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Preliminary communication

Enantiomeric differentiation by a chiral symmetrical crown derived from L-iditol*

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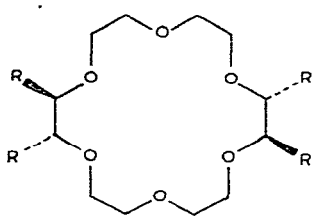
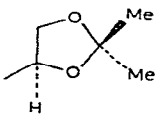
In our design of enzyme analogues around chiral crown compounds derived from carbohydrate precursors, we have incorporated L-threitol[1,2], D-mannitol[1–5], D-glucose[5], and D-galactose[5] into the crown constitution. 1,2:1′,2′:5,6:5′,6′-Tetra-*O*-isopropylidene-3,3′:4,4′-bis-*O*-oxydiethylenedi-D-mannitol[1] DD-(**1**) exhibits[2] enantiomeric differentiation in complexation equilibria towards (*RS*)-α-phenylethylammonium hexafluorophosphate. Accordingly, it was of interest to discover the effect on chiral recognition of formally inverting the configurations at C-2, C-2′, C-5, and C-5′ of DD-(**1**) to give the diastereoisomeric tetra-*O*-isopropylidene derivative LL-(**2**), which we now demonstrate may be obtained from L-iditol[6].

1,2:5,6-Di-*O*-isopropylidene-L-iditol[7] [L-(**3**)], m.p. 84–85°, $[\alpha]_D$ +0.95° (*c* 1.9, chloroform), was isolated in 7% yield after chromatography on silica gel (ether) of the products resulting from partial acetonation of L-iditol[6] by a procedure (acetone–zinc chloride) analogous to that reported[8] for the preparation of the corresponding derivative from D-mannitol. Treatment of L-(**3**) with excess of allyl bromide and potassium hydroxide in toluene gave the diallyl ether L-(**4**) in 66% yield. Ozonolysis of L-(**4**), followed by borohydride reduction (*cf.* Ref. 9), then afforded (88%) the crystalline "half-crown" diol L-(**5**), m.p. 80–85°. Conversion (45%) of L-(**5**) into the "half-crown" bis(toluene-*p*-sulphonate) L-(**6**), $[\alpha]_D$ +7.1° (*c* 0.72, chloroform), which was purified by chromatography on silica gel (ether), was followed by reaction of equimolar proportions of L-(**5**) and L-(**6**) with sodium hydride in dimethyl sulphoxide to afford, after chromatography on alumina (ether), the tetra-*O*-isopropylidene derivative LL-(**2**), m.p. 60–66°, $[\alpha]_D$ −6.9° (*c* 0.49, chloroform); ^{1}H-n.m.r. data (CD_2Cl_2): δ 4.36–3.46 (m, 32 H, CH_2 and CH protons), and 1.34 and 1.30 (2 s, 2 × 12 H, 8 × CH_3) (see Fig. 1*a*). Subsequently,

*Dedicated to the memory of Sir Edmund Hirst, C.B.E., F.R.S.



DD-(1) R =



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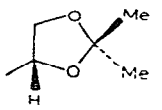
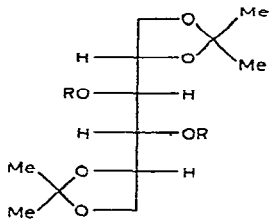
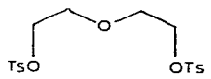




L-(3) R = H
L-(4) R = $CH_2CH{=}CH_2$
L-(5) R = CH_2CH_2OH
L-(6) R = CH_2CH_2OTs



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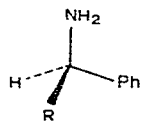
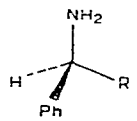


(*R*)-(8) R = Me
(*S*)-(9) R = CO_2Me



(*S*)-(8) R = Me
(*R*)-(9) R = CO_2Me

LL-(2) was obtained in 3.3% yield after chromatography on alumina (ether) of the products resulting from reaction between L-(3), diethylene glycol bis(toluene-*p*-sulphonate)[10] (7), and sodium hydride in dimethyl sulphoxide.

Significant changes were observed in the ^{1}H-n.m.r. spectrum of LL-(2) in $CDCl_3$ in the presence of primary alkylammonium salts, indicating the formation of complexes. A quantitative assessment of complexing power was obtained by measuring stability constants (K_a in l.mol^{-1}) for the equilibrium (*1*) by an ^{1}H-n.m.r. spectroscopic method[11]. Stability constants for R = ^{t}Bu (K_a 800) and R = $PhCH_2$ (K_a >10^7) indicate that the crown LL-(2) is capable of high steric differentiation in common with crown DD-(1) which is characterised[2] by somewhat lower K_a values for R = ^{t}Bu (K_a <30) and R = $PhCH_2$ (K_a 1.5 X 10^6); *i.e.*, crown LL-(2) forms slightly stronger complexes than crown DD-(1).

$$RNH_3{}^+SCN^- + \text{Crown} \overset{K_a}{\rightleftharpoons} RNH_3\text{Crown}^+SCN^- \qquad (1)$$

An ^{1}H-n.m.r. spectroscopic method[12] shows that, although crown LL-(2), in contrast with crown DD-(1), does not exhibit enantiomeric differentiation in complexation equilibria towards (*RS*)-α-phenylethylammonium hexafluorophosphate (*RS*)-(8)·HPF_6, it

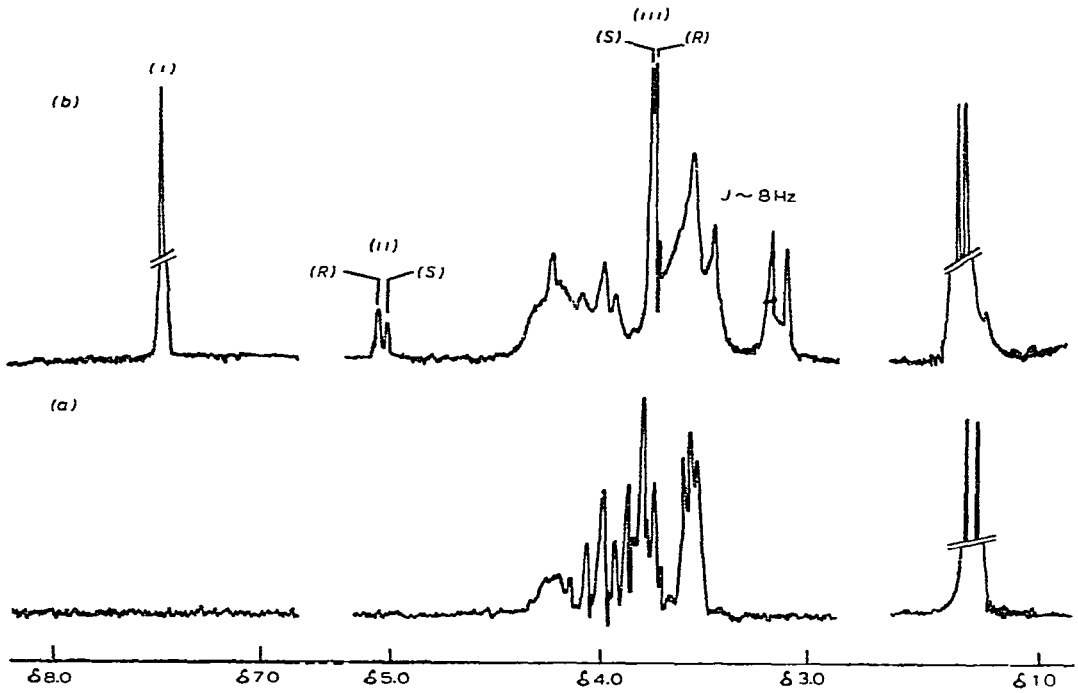


Fig. 1. The ^{1}H-n.m.r. spectra (100 MHz) of (*a*) the crown LL-(2) in CD_2Cl_2 and (*b*) the equilibrated LL-(2)–(*R*)-(9)·$HClO_4$ and LL-(2)–(*S*)-(9)·$HClO_4$ complexes in CD_2Cl_2, showing (*i*) the phenyl protons, (*ii*) the methine protons, and (*iii*) the methyl protons of the complexed salt. The doublet at δ 3.15, J ~8 Hz, is assigned to one of each of the four pairs of carbohydrate methylene protons.

does show chiral recognition towards the perchlorate salt of (*RS*)-phenylglycine methyl ester (*RS*)-(9)·$HClO_4$ in favour of the (*R*)-isomer. The ^{1}H-n.m.r. spectrum (see Fig. 1*b*) in CD_2Cl_2 of the $CDCl_3$-layer concentrate containing the diastereoisomeric complexes LL-(2)–(*R*)-(9)·$HClO_4$ and LL-(2)–(*S*)-(9)·$HClO_4$ in the ratio of 60:40, after equilibration of the crown LL-(2) (1.0 mol. equiv.), lithium perchlorate (3.0 mol. equiv.), and racemic salt (*RS*)-(9)·$HClO_4$ (3.0 mol. equiv.) at 0° between $CDCl_3$ and D_2O, is characterised by small chemical-shift differences between the methine protons [(*ii*)] and the methyl protons [(*iii*)] of (*R*)- and (*S*)-(9)·$HClO_4$. Somewhat surprisingly, crown DD-(1) does not show any chiral recognition towards (*RS*)-(9)·$HClO_4$. The results are summarised in Table I. Comparison between the ^{1}H-n.m.r. spectra (*e.g.*, Fig. 1*b*) of complexes such as LL-(2)–(*RS*)-(9)·$HClO_4$ and the free crown LL-(2) reveals, in the spectra of the complexes, the presence of an isolated, broadened doublet (J ~8 Hz) shifted to substantially higher field and integrating for four protons. We assign this doublet to one of each of the two methylene protons on C-1, C-1′, C-6, and C-6′ in the four 2,2-dimethyl-1,3-dioxolanyl groups. This feature was not evident in the ^{1}H-n.m.r. spectra of complexes involving crown DD-(1), and so it may be concluded that the configurational differences at C-2,

TABLE 1

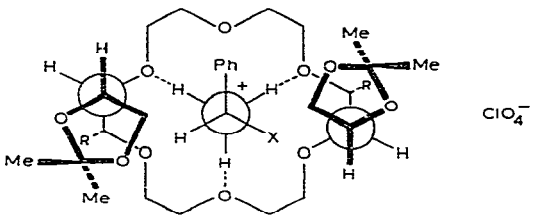
^{1}H-N.M.R. SPECTROSCOPIC DATA FOR THE CONTENTS OF THE $CDCl_3$ LAYER IN CHIRAL RECOGNITION EXPERIMENTS ON CROWNS DD-(1) AND LL-(2) WITH SALTS (*RS*)-(8)·$HClO_4$ AND (*RS*)-(9)·$HClO_4$

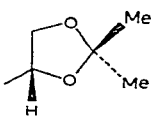
Crown Solvent[a]	δ(J/Hz)[b] (R)-(8)·*HClO$_4$*-[*CH$_3$*][c]	δ(J/Hz)[b] (S)-(8)·*HClO$_4$*-[*CH$_3$*][c]	δ(J/Hz)[b] (R)-(9)·*HClO$_4$*-[*CH*][c]	δ(J/Hz)[b] (S)-(9)·*HClO$_4$*-[*CH*][c]	[*Salt*]/[*Crown*][d]	*Enantiomeric differentiation* (R)-*Salt*:(S)-*Salt*[e]
DD-(1) $CDCl_3$	1.62(7.0)	1.67(7.0)	–	–	1.3	62:38[f]
DD-(1) C_6D_6	–	–	5.23	5.28	1.25	50:50
LL-(2) C_6D_6	1.55(7.0)[g]	1.58(7.0)[g]	–	–	1.55	50:50
LL-(2) CD_2Cl_2	–	–	5.05[h]	5.02[h]	1.0	60:40

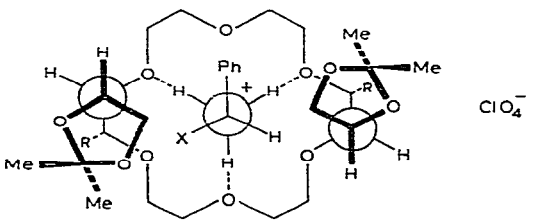
[a] Although equilibrations in the chiral recognition experiments were carried out between $CDCl_3$ and D_2O, it was usually advantageous, from the point of view of obtaining appreciable chemical-shift differences between originally coincident signals arising from the previously enantiomeric salts, to record spectra in other solvents. The fact that no duplications of the signals for the crowns are observed means that exchange between salt and crown is fast on the ^{1}H-n.m.r. time-scale. [b] The spectra were recorded either (*i*) at 100 MHz on a Varian HA100 spectrometer or (*ii*) at 220 MHz on a Perkin-Elmer R34 spectrometer with Me_4Si as "lock" and internal standard. [c] Configurational assignments were made on the basis of spectra obtained for 1:1 complexes between the crowns and the salts containing both enantiomers but enriched in either the (*R*)- or (*S*)-isomer. [d] Salt-to-crown ratios in excess of 1.0 indicate the presence of some 2:1 complex formation. [e] The absolute configurations of (*R*)-(8) and (*S*)-(8) correlate with the absolute configurations of (*S*)-(9) and (*R*)-(9), respectively. [f] This ratio was obtained (see Ref. 2) for the hexafluorophosphate salt (*RS*)-(8)·HPF_6. [g] These chemical shift assignments to (*R*)-and (*S*)-(8)·$HClO_4$ are arbitrary. [h] The methyl protons of the methoxycarbonyl groups of (*R*)- and (*S*)-(9)·$HClO_4$ also exhibited (see Fig. 1*b*) chemical shift non-equivalence with δ 3.75 and 3.77 for (*R*)-(9)·$HClO_4$-[CH_3] and (*S*)-(9)·$HClO_4$-[CH_3], respectively.

C-2′, C-5, and C-5′ in crown LL-(2) confer a spatial arrangement upon the 2,2-dimethyl-1,3-dioxolanyl groups, when they are part of the *ido* configuration, that orients the two pairs of carbohydrate methylene group towards the central complexing cavity on each homotopic face of the crown (see Fig. 2).

The chiral recognition of crown LL-(2) towards (*RS*)-(9)·$HClO_4$ may be accounted for by reference to the three-point binding models for the diastereoisomeric complexes shown in Fig. 2, in which the "best" Newman projections for the cations are displayed. Inspection of Corey–Pauling–Koltun space-filling molecular models indicates that the complex LL-(2)–(*S*)-(9)·$HClO_4$ experiences more steric compression of its methoxycarbonyl group than does the complex LL-(2)–(*R*)-(9)·$HClO_4$, in accordance with the observed (*R*):(*S*) ratio of 60:40 in the chiral recognition test.



LL-(2)-(*R*)-(9) · $HClO_4$ R =  ; X = CO_2Me



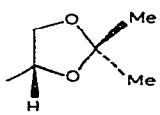
LL-(2)-(*S*)-(9) · $HClO_4$ R =  ; X = CO_2Me

Fig. 2. The diasteroisomeric complexes LL-(2)–(*R*)-(9)·$HClO_4$ and LL-(2)–(*S*)-(9)·$HClO_4$.

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