PREPARATION AND CHIRAL RECOGNITION OF NEW CHIRAL 18-CROWN-6 ETHERS

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Four new chiral macrocyclic polyethers of 18-crown-6 type which have phenyl, 1-naphthyl or tetramethylphenyl substituents were prepared, and their chiral recognition for 1-phenylethylamine was discussed.

Chiral macrocyclic polyethers of 22-crown-6 type derived from (R)- and (S)binaphthols have been shown to exhibit chiral recognition in complexation equilibria towards various racemic primary alkylammonium and amino acid and ester salts.¹⁾ Although those of 18-crown-6 type have shown only the low chiral recognition,²⁾ their ability to complex with primary alkylammonium salts has been most preferable in view of their ring sizes.³⁾ We now report the synthesis and chiral recognition of chiral macrocyclic polyethers of 18-crown-6 type of different rigidity.⁴⁾

Three step reactions from ethyl-(L)-tartarate according to the known procedure⁵⁾ afforded (la) in good yield.⁶⁾ The addition of (la) to 1-naphthol and NaH in DMF at room temperature afforded (lb), which was hydrolyzed to yield (2b).⁷⁾ The reaction of the Grignard reagent from 1-bromonaphthalene or 1-bromo-2,3,5,6-tetramethylbenzene in THF with (la) catalyzed by Li_2CuCl_4 followed by hydrolysis afforded (2c)⁸⁾ or (2d)⁹⁾. Racemic (2a) was prepared through the reduction of benzoin with NaBH₄ followed by isomerization with NaOH at 150°C.¹⁰⁾ The resolution of R- and S- (2a) were carried out by direct crystalliztion from the ether solution of the racemates according to the sign of rotation of the respective crystals dissolved in CHCl_3 .¹¹⁾ Reactions of equimolar proportions of the diols (2a-d) and the bistosylate (4) with NaH in DMF at room temperature for 150-400 h gave the chiral crown ethers (3a-d)¹²⁻¹⁵⁾ after chromatography on silica gel using CHCl₃, n-hexane, and n-hexane-ether(5:1-3:1) successively as eluants.

Scheme

$$\begin{array}{c|cccc} PhC-CHPh & NaBH_4 & NaOH & PhCH-CHPh & Resolution by Direct & PhCH-CHPh \\ \hline \\ 0 & OH & & 150^{\circ}C & OH & OH & Crystallization, Et_2O & OH & OH \\ \hline \\ (2a) \end{array}$$



The chiral recognition was measured by distributing racemic 1-phenylethylamine salt between $H_2O - CHCl_3$ layers, the organic layer of which contained chiral crown ethers(3a-d). Thus, a solution of 5.0 ml of 0.1 M (3) in CHCl₃ was shaken with H_2O 5.0 ml containing racemic 1-phenylethylammonium chloride (1M) and LiPF₆ (1M). After the mixture was centrifuged, the 3.0 ml of CHCl₃ phase was carefully withdrawn using a 5 ml glass syringe.¹⁶) The amount of extracted amine salt in CHCl₃ was measured by glc (Chromosorb 103 at 210°C), whose optical purity was determined by glc (SF-96 coated glass cappillary column, 20 m) after derivatization into diastereomers with N-TFA-L-alanine.¹⁷)

salt in CHCl3		
Crown ether	Extracted Amine in CHCl ₃ /	% ee
	(3) in CHCl ₃ (mol/mol)	
(3a)	0.90	8 (R)
(3b)	0.78	0
(3c)	0.51	14(R)
(3d)	0.56	14(R)

Table Chiral recognition of enantiomers of 1-phenylethylamine salt in CHCl₃

Crown ether (3a), (3c), and (3d) except (3b) recognize the chirality of the amine salt. A rather rigid conformation is assumed for (3a) as the phenyl groups are directly attached to the crown framework. The substituents of (3c) and (3d) are large, but their conformations are not so rigid because they are connected to the crown ring through the flexible CH_2 group. 1-Naphthyl groups of (3b), which are connected to the crown ring through the more flexible CH_2O group, are not large enough to recognize the chirality.

Work is in progress to prepare other chiral 18-crown-6 type ethers with larger and rigid substituents.

References

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- 6) (la): mp 91.3-92.1°C; $[\alpha]_D^{24}$ -12.3°(c=5.0, CHCl₃).
- 7) (2b): mp 158.3-159.4°C; $[\alpha]_D^{23}$ -17.3°(c=3.24, THF); NMR((CD₃)₂SO) δ =3.95-4.43(6H, m), 5.20-5.26(2H, b), 6.70-8.32(14H, m).
- 8) (2c): mp 139.2-141.4°C; $[\alpha]_D^{23}$ +29°(c=0.98, CHCl₃); NMR(CDCl₃) δ =2.07(2H, b), 3.29(4H, d), 3.91(2H, m), 7.03-7.90(14H, m).
- 9) (2d): mp 152.0-153.0°C; $[\alpha]_D^{23}$ -2.4°(c=0.82, CHCl₃); NMR(CDCl₃) δ =2.10(24H, s), 2.92(4H, d), 3.59(2H,m), 6.70(2H, s).
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- 11) J. Read, I. G. M. Campbell, and T. V. Barker, J. Chem. Soc., <u>1930</u>, 2305; G. Berti and F. Bottari, J. Org. Chem., <u>25</u>, 1286(1960); R-(2a): mp 148.0-149.0°C, [α]_D²² +94.8°(c=1.0, EtOH).

- 12) (3a): Yield 65%; mp 109.5-110.5°C; $[\alpha]_{436}^{20}$ +25.0°(c=2.0, CHCl₃); NMR(CDCl₃) δ =3.45-3.95(16H, m, CH₂), 4.43(4H, s, CH), 6.75-7.15(20H, m, ArH); EA Found: C, 75.75; H, 7.16; M⁺ 568. Calcd for C₃₆H₄₀O₆: C, 76.03; H, 7.09; M 568.
- 13) (3b) Yield 32%; mp 153.8-155.7°C; $[\alpha]_D^{22}$ -25.9°(c=4.95, CHCl₃); NMR(CDCl₃) δ = 3.4-4.0(16H, m, OCH₂CH₂O), 4.1-4.6(12H, m, OCHCH₂O), 6.6-8.3(28H, m, ArH); EA Found: C, 75.12; H, 6.44; M⁺ 888.3872. Calcd for C₅₆H₅₆O₁₀: C, 75.65; H, 6.35; M 888.3872.
- 14) (3c): Yield 30%; mp 97.0-98.0°C; $[\alpha]_D^{23}$ -107°(c=0.74, CHCl₃); NMR(CDCl₃) δ = 2.33-3.40(28H, m, CH, CH₂), 7.06-7.98(28H, m, ArH); EA Found: C, 81.83; H, 6.92; MH⁺ 825. Calcd for C₅₆H₅₆O₆: C, 81.55; H, 6.80; M 824.
- 15) (3d): Yield 28%; mp 88.7- 90.6°C; $[\alpha]_D^{22}$ -42.3°(c=1.24, CHCl₃); NMR(CDCl₃) δ =2.17(48H, s, ArCH₃), 2.76-3.28(24H, m, CH₂), 3.57(4H, m, CH), 6.74(4H, s, ArH); EA Found: C, 78.73; H, 9.84; M⁺ 848. Calcd for C₅₆H₈₀O₆: C, 79.25; H, 9.43; M 848.
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