HETEROCYCLES, Vol 28, No 2, 1989

HETEROCYCLIC POLYETHERS DERIVED FROM D-SORBITOL AND D-MANNITOL AS HOSTS FOR CHIRAL AMMONIUM SALTS

Elizabeth A.El'perina, Edward P.Serebryakov* and Marina I.Struchkova
Institute of Organic Chemistry of the USSR Academy of Sciences,
117913 Moscow, the USSR

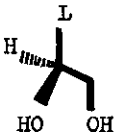
Abstract - Coronands (3a) and (3b) derived from D-sorbitol display but poor or no recognition towards (R)- or (S)-α-phenylethylammonium hexafluorophosphates (PEA.HPF_6) but selectively extract (R)- and (S)-enantiomers, respectively, of the α-phenylglycine methyl ester salt. All novel derivatives of D-mannitol (6,7a-e) show no chiral recognition towards PEA.HPF_6 or PEA.$HClO_4$, the complexing ability of podands 7a-e varying with the nature of side chains.

D-Mannitol and L-iditol are known to be suitable starting materials for the synthesis of homotopic chiral coronands[1,2]. Recently we obtained homotopic coronands from the most available hexitol, D-sorbitol[3], as well as novel coronands and podands based on D-mannitol[4,5]. Here we report about the complexing properties of some of these compounds in respect to chiral cations derived from α-phenylethylamine (PEA) and α -amino esters. An improved procedure to prepare (3a-b) is also included.

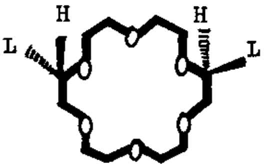
1,3:2,4-Di-O-ethylidene- and 1,3:2,4-di-O-benzylidene-D-sorbitols (1a,b) or 1,4:3,6-dianhydro-D-mannitol(2), available from the parent hexitols in one step, produce in fair yields 18-crown-6 ethers possessing C_2 symmetry when condensed with $TsOCH_2CH_2OCH_2CH_2OTs$ (DEGDT) or $TsO(CH_2CH_2O)_3Ts$ (TEGDT), respectively, in superbase system MOH/DMSO (M=K or Na). In principle, from diols 1a,b both homotopic 2R,12R-disubstituted coronands (3a,b) and their heterotopic 2R,11R-disubstituted positional isomers (4a,b) could be obtained under these conditions. However, different reactivity of the 6-OH and 5-OH groups in 1a,b allows to secure preferential formation of 3a and 3b by means of temperature-controlled two-steps one-pot O-alkylation (see Experimental) in 43 and 36% yield, respectively, the only side products being the corresponding non-complexing 9-crown-3 ethers (5a) and (5b) isolated in 14 and 10% yield. Earlier, 3a and 3b were obtained in lower yields by the regiocontrolled four-step synthesis.[3]

Similarly, in NaOH/DMSO system at 60°C diol 2 reacts with TEGDT to give coronand (6) or undergoes double O-alkylation to give podands (7a-c) and the intermediates for podands (7d,e) in much better yields than in the well-known Hakomori's system (NaH/DMSO)[4,5]. Moreover, in KOH-DMSO system at 60°C the yield of the known coronand (8) from 1,2:5,6-di-O-isopropylidene-D-mannitol and DEGDT rises to 36% as compared with 24% yield in Hakomori's system (cf.[6]).

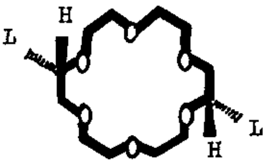
The complexing ability of coronands 3a,b and 6 in respect to hexafluorophosphates of (+)-, (-)-, and (±)-PEA [(R)-, (S)-, and (RS)-9a], of (-) and (±)-α-phenylglycine methyl ester [(R)- and (RS)-10], and of (R)-, (S)-, or (RS)-alanine, (S)- or (RS)-phenylalanine, and (S)- or (RS)-leucine methyl ester was studied by means of the known[7] extraction technique using ^{1}H-nmr spectroscopy[8,9] for the determination of the extracting ability, $R_e = [\text{Host.Guest}]_{CDCl_3}/[\text{Host}]_{CDCl_3}$, host-guest association constant, K_a, and free energy of complexation, ΔG. Enantiomer distribution constant (EDC) was also determined from the areas of signals belonging to (R)- and (S)- enantiomers of the guest in the ^{1}H-nmr spectra of host-guest complexes found in organic phase upon contacting 3a,b or 6 with aqueous solutions of racemic salts. 18-Crown-6 ether and coronand 8 were used as reference compounds. The results are shown in the Table 1. The values of R_e for all coronands tested are close to unity and imply the formation of 1:1 complexes. As for chiral recognition, the ability of 3a to transfer selectively (R)-9a into organic phase is much weaker than that of 8 [(R)-9a/(S)-9a being only 1.10 for 3a against 1.62 for 8] while 3b does not distinguish between (R)- and (S)-9a at all. At the same time coronand 8, inspite of its D_2 symmetry, displays no chiral recognition towards (R)- or (S)-10 whereas coronand 3a shows weak but reliable selectivity towards (R)-10 and coronand 3b is able to transfer preferably (S)-10 into organic phase. This reversal of enantioselectivity seems incompatible with Cram's three-point bind-



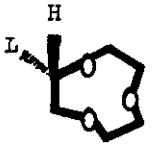
1a,b



3a,b

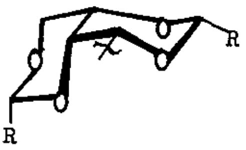


4a,b

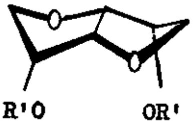


5a,b

where L=

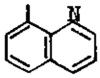


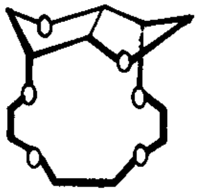
R=Me (1a, 3a, 5a)
R=Ph (1b, 3b, 5b)



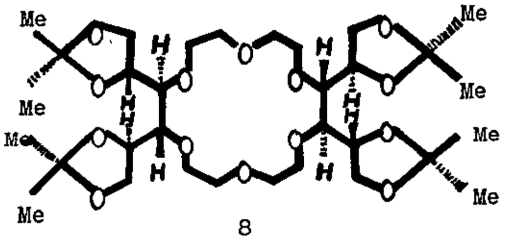
2 R' = H
7a R' = CH_2CH_2OEt
7b R' = $(CH_2CH_2O)_2Et$
7c R' = $CH_2CH(OEt)_2$
7d R' = CH_2CH_2O-R
7e R' = $(CH_2CH_2O)_2$-R

where R =





6



8

ing model and might be tentatively assigned to a kind of hydrophobic interaction of phenyl groups of the host (3b) and the guest (10) in the complex. The total lack of enantioselectivity in the complexation of 6 with 9a and 10 might be due to the similarity of van der Waals volumes of $-CH_2-$ and -O- groups in the heterocyclic nucleus of 6 $(\Delta V_W \sim 5 cm^3/mol)$.

The same explanation can account for total lack of chiral recognition in the case of association of podands 7a-e with perchlorates of (+)-, (-)-, and (±)-

PEA [(R)-9b, (S)-9b, and (RS)-9b] in spite of the fact that the formation of diastereomeric host-guest pairs is manifested by the double sets of signals in ^{1}H-nmr and ^{13}C-nmr spectra of complexes of 7a-e with (RS)-9b. The complexing ability of these podands depends on the nature of side chains. For podands with ether or acetal groups it is low (R_e for 7a, 7b and 7c being 0.10, 0.16 and 0.19, respectively) while podands with 8-hydroxyquinoline residues, 7d and 7e, can bind up to two molecules of 9b (R_e being 1.7 and 2.0, respectively).

The ^{1}H-nmr spectra of complexes formed by coronand 3a with hexafluorophosphates of (RS)-alanine, (RS)-phenylalanine and (RS)-leucine methyl esters display double sets of signals in comparison with the spectra of complexes formed from 3a and individual (R)- or (S)-AlaOMe.HPF$_6$, (S)-PheOMe.HPF$_6$ and (S)-LeuOMe.HPF$_6$. However, in neither case any selectivity of complexation could be observed, the (R):(S) ratio remaining at 1.00 for each of the racemates.

The closest analogues of coronands 3a,b by molecular symmetry (C_2) and the pattern of substitution are monoaza-crowns of types A (X=O or H_2) and B, whose complexation with chiral ammonium salts had be studied by several methods[10,11], and diaza-crowns of type C[12]. Among them compounds of group A (particularly when X=H_2) display well-pronounced chiral recognition in respect to rather bulky α-(1-naphtyl)ethylammonium and O-methyl-α-phenylalaninium ions, while compounds of groups B and C are not able to distinguish between enantiomeric ammonium salts. In aza-crowns of group A the coplanarity of five contiguous links in the macrocycle, the presence of a strongly binding heteroatom in the pyridine nucleus, and the proximity of two chiral centres to this site all contribute to enhance the energy difference between diastereomeric host-guest complexes ($\Delta\Delta G$=0.3-1.6 kcal/mol). Conformationally flexible coronands 3a, b display much lower enantioselectivity ($\Delta\Delta G \leq 0.065$ kcal/mol), although - and this is worth noting - in respect to less bulkier substrates. The fact that 3a and 3b show some degree of chiral recognition towards 9a or 10 whereas their analogues of type C do not might point to the role of bulky side groups of 3a,b in complexation.

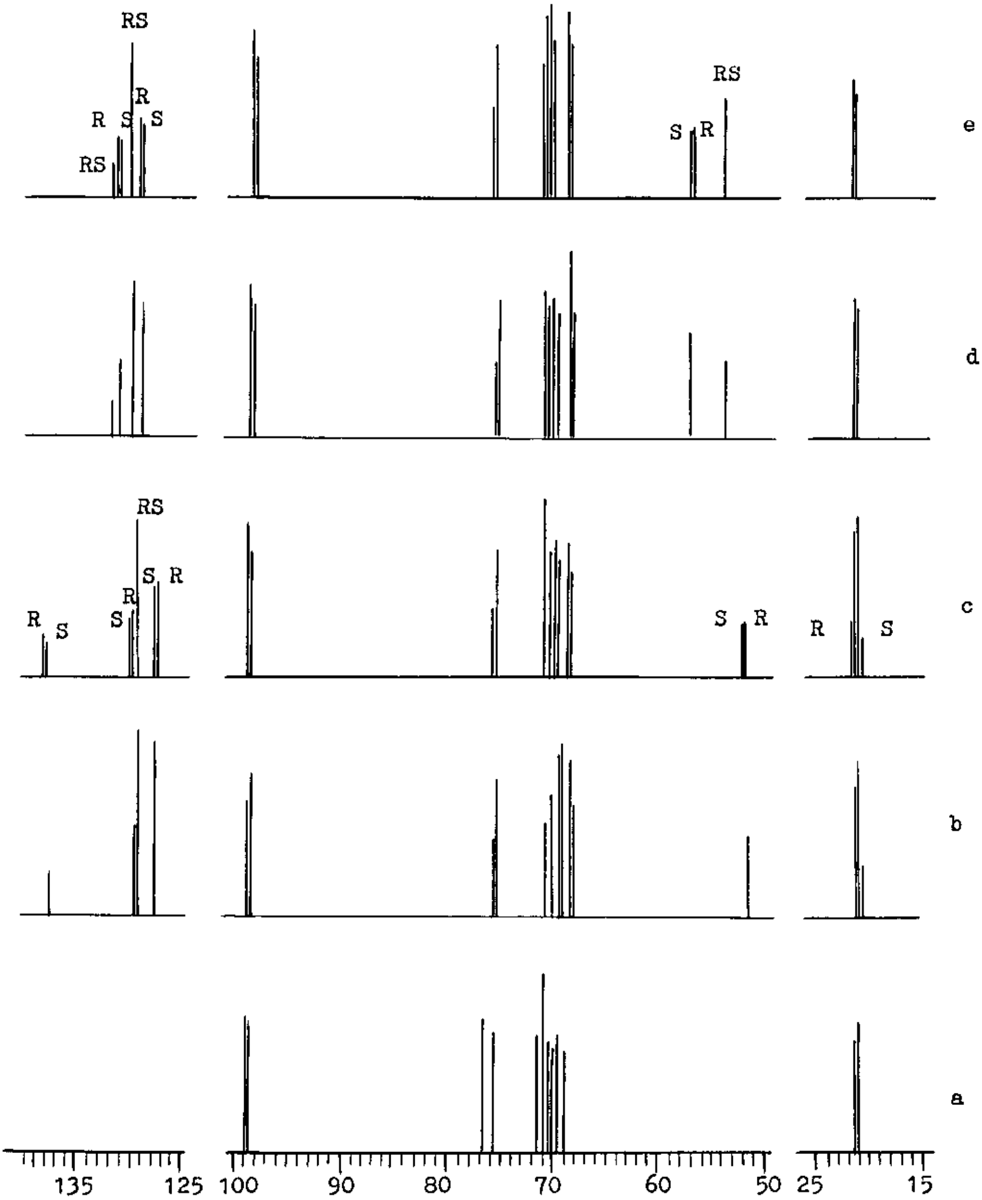
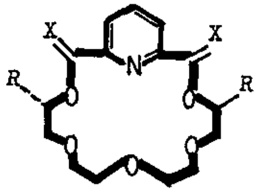
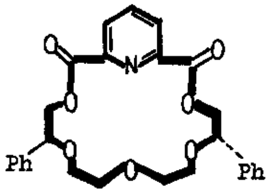


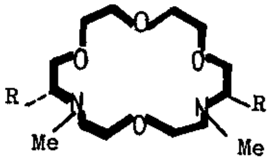
Fig.1. Formation of host-guest complexes as evidenced by the broad-band decoupled ^{13}C-nmr spectra in CD_2Cl_2 (75,5 MHz, 20°C): (a) 3a ; (b) 3a+(S)-9a; (c) 3a+(RS)-9a; (d) 3a+(R)-10; (e) 3a+(RS)-10. The pattern of spectra (c) and (e) reflects a slow exchange of enantiomeric cations in complexes and a rapid complexation-decomplexation on ^{13}C-nmr time scale (cf.2).



A



B



C

EXPERIMENTAL

Molecular weight of novel coronands and podands was determined mass spectrometrically on a Varian MAT-44S instrument by independent use of EI (thermodesorbtion), CI(NH_3) and LSI technique (NaCl-H_2O-glycerol). ^{1}H-Nmr spectra were recorded in $CDCl_3$ at 20±2°C on Bruker WM-250 spectrometer.

(2R,12R)-Di- {(1'S,2'R,6'S,9'R)-2'- (4',9'-dimethyl-3',5',8',10'-tetraoxabicyclo [4,4,0]decyl} -1,4,7,10,13,16-hexaoxacyclooctadecane (3a):

To a stirred suspension of 50 mmol of freshly melted (under Ar) and ground to powder potassium hydroxide in 100 ml of dry DMSO 10 mmol of diol 1a was added and the stirring was continued for 1 h under Ar. Then 6 mmol of DEGDT in 50 ml of DMSO were gradually added at 20°C in span of 8 h and the stirring at this temperature was continued for 12 h. Then temperature was raised to 65°C and another portion of DEGDT (6 mmol) in 50 ml of DMSO was added, after which the mixture was kept stirring at 65°C for 48 h and finally poured into 600 ml of cold water. Extraction with chloroform (11), washing of the extract with 100 ml of water and evaporation to dryness afforded a residue which was chromatographed on a column with 150 g of neutral alumina (activity grade II + 4% of water by weight). Elution with ether-chloroform (gradient 100:1 → 10:1) gave pure 3a as a clear viscous oil with $[\alpha]^{20}_{D}$ - 9.4° (in $CHCl_3$); yield 43%.

The best procedure to obtain its benzylidene analogue 3b (white amorphous solid with mp 218° and $[\alpha]^{20}_{D}$ + 8.49°) differs from the procedure above in that it was carried out with NaOH in DMSO instead of KOH and the temperature ranges from 50° to 75°C. Yield 36%.

TABLE 1. Characteristics of complexation of coronands 3a, 3b and 6 with hexafluorophosphates of α-phenylethylammonium (9a) and α-phenylglycine methyl ester (10)

Host	Guest	Guest's signals in ^{1}H-nmr spectrum (δ, in ppm)[a]			R_e	K_a (l/mol)	ΔG (kcal/mol)	EDC (R / S)
		Me	α-CH	OMe				
18-C-6	(RS)-9a	1.650d	4.220q	-	0.97	4.00×10^4	6.2	
	(RS)-10	-	4.730s	3.770s	0.99	12.30×10^4	6.8	
3a	(RS)-9a	1.650d(S) 1.635d(R)	4.395q(R,S)	-	0.93	1.60×10^4	5.6	1.10(53:47)
	(RS)-10	- -	b b	3.769s(R) 3.787s(S)	0.96	2.90×10^4	6.0	1.09(52:48)
3b	(RS)-9a	1.508d(S) 1.470d(R)	b b		0.89	0.96×10^4	5.3	1.00(50:50)
	(RS)-10		5.107s(S) 5.087s(R)	3.740s(R,S)	0.82	0.52×10^4	5.0	0.82(45:55)
6	(RS)-9a	1.670d(S) 1.661d(R)	4.445q(S) 4.435q(R)	-	0.87	0.79×10^4	5.2	1.00(50:50)
	(RS)-10	-	5.032q(S) 5.015q(R)	3.810s(S) 3.790s(R)	0.80	0.45×10^4	4.9	1.00(50:50)
8	(RS)-9a	1.656d(S) 1.552d(R)	4.370q(R,S)	-	0.92	1.30×10^4	5.6	1.62(62:38)
	(RS)-10		4.922s(S) 4.907s(R)	3.780s(R) 3.800s(S)	0.82	0.52×10^4	5.0	1.00(50:50)

[a] Assignments based on the spectra of complexes formed with (R)- and (S)-9a and (R)-10.

[b] Overlap with host's signals.

REFERENCES

1. J.F.Stoddart, "Progress in Macrocyclic Chemistry", Vol.2, ed. by R.M.Izatt and J.J.Christensen, Wiley-Interscience, New York, 1981, pp.173-250.
2. J.F.Stoddart, Chem.Soc.Rev., 1979, 8, 85.
3. E.P.Serebryakov, R.I.Abylgaziev, E.A.El'perina, and M.I.Struchkova, Izvest. Akad.Nauk SSSR, Ser.Khim., 1988, 112.
4. E.A.El'perina, R.I.Abylgaziev, M.I.Struchkova, and E.P.Serebryakov, Izvest. Akad. Nauk SSSR, Ser.Khim., 1988, 627.
5. E.A.El'perina, R.I.Abylgaziev, and E.P.Serebryakov, Izvest.Akad.Nauk SSSR, Ser.Khim., 1988, 632.
6. W.D.Curtis, D.A.Laidler, J.F.Stoddart, and G.H.Jones, J.Chem.Soc., Perkin Trans. I, 1977, 1756.
7. J.M.Timko, R.C.Helgeson, M.Newcomb, G.W.Gokel, and D.Cram, J.Am.Chem.Soc., 1974, 96, 7097.
8. E.P.Kyba, R.C.Helgeson, K.Madan, G.W.Gokel, T.L.Tarnowski, S.S.Moore, and D.J.Cram, J.Am.Chem.Soc., 1977, 99, 2564.
9. J.M.Timko, S.S.Moore, D.M.Walba, P.C.Hiberty, and D.Cram, J.Am.Chem.Soc., 1977, 99, 4207.
10. J.S.Bradshaw, B.A.Jones, R.B.Davidson, J.J.Christensen, J.D.Lamb, and R.M. Izatt, J.Org.Chem., 1982, 47, 3362.
11. B.A.Jones, J.S.Bradshaw, P.R.Brown, J.J.Christensen, and R.M.Izatt, J.Org. Chem., 1983, 48, 2635.
12. D.J.Chadwick, I.A.Cliffer, I.D.Sutherland, and R.F.Newton, J.Chem.Soc.Perkin Trans. I, 1984, 1707.

Received, 10th August, 1988