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Preparation of homochiral azophenolic crown ethers containing 1-phenylethane-1,2-diol and 2,4-dimethyl-3-oxapentane-1,5-diol as a chiral subunit: enantiomer recognition behaviour towards chiral 2-aminoethanol derivatives

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Abstract: Enantiomerically pure azophenolic crown ethers **1–4** containing (*S*)- or (*R*)-1-phenylethane-1,2-diol moieties and (2*S*,4*S*)-2,4-dimethyl-3-oxapentane-1,5-diol moiety as a chiral subunit were prepared; crown ethers (*S,S,S,S*)-**1** showed high chiral recognition behaviour in complexation with 2-substituted 2-aminoethanol derivatives. © 1997 Published by Elsevier Science Ltd. All rights reserved.

A variety of chiral molecular receptors possessing a well-defined three dimensional cavity have recently been prepared and their characteristic complexation with chiral guests has been studied,[1] while chiral crown ethers possessing a planar binding cavity are still of interest for obtaining basic information on chiral recognition behaviour in complexation. We are also seeking a crown ether of 18-crown-6 type showing high chiral recognition and have prepared homochiral crown ethers using various types of chiral subunits.[2] Herein we report the preparation of enantiomerically pure azophenolic crown ethers **1–4** containing (*S*)- or (*R*)-1-phenylethane-1,2-diol moieties and (2*S*,4*S*)-2,4-dimethyl-3-oxapentane-1,5-diol moiety as a chiral subunit. These crown ethers also contain a phenol moiety possessing an intra-annular OH group as a binding site towards neutral amines, and an additional 2,4-dinitrophenylazo group was introduced at its *para*-position which also serves as a chromophore, enhancing the binding ability. Their chiral recognition behaviour in complexation with 2-aminoethanol derivatives is examined.

Chiral subunits (1*S*)-**6** and (1*R*)-**6** were prepared from (*S*)- and (*R*)-mandelic acid, respectively, as the mixture of the diastereoisomers[3] and used without separation of diastereoisomers. Condensation of 2 mol equiv. of (1*S*)-**6** with 1,3-bis(bromomethyl)-2,5-dimethoxybenzene in the presence of NaH in boiling THF gave **8**, which was treated with methanol containing a small amount of hydrochloric acid to give (*S,S*)-**9**, $[\alpha]_D^{22}$ +39.3 (10^{-1} deg cm^2 g^{-1}) ($CHCl_3$) in 57% overall yield. High-dilution condensation of (*S,S*)-**9** with (*S,S*)-**7**, $[\alpha]_D^{29}$ +3.40 ($CHCl_3$), prepared from ethyl (*S*)-lactate,[4] in the presence of NaH and KBF_4 in DMF at 100°C gave crown ether (*S,S,S,S*)-**10**, $[\alpha]_D^{22}$ +143 ($CHCl_3$) in 37% yield. Demethylation of (*S,S,S,S*)-**10** with sodium ethanethiolate in DMF at 90°C[5] gave phenolic crown ether (*S,S,S,S*)-**11**, $[\alpha]_D^{22}$ +133 ($CHCl_3$) in 80% yield. By oxidation with cerium(IV) ammonium nitrate (CAN) in acetonitrile followed by treatment with 2,4-dinitrophenylhydrazine and H_2SO_4 in a mixture of methylene dichloride and ethanol, (*S,S,S,S*)-**11** was converted to azophenolic crown ether (*S,S,S,S*)-**1**[6] in 81% yield after purification on silica gel column chromatography and preparative recycling HPLC. Similarly, condensation of 2 mol equiv. of (1*S*)-**6** with (*S,S*)-**7** followed by removal of the protecting group gave (*S,S,S,S*)-**13**, $[\alpha]_D^{25}$ +94.0 ($CHCl_3$) in 28% overall yield via **12**. High-dilution condensation of (*S,S,S,S*)-**13** with 1,3-bis(bromomethyl)-2,5-dimethoxybenzene followed by demethylation gave (*S,S,S,S*)-**15**, $[\alpha]_D^{25}$ +133 ($CHCl_3$) in 25% overall yield via (*S,S,S,S*)-**14**, $[\alpha]_D^{25}$

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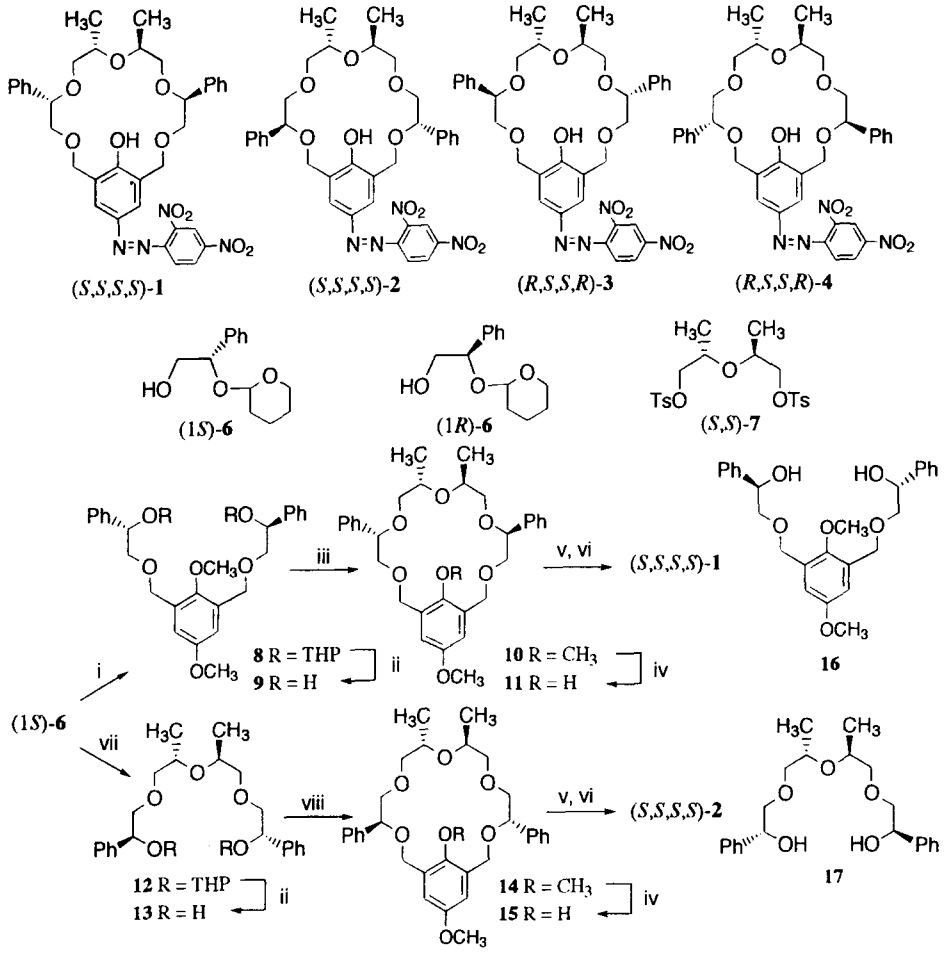


Scheme 1. *Reagents*: i, 1,3-bis(bromomethyl)-2,5-dimethoxybenzene, NaH; ii, MeOH, HCl; iii, (*S,S*)-**7**, NaH, KBF_4; iv, C_2H_5SH, NaH; v, CAN; vi, 2,4-dinitrophenylhydrazine; vii, (*S,S*)-**7**, NaH; viii, 1,3-bis(bromomethyl)-2,5-dimethoxybenzene, NaH, KBF_4.

+143 ($CHCl_3$). Azophenolic crown ether (*S,S,S,S*)-**2**[6] was prepared from (*S,S,S,S*)-**15** in 74% overall yield by treating successively with CAN and with 2,4-dinitrophenylhydrazine.

Using (1*R*)-**6** and (*S,S*)-**7** as a chiral subunit, (*R,S,S,R*)-**3**[6] and (*R,S,S,R*)-**4**[6] were prepared via (*R,R*)-**16**, $[\alpha]_D^{25}$ −37.3 ($CHCl_3$) and (*R,S,S,R*)-**17**, $[\alpha]_D^{25}$ −59.6 ($CHCl_3$), respectively, by a similar sequence of reactions to that described in Scheme 1.

Since crown ethers **1–4** showed rather large binding ability towards amines having a bulky substituent, the association constants for their complexes with chiral 2-aminoethanol derivatives were determined by the Rose–Drago method[7] on the basis of the absorption in the UV–visible spectrum in chloroform at 25°C. The observed *K*a-values together with the λmax-values for complexes are summarized in Table 1.

The data listed in Table 1 demonstrate that the arrangement of chiral barriers on the polyether framework affected markedly the enantiomer selectivity towards 2-substituted 2-aminoethanol derivatives **19**, **20** and **21**; the enantiomer selectivities of crown ethers (*S,S,S,S*)-**1** and (*R,S,S,R*)-**3** possessing phenyl barriers located near the diethylene glycol bridge were higher than those of crown ethers

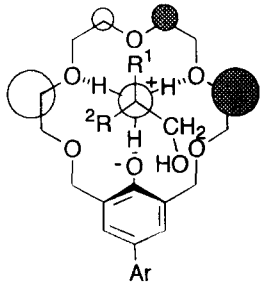
Table 1. Association constants *Ka* (M^{-1}) and λmax for the complexes with chiral amines in $CHCl_3$ at 25°C

crown ether	amine[a]	Ka^R (λmax/nm)[b]	Ka^S (λmax/nm)[b]	Ka^R/Ka^S	$\Delta\Delta G$[c] kcal mol^{-1}
(*S,S,S,S*)-**1**	**18**	$5.95x10^3$ (560)	$2.54x10^3$ (564)	2.3	0.50
(*S,S,S,S*)-**1**	**19**	$9.55x10^3$ (558)	$1.55x10^3$ (570)	6.2	1.1
(*S,S,S,S*)-**1**	**20**	$1.57x10^3$ (564)	$3.06x10^2$ (569)	5.1	0.97
(*S,S,S,S*)-**1**	**21**	$4.76x10^3$ (558)	$4.10x10^2$ (567)	11.6	1.5
(*S,S,S,S*)-**2**	**18**	$3.96x10^3$ (565)	$1.69x10^3$ (563)	2.3	0.50
(*S,S,S,S*)-**2**	**19**	$4.63x10^3$ (561)	$2.77x10^3$ (565)	1.7	0.30
(*S,S,S,S*)-**2**	**20**	$8.66x10^2$ (569)	$7.30x10^2$ (566)	1.2	0.10
(*S,S,S,S*)-**2**	**21**	$1.27x10^3$ (564)	$4.10x10^2$ (561)	3.1	0.67
(*R,S,S,R*)-**3**	**18**	$1.50x10^3$ (565)	$3.12x10^3$ (562)	0.48	0.43
(*R,S,S,R*)-**3**	**19**	$1.68x10^3$ (565)	$4.70x10^3$ (562)	0.36	0.61
(*R,S,S,R*)-**3**	**20**	$2.18x10^2$ (567)	$9.47x10^2$ (566)	0.23	0.87
(*R,S,S,R*)-**3**	**21**	$4.72x10^2$ (573)	$2.75x10^3$ (559)	0.17	1.0
(*R,S,S,R*)-**4**	**18**	$6.08x10^2$ (564)	$1.42x10^3$ (559)	0.43	0.50
(*R,S,S,R*)-**4**	**19**	$9.19x10^2$ (563)	$1.67x10^3$ (560)	0.55	0.35
(*R,S,S,R*)-**4**	**20**	$1.94x10^2$ (563)	$3.23x10^2$ (564)	0.66	0.30
(*R,S,S,R*)-**4**	**21**	$2.69x10^2$ (574)	$4.17x10^2$ (560)	0.65	0.26

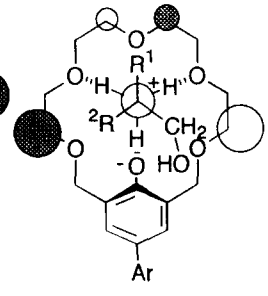
a) **18**: 1-amino-2-propanol; **19**: 2-amino-1-propanol; **20**: 2-amino-3-methyl-1-butanol; **21**: 2-amino-2-phenylethanol b) Ka^R for the complex with (*R*)-amine and Ka^S for the complex with (*S*)-amine c) $\Delta\Delta G = RT \ln (Ka^{\text{more stable}} / Ka^{\text{less stable}})$ at T=298 K

(*S,S,S,S*)-**2** and (*R,S,S,R*)-**4** in which the phenyl barriers are placed near the phenol moiety. Especially, (*S,S,S,S*)-**1** showed good enantiomer selectivity towards 2-amino-2-phenylethanol **21**.

Next we interpreted the enantiomer selectivities observed at 25°C in terms of steric interactions between the substituents of the amine and the crown ether. Using the assumption described in the previous paper,[8] the predicted geometries **22**, **23**, **24** and **25** [for the (*R*)-enantiomer; R^1=Ph, R^2=H and for the (*S*)-enantiomer; R^1=H, R^2=Ph] are illustrated for the complexes of (*S,S,S,S*)-**1**, (*S,S,S,S*)-**2**, (*R,S,S,R*)-**3** and (*R,S,S,R*)-**4** with 2-amino-2-phenylethanol **21**, respectively, by an examination of CPK molecular models of the complexes.



22



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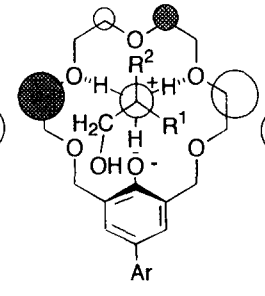

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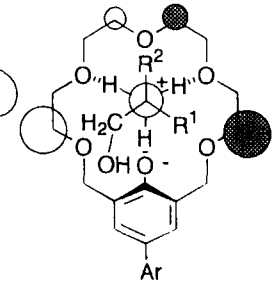

25

Judging from the steric requirements of CPK molecular models of the diastereoisomeric complexes, the observed *R*-selectivity of (*S,S,S,S*)-**1** towards **21** would be due to steric interactions between the phenyl substituent of the amine and the C-2 and the C-4 methylene groups destabilising the (*S,S,S,S*)-**1**–(*S*)-**21** complex with the geometry **22** in which the phenyl substituent of (*S*)-**21** is placed at the narrow space over the oxygen atom at the 8 o'clock position. Similarly, the *S*-selectivity in complexation of (*R,S,S,R*)-**3** with **21** is interpreted from the geometry **24**; the phenyl substituent of (*R*)-**21** is placed at the narrow space near the C-14 and the C-16 methylene groups. The *R*-selectivity of (*S,S,S,S*)-**2** towards **21** is straightforwardly interpreted from the geometry **23**; a steric repulsion between the phenyl substituent of the amine and the phenyl steric barrier destabilized the (*S,S,S,S*)-**2**–(*S*)-**21** complex in

which the phenyl substituent occupies the hindered area near the phenyl barrier. From the geometry **25**, the *S*-selectivity of (*R,S,S,R*)-**4** towards **21** is rationalized in terms of a similar steric interaction.

Acknowledgements

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6. All new compounds gave satisfactory analytical and spectral data and the spectral data of azophenolic crown ethers are listed as follows; (***S,S,S,S***)-**1**: λmax ($CHCl_3$)/nm (ϵ dm^3 mol^{-1} cm^{-1}) 405 (2.34×10^4); δH ($CDCl_3$) 1.12(6H, d, *J* 6.6, CH_3), 3.27(2H, dd, *J* 2.5, 9.5, OCH_2), 3.46(2H, dd, *J* 9.1, 9.5, OCH_2), 3.70(2H, t, *J* 10.3, OCH_2), 3.84(2H, dd, *J* 2.6, 10.3, OCH_2), 4.11–4.50(2H, m, CHMe), 4.60 (2H, dd, *J* 2.5, 9.1, CHPh), 4.78(2H, d, *J* 11.1, CH_2Ar), 4.88(2H, d, *J* 11.1, CH_2Ar), 7.28–7.37(10H, m, C_6H_5), 7.83(1H, d, *J* 8.9, $HAr(NO_2)_2$), 7.85(2H, s, HAr(OH)), 8.49(1H, dd, *J* 2.3, 8.9, $HAr(NO_2)_2$), 8.75(1H, d, *J* 2.3, $HAr(NO_2)_2$), 9.45(1H, s OH); *m/z* (FAB^+) 687 $(M+1)^+$. (***S,S,S,S***)-**2**: λmax ($CHCl_3$) 406 (2.38×10^4); δH ($CDCl_3$) 1.22(6H, d *J* 6.6, CH_3), 3.40(2H, dd *J* 4.5, 9.6, OCH_2), 3.55(2H dd, *J* 2.7, 10.9, OCH_2), 3.69(2H, t, *J* 9.6, OCH_2), 3.71(2H, dd, *J* 5.8, 10.9, OCH_2), 4.28–4.39(2H, m, CHMe), 4.60(2H, dd, *J* 2.7, 10.9, CHPh), 4.61(2H, d, *J* 11.1, CH_2Ar), 4.71(2H, d, *J* 11.1, CH_2Ar), 7.34–7.47(10H, m, C_6H_5), 7.78(1H, d, *J* 8.9, $HAr(NO_2)_2$), 7.71(2H, s, HAr(OH)), 8.46(1H, dd, *J* 2.5, 8.9, $HAr(NO_2)_2$), 8.73(1H, d, *J* 2.5, $HAr(NO_2)_2$), 9.53(1H, s OH); *m/z* (FAB^+) 687 $(M+1)^+$. (***R,S,S,R***)-**3**: λmax ($CHCl_3$) 400 (2.46×10^4); δH ($CDCl_3$) 1.16(6H, d, *J* 6.3, CH_3), 3.28(2H, dd, *J* 7.3, 8.9, OCH_2), 3.54(2H, dd, *J* 4.0, 8.9, OCH_2), 3.70(2H dd, *J* 8.9, 11.2, OCH_2), 3.77(2H, dd, *J* 3.0, 11.2, OCH_2), 4.00–4.70(2H, m, CHMe), 4.68(2H, dd, *J* 3.0, 8.9, CHPh), 4.82(2H, d, *J* 10.6, CH_2Ar), 4.87(2H, d, *J* 10.6, CH_2Ar), 7.29–7.41(10H, m, C_6H_5), 7.81(1H, d, *J* 8.9, $HAr(NO_2)_2$), 7.84(2H, s, HAr(OH)), 8.48(1H, dd, *J* 2.5, 8.9, $HAr(NO_2)_2$), 8.75(1H, d, *J* 2.5, $HAr(NO_2)_2$), 9.53(1H, s, OH); *m/z* (FAB^+) 687 $(M+1)^+$. (***R,S,S,R***)-**4**: λmax ($CHCl_3$) 404 (2.23×10^4); δH ($CDCl_3$) 1.12(6H, d, *J* 6.4, CH_3), 3.46(2H, dd, *J* 4.9, 9.2, OCH_2), 3.58–3.77(6H, m, OCH_2), 4.07–4.11(2H, m, CHMe), 4.73–4.76(6H, m, CHPh and CH_2Ar), 7.33–7.42(10H, m, C_6H_5), 7.72(2H, s, HAr(OH)), 7.79(1H, d, *J* 8.9, $HAr(NO_2)_2$), 8.47(1H, dd, *J* 2.5, 8.9, $HAr(NO_2)_2$), 8.74(1H, d, *J* 2.5, $HAr(NO_2)_2$), 9.53(1H, s, OH); *m/z* (FAB^+) 687 $(M+1)^+$.
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