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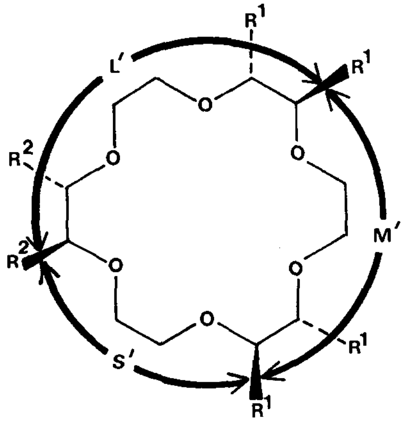
THE SYNTHESIS OF A CHIRAL RECEPTOR MOLECULE CONTAINING THREE CARBOHYDRATE RESIDUES WITHIN A 20-CROWN-6 CONSTITUTION

David G. Andrews, Peter R. Ashton, Dale A. Laidler, J. Fraser Stoddart[1], and John B. Wolstenholme

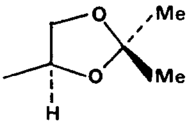
Department of Chemistry, The University, Sheffield S3 7HF

The rationale behind designing and the approach to synthesising chiral crown ethers incorporating three trigonally-disposed carbohydrate residues is presented as a prelude to attaining chiral discrimination in the complexation of (R)- and (S)-α-phenylethylammonium perchlorate.

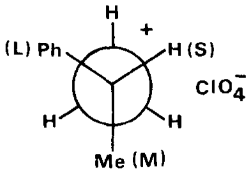
In our search[2] for chiral receptor molecules which will differentiate between the enantiomers of racemic substrates, optically-active macrocyclic polyethers incorporating carbohydrate residues have been derived[3] directly or formally from L-threitol, D-mannitol, L-iditol, D-glucose, D-galactose, D-mannose, and D-altrose. Previously, however, we have built only one, or at the most two, carbohydrate residues into 18- or 20-crown-6 constitutions. Inspection of Corey-Pauling-Koltun (CPK) space-filling molecular models led us to the belief that chiral recognition of racemic primary alkylammonium salts such as *(RS)*-$PhCHMeNH_3^+ClO_4^-$ *(RS)*—(1).$HClO_4$ might conceivably be improved by including three carbohydrate residues—two the same and one different—into the 18-crown-6 constitution. The general design of such a molecular receptor containing C_2 symmetry with large (L'), medium (M'), and small (S') cavities on each of the homotopic faces[4] to match sterically the large (L), medium (M), and small (S) ligands attached to the chiral centres of *(R)* - 1.$HClO_4$ and *(S)*-1.$HClO_4$ suggested[5] the 18-crown-6 derivative DDL-(2) incorporating two 1,2:5,6-di-*O*-isopropylidene-D-mannitol[6] D-(3) residues and one 1,4-di-*O*-benzyl-L-threitol[2,7] L-(4) residue a
a possible synthetic goal. However, we felt that molecular receptor complexes embracing attractive electronic interactions of a dipole-induced dipole type between a 1,3-dioxan ring and a phenyl group[8] might lead to them being more highly structured with a better



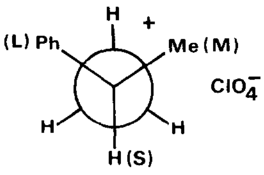
DDL-2 R^1 =



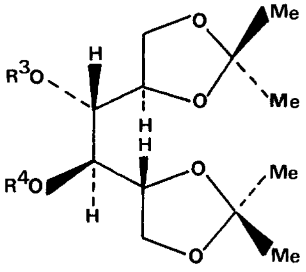
; $R^2 = CH_2OCH_2Ph$



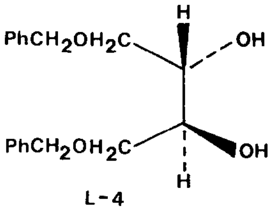
(R)-1.$HClO_4$



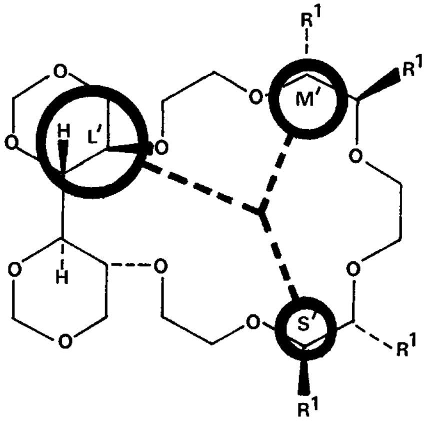
(S)-1.$HClO_4$



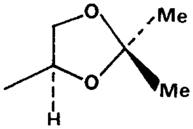
	R^3	R^4
D-3	H	H
D-7	$CH_2CH{=}CH_2$	H
D-8	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$
D-9	CH_2CH_2OH	H
D-10	CH_2CH_2OH	CH_2CH_2OH
D-11	$CH_2CH_2OSiMe_2Bu^t$	H
D-12	$CH_2CH_2OSiMe_2Bu^t$	CH_2CH_2OH
D-13	$CH_2CH_2OSiMe_2Bu^t$	$CH_2CH_2OSiMe_2Bu^t$
D-14	$CH_2CH_2OSiMe_2Bu^t$	CH_2CH_2OTs

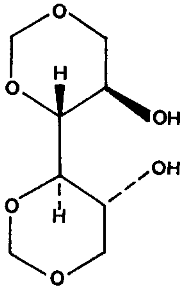


L-4

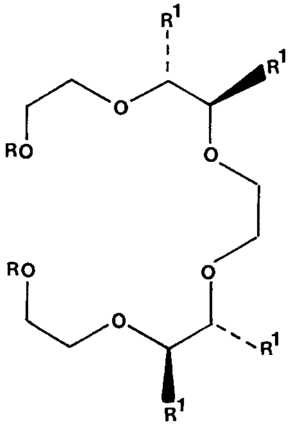


DDD-5 R^1 =

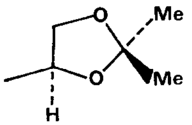




D-6



R^1 =



DD-15 R = $SiMe_2Bu^t$

DD-16 R = H

DD-17 R = Ts

chance consequently of exhibiting good chiral recognition towards *(RS)*-1.$HClO_4$. In this communication, we describe the synthesis of a 20-crown-6 derivative DDD-(5) incorporating two 1,2:5,6-di-*O*-isopropylidene-D-mannitol D-(3) and one 1,3:4,6-di-*O*-methylene-D-mannitol[9] D-(6) residue and report on some preliminary observations regarding its complexing and chiral recognition properties.

Diacetone-D-mannitol D-(3) was converted[2] into a mixture of its mono- D-(7) and di- D-(8) allyl ethers which were separated by medium pressure liquid chromatography (m.p.l.c.)[10] (light petroleum, b.p. 60-80°C:Et_2O, 6.7:1 → 1:1) on SiO_2. Both D-7 and D-8 were subjected to ozonolysis in MeOH followed by reduction with $NaBH_4$ in MeOH/H_2O to give[11] the 'half-extended' diol D-(9), $[\alpha]_D$ + 8° (*c* 2.3, Table. Temperature dependent ^{1}H n.m.r. spectral data and kinetic and thermodynamic parameters for the 1:1 complexes between (*R*)- and (*S*)-1.$HClO_4$ and DDD-5 [a]

1.$HClO_4$	δ-H_A [b]	δ-H_B [b]	T_c, °C ±3°	Δν(-90°C), ±2 Hz	k_c s^{-1}	$\Delta G_c^{\ddagger}$, ±0.3 kcal mol^{-1}
(*R*) -Isomer	5.06 [c]	4.60	-59	28.9	64	10.6
(*S*) -Isomer	5.02 [d]	4.55	-64	19.6	44	11.5

[a] Spectra were recorded in CD_2Cl_2 at 220 MHz on a Perkin Elmer R34 spectrometer with Me_4Si as "lock" and internal standard. Abbreviations used are: T_c, coalescence temperature; Δν, frequency separation for H_A of the OCH_2O protons at -90°C; k_c, exchange rate constant at T_c calculated from the expression $k_c = \pi\Delta\nu/2^{\frac{1}{2}}$; $\Delta G_c^{\ddagger}$, free energy of activation at T_c calculated from the Eyring equation.

[b] Chemical shifts of the OCH_2O protons at +30°C.

[c] This signal separates out into two doublets centred on δ 5.07 and 5.20 at -90°C.

[d] This signal separates out into two doublets centred on δ 5.09 and 5.18 at -90°C.

$CHCl_3$) as an oil and the 'fully-extended' diol D-(10), m.p. 76-77°, $[\alpha]_D$ + 14.2° (*c* 1.65, $CHCl_3$). Treatment (*cf.* ref. 12) of D-9 in Me_2NCHO at 35°C with 1.0 molar equivs. of Bu^tMe_2SiCl in the presence of imidazole as base gave (88%) pure mono-*t*-butyldimethylsilyl ether D-(11), $[\alpha]_D$ + 3° (*c* 2.4, $CHCl_3$) without resort to chromatography. Partial silylation of D-10 with 1.0 molar equivs. of Bu^tMe_2SiCl afforded a mixture (46 and 15%, respectively) of the mono- D-(12), $[\alpha]_D$ + 13.6° (*c* 3.0, $CHCl_3$) and di- D-(13), $[\alpha]_D$ + 14.0° (*c* 1.8, $CHCl_3$) silyl ethers which were separated from each other and starting material by m.p.l.c. (light petroleum, b.p. 60-80°C : $MeCO_2Et$, 3:1) on SiO_2. After near quantitative (98%) conversion of D-12 into its tosylate D-(14), $[\alpha]_D$ + 12.6° (*c* 1.8, $CHCl_3$), D-11 was condensed with D-14 in tetrahydrofuran in the presence of Bu^tOK at 60°C to give the disilyl ether DD-(15), $[\alpha]_D$ + 19.7° (*c* 0.97, $CHCl_3$) in 23% yield after m.p.l.c. (CH_2Cl_2:$MeCO_2Et$, 9:1) on SiO_2. Treatment (*cf.* ref.12) of DD-15 with $Bu^n_4N^+F^-$ in tetrahydrofuran at 35°C afforded (77%) the diol DD-(16), $[\alpha]_D$ + 23.8° (*c* 1.5, $CHCl_3$) after column chromatography ($MeCO_2Et$) on SiO_2. Conversion (80% isolated yield) of DD-16 into its pure ditosylate DD-(17), $[\alpha]_D$ + 16.0° (*c* 0.88, $CHCl_3$) proceeded smoothly in the presence of 3.5 molar equivs. of TsCl in C_5H_5N below 0°C. Condensation (NaH/Me_2SO) of D-6 with DD-17 at 60°C afforded in 4% yield—after column chromatography (Et_2O) on SiO_2—the 20-crown-6 derivative DDD-(5), m.p. 50-54°, $[\alpha]_D$ - 1.6° (*c* 0.99, $CHCl_3$), ^{1}H n.m.r. data : δ (CD_2Cl_2) 1.34 and 1.41 (2xs, 24H, 8xCH_3), 3.27-4.38 (m, 36H, all other protons other than OCH_2O protons), and 4.62 and 5.03 (4H, AB system, J_{AB} = 6 Hz, OCH_2O).

Variable temperature ^{1}H n.m.r. spectroscopy in CD_2Cl_2 of the 1:1 complexes formed between (*R*)- and (*S*)-1.$HClO_4$ and DDD-5 resulted in each case in the separation of the A portion[13] of the AB system for the OCH_2O protons into two doublets at low temperatures (*i.e.* -90°C). This behaviour indicates that the phenyl groups are interacting electronically with the 1,3-dioxan rings and that both complexes are highly structured. The kinetic and thermodynamic data for these 1:1 complexes are summarized in the Table. The $\Delta G_c^{\ddagger}$ values can be equated (*cf.* ref. 8) with the free energies of activation ($\Delta G_d^{\ddagger}$) for dissociation of the complexes in a process in which the cations are exchanging between the homotopic faces of DDD-5. On the assumption that the free energies of the transition states for dissociation of the complexes are characterized predominantly by the dissociated crown and enantiomeric cations, the difference of 0.9 kcal mol^{-1} in the $\Delta G^{\ddagger}_{d}$ values reflects (*cf.* ref. 8) the difference in the ground state free energies of the diastereoisomeric complexes. Thus, DDD-5 exhibits modest chiral recognition towards *(RS)*-1.$HClO_4$ in favour of the *(S)*-isomer at low temperatures in CD_2Cl_2.[14] This observation is in accordance with the prediction gleaned from inspection of CPK space-filling molecular models. These show that the *(S)*- isomer of 1.$HClO_4$ experiences (see ref. 4) a better match electronically and sterically with DDD-5 than does the *(R)*-isomer. Clearly, chiral crown ethers containing *three* carbohydrate residues disposed *trigonally* have much more potential to discriminate between enantiomeric salts than do chiral crown ethers containing *two* carbohydrate residues disposed *diagonally*.

References and Footnotes

1. Address all correspondence to this author at the Corporate Laboratory, Imperial Chemical Industries Ltd., P.O. Box No. 11, The Heath, Runcorn, Cheshire WA7 4QE.
2. W.D. Curtis, D.A. Laidler, J.F. Stoddart, and G.H. Jones, *J.C.S. Perkin 1*, 1756 (1977).
3. D.A. Laidler, J.F. Stoddart, and J.B. Wolstenholme, *Tetrahedron Lett.*, 465 (1979) and earlier communications in this series.
4. We have indicated by means of arrows and the symbols L', M', and S' the relative dispositions of the large, medium, and small cavities on the top face of the formula for DDL-2. If the 1,3-dioxan ring in DDD-5 underneath the circular area denoted by L' is assumed to interact attractively with a phenyl group, then the medium and small cavities on the top face have the relative dispositions defined by M' and S' respectively within the circular areas shown.
5. Although three binaphthyl units have been incorporated (E.P. Kyba, G.W. Gokel, F. de Jong, K. Koga, L.R. Sousa, M.G. Siegel, L. Kaplan, G.D.Y. Sogah, and D.J. Cram, *J. Org. Chem.*, 42, 4173 (1977)) into 24-crown-6 derivatives, these chiral compounds failed (F. de Jong, M.G. Siegel, and D.J. Cram, *J.C.S. Chem. Comm.*, 551 (1975)) to complex with primary alkylammonium ions.
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10. A detailed specification of our 'home-built' m.p.l.c. system will be supplied upon request.
11. The compositions of all new compounds were confirmed by elemental analyses. Structural assignments were based upon the results of mass spectrometry and ^1H n.m.r. spectroscopic evidence.
12. E.J. Corey and A. Venkateswarlu, *J. Amer. Chem. Soc.*, 94, 6190 (1972).
13. In each case, the B portion was obscured by signals for other protons in the 1:1 complexes at low temperatures.
14. An attempt to assess the chiral recognition properties of DDD-5 towards *(RS)*-$PhCHMeNH_3^+PF_6^-$, following equilibration of the diastereoisomeric complexes in the presence of excess of racemic salt and $LiPF_6$ between $CDCl_3$ and D_2O (*cf.* ref. 2), was thwarted by lack of resolution in the ^1H n.m.r. spectrum at 220 MHz of any of the ^1H n.m.r. probes in the previously enantiomeric salts.

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