CHIRAL RECOGNITION PROPERTIES OF CHIRAL 18-CROWN-6 ETHERS WITH AROMATIC SUBSTITUENTS

Junzo Yamashita,* Hideaki Takahashi, Harukichi Hashimoto, Keiichi Kitahara,† and Hisao Sato†
Department of Applied Chemistry, Faculty of Engineering, Tohoku University, Aramaki-Aoba, Sendai 980, JAPAN
†Department of Chemistry, Tokyo Medical College, Shinjuku, Tokyo 160, JAPAN

ABSTRACT. The chiral recognition properties of chiral 18-crown-6 ethers with phenyl, 1-naphthoxymethyl, 1-naphthylmethyl, or 2,3,5,6-tetramethylphenylmethyl substituents for α-phenylglycine methyl ester and 1-phenylethylamine perchlorate were investigated by a standard extraction procedure. The chiral recognition factor of 1-naphthoxymethyl substituted crown ether is 2.0 for the former salt but near 1.0 for the latter, whereas that of the other crown ethers is not so dependent on the structure of salts, which indicates the importance of the mutual relation of the structure of host and guest molecules.

1. INTRODUCTION

Chiral crown ethers derived from binaphthol, pentahelicene, biphenanthrol, and other natural precursors have been prepared in recent years.[1] Their chiral recognition in complexation equilibria towards various primary alkylammonium and amino acids and ester salts as well as the structural requirements of this phenomenon have been investigated. The crown ethers based on 18-crown-6 structure are known to form most stable complexes with primary ammonium salts in view of the ring sizes,[2] though their chiral recognition properties have been rather low, which should be improved with the appropriate(bulky and rigid) substituents to the crown framework.

In the present paper, we report the synthesis of chiral 18-crown-6 ethers with aromatic substituents of various rigidity and bulkiness, and the effects of substituents on their chiral recognition properties for 1-phenylethylamine and α-phenyl glycine methyl ester perchlorate.[3]

2. EXPERIMENTAL

2.1. Materials and Analysis

Reagent grade dimethylformamide(DMF), tetrahydrofuran(THF) and ether

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were dried and distilled before use under argon atmosphere according to the known procedure. (-)-(L)-N-Trifluoroacetylalanine(mp 56.5-57.0 °C, $[\alpha]_D^{22}$ 59.8°(c 2.15, H_2O)),[4] 3-oxapentane-1,5-diyl ditosylate(1) (mp 88.7-89.8 °C),[5] (RS)-α-phenylglycine methyl ester perchlorate (mp 157-159 °C)[6] and (-)-(4S,5S)-4,5-ditosyloxymethyl-2,2-dimethyl-1,3-dioxolane(2)(mp 91.3-92.1 °C, $[\alpha]_D^{24}$ -12.3°(c 5.0, $CHCl_3$))[7] were prepared according to the known procedure. The other materials were used as purchased.

^1H NMR Spectra were taken on a Hitachi R-90H spectrometer with Me_4Si as an internal standard. Optical rotations were determined with Union Giken PM-101 digital polarimeter. Infrared spectra were taken on a Shimadzu IR-430 spectrometer. Mass spectra were taken on a JEOL JMS D-300 mass spectrometer using EI and FD mode.

2.2. Preparation of Chiral Diols and Crown Ethers

(+)-(1R,2R)-1,2-Diphenyl-1,2-ethanediol(3a)[8]: When the ether solution of racemic 1,2-dipheny-1,2-ethanediol, which was prepared according to the known procedure[9], was permitted to evaporate gradually in about two weeks, large crystals of R- and S- diols were formed separately and identified by measuring their optical rotations. This procedure easily gave near quantitative yields of R-diol as well as S-diol after recycling (R: mp 148-149 °C, $[\alpha]_D^{22}$ +94.8°(c 1.0 EtOH), ^1H NMR $(CD_3)_2CO$ δ=4.17(2H, s), 4.41(2H, s), 6.88(10H, s)).

(-)-(2S,3S)-1,4-Bis(1-naphthoxy)-2,3-butanediol(3b): To the suspension of 5 g(0.10 mol) of NaH(50 % suspension in mineral oil) in 150 ml of DMF, was added 13 g(0.09 mol) of 1-naphthol in 60 ml of DMF at room temperature, stirred for 1 h, added 19 g(0.04 mol) of (2) in 90 ml of DMF, and then stirred for 200 h at room temperature under argon atmosphere. The solution was evaporated to dryness under vacuum. The residue was stirred with 100 ml of ether, filtered, and washed with ether(50 ml x 2). The filtrates were washed with water(50 ml x 2), 10 % NaOH aqueous solution(50 ml x 2) and water(50 ml x 2) successively, dried with Drierite and evaporated. The concentrate was chromatographed on silica gel(Wako gel C-200) eluted with hexane-ether(75:25) to give 8.75 g solid, which was quantitatively hydrolyzed in 0.1 mol HCl of 90 % aqueous ethanol solution to afford (3b)(7.9 g, yield 52 %)(mp 158.3-159.4 °C; $[\alpha]_D^{23}$ -17.3°(c 3.24, THF); ^1H NMR($(CD_3)_2SO$ δ=3.95-4.43(6H, m, CH,CH_2, 5.20-5.26(2H, b, OH), 6.70-8.32(14H, m, ArH); EA Found: C, 76.75; H, 6.01; Calcd for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92).

(+)-(2S,3S)-1,4-Bis(1-naphthyl)-2,3-butanediol(3c): To the 1-naphthylmagnesium bromide solution, which was prepared from 2.72 g (112 mmol) of Mg, 20.45 g(98.8 mmol) of 1-bromonaphthalene and 60 ml of THF, was added 9.40 g of (2), 60 ml of benzene and 0.2 mmol of Li_2CuCl_4 in 2 ml of THF and refluxed for 7 h. The mixture was filtered after the addition of saturated aqueous NH_4Cl solution. The residue was extracted with ether in a Soxhlet extractor. The combined filtrate and extract were dried over Drierite, evaporated and hydrolyzed with conc. HCl(1 ml), H_2O(5 ml) and EtOH(60 ml) at refluxing temperature for 7 h. The solution was neutralized with aqueous $NaHCO_3$ and filtered. The precipitate was washed with H_2O and recrystallized from hexane-benzene

to afford (3c)(1.66 g, yield 24 %)(mp 139.2-141.4 °C; $[\alpha]_D^{23}$ +29°(c 0.98, $CHCl_3$); ^1H NMR($CDCl_3$) δ=2.07(2H, b), 3.29(4H, d), 3.91(2H, m), 7.03-7.90(14H, m); EA Found: C, 83.75, H, 6.44; Calcd for $C_{24}H_{22}O_2$: C, 84.21; H, 6.43).

(-)-(2S,3S)-1,4-Bis(2,3,5,6-tetramethylphenyl)-2,3-butanediol(3d): To the mixture of 7.52 g(16.0 mmol) of (2), 0.2 mmol Li_2CuClO_4 in 2 ml of THF and 30 ml of THF, was added 2,3,5,6-tetramethylphenylmagnesium bromide solution, which was prepared from 2.11 g(86.8 mmol) of Mg, 14.07 g(66.1 mmol) of 1-bromo-2,3,5,6-tetramethylbenzene and 70 ml of THF, at 0-5 °C and stirred for 20 min. The mixture was heated at 53 °C for 13 h, refluxed for 7 h and cooled. The reaction mixture was filtered after the addition of saturated aqueous NH_4Cl solution. The residue was washed with ether and the combined filtrates were dried with Drierite, evaporated and chromatographed on silica gel(Wako gel C-200) eluted successively with hexane and hexane-ether(7:1) to afford a solid(2.57 g), which was quantitatively hydrolyzed in 0.1 mol/l HCl of 90 % aqueous EtOH solution to afford (3d)(2.26 g, yield 41 %)(mp 152.0-153.0 °C; $[\alpha]_D^{23}$ -2.4°(c 0.82, $CHCl_3$); ^1H NMR($CDCl_3$) δ=2.10(24H, s), 2.92(4H, d), 3.59(2H, m), 6.70(2H, s); EA Found: C, 81.13; H, 9.64; Calcd for $C_{24}H_{34}O_2$: C, 81.36; H, 9.60).

(+)-(2R,3R,11R,12R)-2,3,11,12-Tetraphenyl-1,4,7,10,13,16-hexaoxacyclooctadecane(4a): To the mixture of 2.09 g(43.6 mmol) of NaH(50 % dispersion in mineral oil) and 700 ml of DMF, was added 4.68 g (21.8 mmol) of (3a) in 100 ml of DMF and stirred at room temperature for 20 h under argon atmosphere, followed by adding 9.04 g(21.8 mmol) of (1) in 100 ml of DMF and stirring for 72 h. And then, to the mixture, was added 9.04 g of (1) and 2.09 g of NaH in 100 ml of DMF, stirred at two weeks at room temperature. The reaction mixture was neutralized with dry ice and water to pH 8-9, evaporated at 35-45 °C under vacuum. The residue was dissolved in 200 ml of water and extracted with ether (100 ml x 4). The combined extracts were dried over Drielite, filtered, evaporated and chromatographed on silica gel(Wako gel C-200) eluted successively with ether-hexane(1:1) and (2:1) to give (4a) (4.0 g, yield 65 %) (mp 109.5-110.5 °C; $[\alpha]_{436}^{20}$ +25.0°(c 2.0, $CHCl_3$); ^1H NMR($CDCl_3$) δ=3.45-3.95(16H, m, CH_2), 4.43(4H, s, CH), 6.75-7.15(20H, m, ArH); EA Found: C, 75.75; H, 7.16; M^+, 568; Calcd for $C_{36}H_{40}O_6$: C, 76.03; H, 7.09; M 568).

(-)-(2S,3S,11S,12S)-2,3,11,12-Tetrakis(1-naphthyloxymethyl)-1,4,7,10,13,16-hexaoxacyclooctadecane(4b): A procedure similar to that for (4a) using (3b)(7.52 g, 20.0 mmol) gave (4b)(2.86 g, yield 32 %) (mp 153.8-155.7 °C; $[\alpha]_D^{22}$ -25.9°(c 4.95, $CHCl_3$; ^1H NMR($CDCl_3$) δ=3.4-4.0 (16H, m, OCH_2CH_2O), 4.1-4.6(12H, m, $OCHCH_2O$), 6.6-8.3(28H, m, ArH); EA Found: C, 75.12; H, 6.44; M^+ 888.3872; Calcd for $C_{56}H_{56}O_{10}$: C, 75.65; H, 6.35; M 888.3872).

(-)-(2S,3S,11S,12S)-2,3,11,12-Tetrakis (1-naphthylmethyl)-1,4,7,10,13,16-hexaoxaoctadecane(4c): A procedure similar to that for (4a) using (3c)(3.35 g, 9.79 mmol) gave (4c)(1.21 g, yield 30 %)(mp 97.0-98.0 °C; $[\alpha]_D^{23}$ -107°(c 0.74, $CHCl_3$); ^1H NMR($CDCl_3$) δ=2.33-3.40(28H, m, CH,CH_2), 7.06-7.98(28H, m, ArH); EA Found: C, 81.83; H, 6.92; MH^+ 825; Calcd for $C_{56}H_{56}O_6$: C, 81.55; H, 6.80; M 824).

(-)-(2S,3S,11S,12S)-2,3,11,12-Tetrakis(2,3,5,6-tetramethylphenyl)-

1,4,7,10,13,16-hexaoxaoctadecane(4d): A procedure similar to that for (4a) using (3d)(2.74 g, 7.73 mmol) gave (4d)(0.92 g, yield 28 %) (mp 88.7-90.6 °C; $[\alpha]_D^{22}$ -42.3°(c 1.24, $CHCl_3$); ^1H NMR($CDCl_3$) δ=2.17(48H, s, $ArCH_3$), 2.76-3.28(24H, m, CH_2), 3.57(4H, m, CH), 6.74(4H, s, ArH); EA Found: C, 78.73; H, 9.84; M^+ 848; Calcd for $C_{56}H_{80}O_6$: C, 79.25; H, 9.43; M 848).

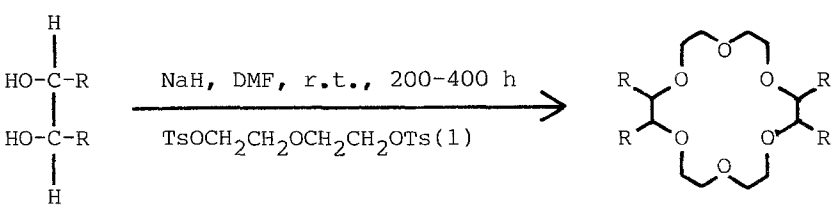
2.3. Chiral recognition procedures

Chiral recognition for α-phenylglycine methyl ester perchlorate(5). A solution of 5.0 ml of 0.1 mol/l (4) in $CDCl_3$ was shaken with 5.0 ml of D_2O containing racemic α-phenylglycine methyl ester perchlorate(5) (1 mol/l) in 12 ml vial at room temperature for 15 min and then centrifuged for 20 min. The 0.5 ml portion of organic phase, carefully withdrawn, was used for determining the amount of extracted amino ester by ^1H NMR integration. Another 10 μl portion of organic phase was derivatized to N-trifluoroacetylphenylglycine butyl ester according to the known procedure[10] and used for the determination of chiral recognition factor[11](CRF: [the amount of the enantiomer more complexed in organic phase]/[the amount of the enantiomer less complexed in organic phase]) by HPLC(Pirkle's chiral column 25 cm x 4.6 mm eluted with 5 % isopropyl alcohol in hexane).[12]

Chiral recognition for 1-phenylethylamine perchlorate(6). Extraction of aqueous 1-phenylethylamine perchlorate(6) with crown ethers(4) and the determination of the amount of extracted amine was carried out by the same procedure as described for α-phenylglycine methyl ester perchlorate. Another 10 μl portion of organic phase was derivatized with (-)-(L)-N-trifluoroacetylalanine[13] and used for the determination of CRF by GLC(OV-17 coated glass capillary column at 160 °C).

3. RESULTS AND DISCUSSION

Chiral crown ethers of (4a)-(4d) were prepared from chiral diols(3a)-(3d) and ditosylate(1) in fairly good yields. The addition of extra amount of (1) at the intermediate stage of the reaction and the addi-



(3a-d) (4a-d)

(3a)(4a) R= (R)-Phenyl
(3b)(4b) (S)-1-Naphthoxymethyl
(3c)(4c) (S)-1-Naphthylmethyl
(3d)(4d) (S)-2,3,5,6-Tetramethylphenylmethyl

tional reaction was necessary to improve the yield. Without the above procedure, a large amount of intermediate acyclic diols was recognized and the yield was low.

The chiral recognition properties of crown ethers(4) for racemic α-phenylglycine methyl ester perchlorate(5) and 1-phenylethylamine perchlorate(6) were tested by standard extraction experiments.[11,14] No appreciable amount of crown ethers was detected in aqueous layers. The relative amount of complexed salts to crown ethers in $CDCl_3$ layers was determined by ^1H NMR integrations. When (5) is complexed with (4), the signal of ester methyl protons is moved and separated into two signals for each enantiomer. When (6) is complexed with (4), the signal of methyl protons(doublet) is only shifted but not separated. The ratio of enantiomers of complexed salts was determined by HPLC using a chiral column for (5)[12] or by GLC for (6) as diastereomeric isomers of (-)-(L)-N-trifluoroacetylalanine.[13] The results are summarized in Table I and II.

Table I. Chiral recognition properties of crown ethers for α-phenylglycine methyl ester perchlorate

Crown ether	Ratio of (5)/(4) in $CDCl_3$(mol/mol)	Chemical shift of (5)[a] $-COOCH_3$(δ vs TMS)	CRF[b]
(4a)	0.96	3.92(s)[c], 3.97(s)[d]	1.9
(4b)	0.94	3.30(s)[d], 3.42(s)[c]	2.0
(4c)	0.85	3.84(s)[c], 3.90(s)[d]	1.5
(4d)	0.86	3.78(s)[c], 3.83(s)[d]	1.3

a) Chemical shift of ester methyl protons without crown ethers is 3.77(s).
b) R-enantiomer is the more complexed.
c) R-enantiomer
d) S-enantiomer

Table II. Chiral recognition properties of crown ethers for 1-phenylethylamine perchlorate

Crown ether	Ratio of (6)/(4) in $CDCl_3$(mol/mol)	Chemical shift of (6)[a] $-CH_3$(δ vs TMS)	CRF[b]
(4a)	1.0	1.92(d)	1.2
(4b)	0.97	1.51(d)	1.04
(4c)	0.81	1.91(d)	1.3
(4d)	0.89	2.11(d)	1.3

a) Chemical shift of CH_3 protons without crown ethers is 1.59.
b) R-enatiomer is the more complexed.

These salts seem to form 1:1 complexes with the crown ethers. When (5) is complexed with crown ether (4a), (4c), or (4d), the signal of

ester methyl protons is moved downfield and separated into two signals; the lower one corresponds to the less complexed S-enantiomer and the upper one corresponds to the more complexed R-enantiomer. The larger shift of S-enantiomer means that it is subject to the more influence of the deshielding effect and thus the sterric effect of aromatic rings of (4), which is reflected in the CRF. A rather rigid conformation is assumed for (4a) as the phenyl groups are directly attached to the crown framework, whereas the conformations of (4c) and (4d) may not be so rigid because their substituents are connected to the crown ring through the more flexible CH_2 group, which may be reflected in the value of CRF. In case of (4b), the proton signal is moved upfield which means that the proton is in the shielding region of naphthalene ring in contrast with the case of (4a), (4c), and (4d). It is not easy to explain but the aromatic rings of (4b) are large but are separated from the crown framework with $-CH_2O-$ moiety which may lead to form the complex in a different conformation from the other resulted in the higher field shift of proton signal. The largest separation of proton signals between the complexed enantiomers of (5) with (4b) coupled with the largest shifts means the strongest interaction between (4b) and (5) which is reflected in the largest CRF(2.0.) Although (4a) has R configuration and the others have S configuration, all (4) prefer R enantiomer of (5). This is not yet to be explained.

When (6) is complexed with (4a), (4c), or (4d), the signal of methyl protons is moved downfield but not separated, which suggests that the chiral recognition ability of these crown ethers is not sufficient for the small methyl group of chiral center of (6) resulting in rather small CRFs. When (6) is complexed with (4b), the signal of methyl protons is only slightly moved upfield which is reflected in the very small CRF. The far separated aromatic rings from the crown framework of (4b) may not effective to interact with small methyl group of (6). The large difference of CRF of (4b) between (5) and (6) indicates that the chiral recognition properties of crown ethers with the flexible substituents(4b) is more sensitive to the structure of guest molecules than that with the rigid substituents(4a, 4c, 4d). The CRFs of (4) are fairly high compared with those of other 18-crown-6 ethers,[15] though the precice comparison is difficult because of the difference of the experimental conditions.

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4. References

1) S. T. Jolley, J. S. Bradshaw, and R. M. Izatt, J. Heterocyclic Chem., 19, 3(1982); M. Nakazaki, K. Yamamoto, T. Ikeda, T. Kitsuki, and Y. Okamoto, J. Chem. Soc., Chem. Commun., 1983, 787; R. B.

Davidson, J. S. Bradshaw, B. A. Jones, N. K. Dalley, J. S. Christensen, and R. M. Izatt, J. Org. Chem., **49**, 353(1984), and references cited therein.

2) J. M. Timko, R. C. Helgeson, M. Newcomb, G. W. Gokel, and D. J. Cram, J. Am. Chem. Soc., **96**, 7097(1974).

3) Preliminary communication: J. Yamashita, M. Minagawa, A. Sonobe, S. Ohashi, M. Kawamura, K. Shimizu, and H. Hashimoto, Chem. Lett., **1982**, 1409; A part of this work was presented at The 3rd International Synposium on Clathrate Compounds and Molecular Inclusion Phenomena and The 2nd International Synposium on Cyclodextrin(Abs. No. 1002), Tokyo, Japan, July 24, 1984.

4) F. Weygand and R. Geiger, Chem. Ber., **89**, 647(1956).

5) J. Dale and P. O. Kristiansen, Acta. Chem. Scand., **26**, 1471(1972).

6) D. S. Lingenfelter, R. C. Helgeson, and D. J. Cram, J. Org. Chem., **46**, 393(1981).

7) L. J. Ruben, H. A. Lardy, and H. O. Fischer, J. Am. Chem. Soc., **74**, 425(1952).

8) G. Berti and F. Bottari, J. Org. Chem., **25**, 1286(1959).

9) A. Collet, Synthesis, **1973**, 664.

10) D. Roach and C. W. Gehrke, J. Chromatogr., **44**, 269(1969).

11) S. S. Peacock, D. M. Walba, F. C. A. Gaeta, R. C. Helgeson, and D. J. Cram, J. Am. Chem. Soc., **102**, 2043(1980).

12) W. H. Pirkle, D. W. House, and J. M. Finn, J. Chromatogr., **192**, 143(1980).

13) K. Kruse, W. Francke, and W. A. Koenig, J. Chromatogr., **170**, 423(1979).

14) S. C. Peacock, L. A. Domeier, F. C. A. Gaeta, R. C. Helgeson, J. M. Timko, D. J. Cram, J. Am. Chem. Soc., **100**, 8190(1978).

15) W. S. Curtis, D. A. Laidler, J. F. Stoddart, and G. H. Jones, J. Chem. Soc., Perkin I, **1977**, 1756; W. Bussman, J. M. Lehn, U. Oesch, P. Plumere, and W. S. Simmon, Helv. Chim. Acta., **64**, 657(1981).