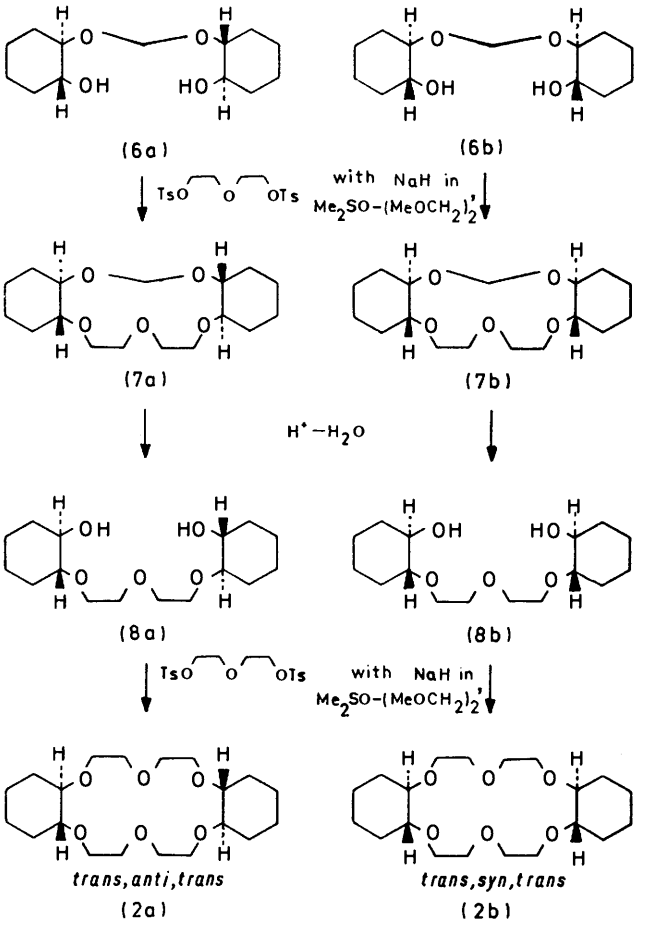
(9)



(10)

(9) in dimethyl sulphoxide with sodium hydride. The *trans,syn,trans*-isomer (2b) was obtained crystalline from acetonitrile. After chromatography on silica gel, the mother liquors afforded *trans*-cyclohexyl-9-crown-3 (10) and *trans,anti,trans*-dicyclohexyl-18-crown-6 (2a), both as crystalline compounds.

*Crystalline Complexes.*—Crystalline complexes of *trans,syn,trans*-dicyclohexyl-18-crown-6 (2b) with alkali




SCHEME Stereospecific synthesis of the *trans,anti,trans*- (2a) and *trans,syn,trans*-(2b) isomers of dicyclohexyl-18-crown-6

metal, ammonium, and primary alkylammonium salts were obtained by methods similar to those employed by Pedersen.[1,3] A list of complexes and their m.p.s *etc.* is given in Table 1, which also gives the m.p.s of the salts. The m.p.s of the complexes differ considerably in most cases from those of the salts and that (120—121°) of the *trans,syn,trans*-isomer (2b). The complexes were obtained by allowing a solution of the ligand and the salt in 1 : 1 stoicheiometric proportions in methanol or chloroform to evaporate slowly at room temperature. The ratio of ligand to salt was 1 : 1 in all the crystalline complexes obtained. In the case of the benzylammonium thiocyanate complex (VIII) and the t-butylammonium thiocyanate complex (X), removal of the solvent yielded syrups which slowly crystallised. Attempts to prepare an ammonium bromide complex of the *trans,syn,trans*-isomer (2b) with either methanol or acetone as solvent were unsuccessful. The ammonium thiocyanate complex (VII) crystallised from dilute methanolic solution in a form sufficiently pure for elemental analysis. The solvated sodium iodide (IV)

[33] N. A. Bailey and S. Chidlow, personal communication.

and ammonium thiocyanate (VII) complexes were identified from the hydroxy stretching bands in their i.r. spectra, which could be attributed to methanol of crystallisation. The postulated composition of the methylammonium thiocyanate complex (IX), in which it is proposed that there is one-third of a mole of chloroform per mole of complex, is based solely upon the elemental analysis.

In the complexes involving sodium and potassium ions the ligand presumably encircles the cation, and solution were measured potentiometrically with ion selective electrodes. The stability constants which are defined by the equilibrium constants ($K'$ in l mol$^{-1}$) for complex formation according to equation (i) were

$$L + M^{+}nMeOH \overset{K'}{\rightleftharpoons} LM^{+} + nMeOH \qquad (i)$$

obtained essentially by the method described by Frensdorff,[15] assuming only 1 : 1 complex formation. They were determined at room temperature, which varied slightly from day to day but was constant to within

TABLE 1

Crystalline complexes (1 : 1) of *trans,syn,trans*-dicyclohexyl-18-crown-6 (2b) with selected salts

| Complex | Salt | M.p. of salt (°C) | M.p. of complex (°C) | Yield (%) | Formula of complex | Required (%) C | H | N | Found (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| (I) | KI | 685 [d] | 165—169 [a] | 100 | $C_{20}H_{36}O_6$,KI | 44.6 | 6.75 | (I, 23.6) | 44.2 | 7.0 | (I, 23.8) |
| (II) | KBr | 730 [e] | 117—120 [a] | 100 | $C_{20}H_{36}O_6$,KBr | 48.9 | 7.35 | (Br, 16.3) | 48.6 | 7.25 | (Br, 16.3) |
| (III) | KSCN | 175 [d] | 116—127 [a] | 100 | $C_{20}H_{36}O_6$,KSCN | 53.7 | 7.75 | 2.98 (S, 6.85) | 53.9 | 7.95 | 2.9 (S, 6.9) |
| (IV) | NaI | 651 [e] | 90.5—92 [a] | 100 | $C_{20}H_{36}O_6$,NaI,$CH_3OH$ [f] | 45.5 | 7.25 | (I, 22.9) | 45.0 | 7.25 | (I, 22.8) |
| (V) | NaBr | 755 [e] | 118—119 [a] | 100 | $C_{20}H_{36}O_6$,NaBr | 50.5 | 7.65 | (Br, 16.8) | 50.9 | 7.65 | (Br, 16.6) |
| (VI) | $NH_4I$ | 551 [e] | 150—155 [a] | 100 | $C_{20}H_{36}O_6$,$NH_4I$ | 46.4 | 7.8 | 2.71 (I, 24.5) | 46.1 | 7.55 | 2.7 (I, 24.8) |
| (VII) | $NH_4SCN$ | 149 [d] | 71—76 [a] | 45 | $C_{20}H_{36}O_6$,$NH_4SCN$, $CH_3OH$ [f] | 55.0 | 9.2 | 5.83 (S, 6.65) | 55.1 | 9.05 | 5.8 (S, 6.15) |
| (VIII) | $PhCH_2NH_3SCN$ [g] | 97 | 68—71 [a] | 100 | $C_{20}H_{36}O_6$,$PhCH_2NH_3SCN$ | 62.4 | 8.6 | 5.20 (S, 5.95) | 61.2 | 8.4 | 5.35 (S, 6.2) |
| (IX) | $MeNH_3SCN$ [h] | 68 | 95—96 [b] | 100 | $C_{20}H_{36}O_6$,$MeNH_3SCN$, 0.33$CHCl_3$ | 53.4 | 8.5 | 5.55 (S, 6.35; Cl, 70.6) | 53.7 | 8.55 | 5.65 (S, 6.6; Cl, 6.1) |
| (X) | $Bu^tNH_3SCN$ [h] | 123 | 85—90 [c] | 100 | $C_{20}H_{36}O_6$,$Bu^tNH_3SCN$ [i] | 59.5 | 9.6 | 5.55 (S, 6.55) | 59.2 | 9.55 | 5.2 (S, 6.55) |

[a] From MeOH. [b] From MeOH–$CHCl_3$. [c] From $CHCl_3$. [d] From ref. 3. [e] 'Handbook of Chemistry and Physics,' 1972, 53rd edn., ed. R. C. Weast, The Chemical Rubber Co., Cleveland, U.S.A. [f] Hydroxy stretching bands in the i.r. spectra support the presence of methanol. [g] Supplied by Mr. W. D. Curtis. [h] Supplied by Mr. D. A. Laidler.

TABLE 2

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

| Ligand | log $K'$ [a] (temp. in °C) $Na^+$ | $K^+$ | $Rb^+$ | $Cs^+$ |
|---|---|---|---|---|
| *trans,anti,trans*-Isomer (2a) | 2.52 (24.5) | 3.26 (19) | 2.73 (22) | 2.27 (19.5) |
| *trans,syn,trans*-Isomer (2b) | 2.99 (21) | 4.14 (22.5) | 3.42 (23) | 3.00 (19) |
| *cis, anti,cis*-Isomer (2c) | 3.68 (25) [b,c] | 5.38 (25) [b,c] | | 3.49 (25) [b,c] |
| *cis,syn,cis*-Isomer (2d) | 4.08 (25) [b,c] | 6.01 (25) [b,c] | | 4.61 (25) [b,c] |
| 18-Crown-6 | 4.34 (21.5) | 6.10 (23), [d] | 5.35 (25), [d] | 4.70 (22) |
| | | 6.08 (24) [d] | 5.32 (23) [d] | |
| | 4.32 (25) [b,c] | 6.10 (25) [b,c] | | |

[a] log $K'$ ±0.1 unless otherwise stated for the chlorides. [b] Values from ref. 15. [c] Error of ±0.04. [d] Values obtained on separate occasions.

binding is probably largely a result of electrostatic attractions between the electronegative oxygens of the C–O dipoles of the ligand and the cation.[3] On the other hand, with the ammonium and primary alkylammonium ions, the complexes are probably of a face-to-face type involving hydrogen bonding of three N–H bonds to alternate oxygen atoms in the 18-crown-6 array with additional electrostatic stabilisation superimposed.[8]

*Complexes in Solution.*—Qualitative tests indicated that both the *trans,anti,trans*- (2a) and *trans,syn,trans*- (2b) isomers of dicyclohexyl-18-crown-6 form stable complexes with salts in organic solvents (*e.g.* they readily solubilise potassium permanganate in benzene).

The concentration stability constants for the formation of 1 : 1 polyether–cationic complexes of (2a) and (2b) with $Na^+$, $K^+$, $Rb^+$, and $Cs^+$ ions in methanolic ±0.2 °C during any particular run. In fact, variations of a few degrees do not affect the results within the experimental errors quoted. Table 2 lists the stability constants (log $K'$) obtained for complexation of *trans,anti,trans*- (2a) and *trans,syn,trans*- (2b) dicyclohexyl-18-crown-6 with $Na^+$, $K^+$, $Rb^+$, and $Cs^+$ ions in methanolic solution. Values of log $K'$ for 18-crown-6 are included in Table 2 since this compound serves as a 'standard' for comparison. The stability constants (log $K'$) for complexation of $Na^+$, $K^+$, and $Cs^+$ ions by *cis,anti,cis*- (2c) and *cis,syn,cis*- (2d) dicyclohexyl-18-crown-6 from the literature[15] are also included in Table 2.

A number of features and trends in Table 2 deserve comment. (i) The values of the stability constants obtained for complexation of 18-crown-6 with $Na^+$, $K^+$,

and $Cs^+$ ions agree with those reported by Frensdorff.[15] (ii) The stabilities of the complexes of the *trans,anti,trans*- (2a) and *trans,syn,trans*- (2b) isomers with these three metal cations are lower than the corresponding values obtained [15] for the *cis,anti,cis*- (2c) and *cis,syn,cis*- (2d) isomers. (iii) For $Na^+$, $K^+$, $Rb^+$, and $Cs^+$ ions, the stability constants for the *trans,syn,trans*-isomer (2b) are higher than the corresponding values for the *trans,anti,trans*-isomer (2a). Similarly, the stability constants for the *cis,syn,cis*-isomer (2d) were found [15] to be higher than those for the *cis,anti,cis*-isomer (2c). (iv) The *trans,anti,trans*- (2a) and *trans,syn,-trans*- (2b) isomers reflect the same general trends for complex formation as the *cis,anti,cis*- (2c) and *cis,syn,cis*- (2d) isomers in that they are selective for $K^+$ over $Na^+$, $Rb^+$, and $Cs^+$ ions. This is to be expected for a macrocyclic polyether with an 18-membered ring containing six symmetrically placed oxygen atoms on the basis of steric considerations, *i.e.* the size of the hole.[1,3] (v) There is a considerable difference in the complexing ability of the four isomers of dicyclohexyl-18-crown-6 (2) for $K^+$ ions. The values for log $K'$ are **3.26**, **4.14**, **5.38**, and **6.01**, respectively, for the *trans,anti,trans*- (2a), *trans,syn,trans*- (2b), *cis,anti-cis*- (2c), and *cis,syn,cis*- (2d) isomers. The same general trend in stability constants is also apparent for $Na^+$ and $Cs^+$ ions.

As a general rule,[4] the greater the departure of the ligand conformation in the complex from the equilibrium conformation of the ligand, the greater will be the destabilisation introduced by the ligand deformation on complexation. Although entropy effects will also be important,[4] and arise most obviously from (i) the increase in the translational entropy of the methanol molecules displaced from the cation on complexation and (ii) the decrease in ligand internal entropy on complex formation, their contribution to the free energy of the system is not liable to be markedly different for the four isomers of dicyclohexyl-18-crown-6 (2).

Assuming a degree of correspondence between the solid and solution state conformations, the conformational changes undergone by the *trans,anti,trans*- (2a) and *trans,syn,trans*- (2b) isomers on complexation of metal cations to give ligand–cation complexes (in which the conformations of the ligands are expected to be such that all the oxygens ' point ' towards the centres of the molecular cavities) differ considerably. In the crystal structure [33] of the *trans,syn,trans*-isomer (2b), *four* of the six oxygens ' point ' towards the centre of the molecular cavity in the free ligand and so a *relatively small* conformational change is required on complexation to reorient the other two oxygens to ' point ' inside. In contrast, the crystal structure [33] of the *trans,anti,trans*-isomer (2a) indicates that only *one* of the six oxygen atoms ' point ' towards the centre of the molecular cavity in the free ligand and hence a *relatively large* conformational change has to occur on complexation in order to reorient the other five oxygens to ' point ' inside. Thus, the stability constants for complexation of metal cations by the *trans,syn,trans*-isomer (2b) are expected to be higher than those for the *trans,anti,trans*-isomer (2a). Indeed, this is the case.

The *cis,anti,cis*- (2c) and *cis,syn,cis*- (2d) isomers both have four oxygen atoms ' pointing ' into the centres of their molecular cavities in the crystal structures [25] of their free ligands. Both these isomers form more stable complexes (see Table 2) than do the di-*trans*-isomers (2a and b). The reasons for this trend are not immediately apparent, although we note that whereas the cyclohexane rings of (2a and b) are rigid they are flexible in the di-*cis*-isomers (2c and d).

We thank Dr. F. S. H. Head of the Shirley Institute for pure specimens of the diastereoisomeric methylenedioxydicyclohexanols, Dr. G. H. Jones of the Corporate Laboratory of Imperial Chemical Industries Limited for giving advice on the potentiometric determination of stability constants with cation-selective electrodes, and Mr. R. M. King for technical assistance. A Postgraduate Studentship (to A. C. C.) from the S.R.C. is acknowledged.

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