



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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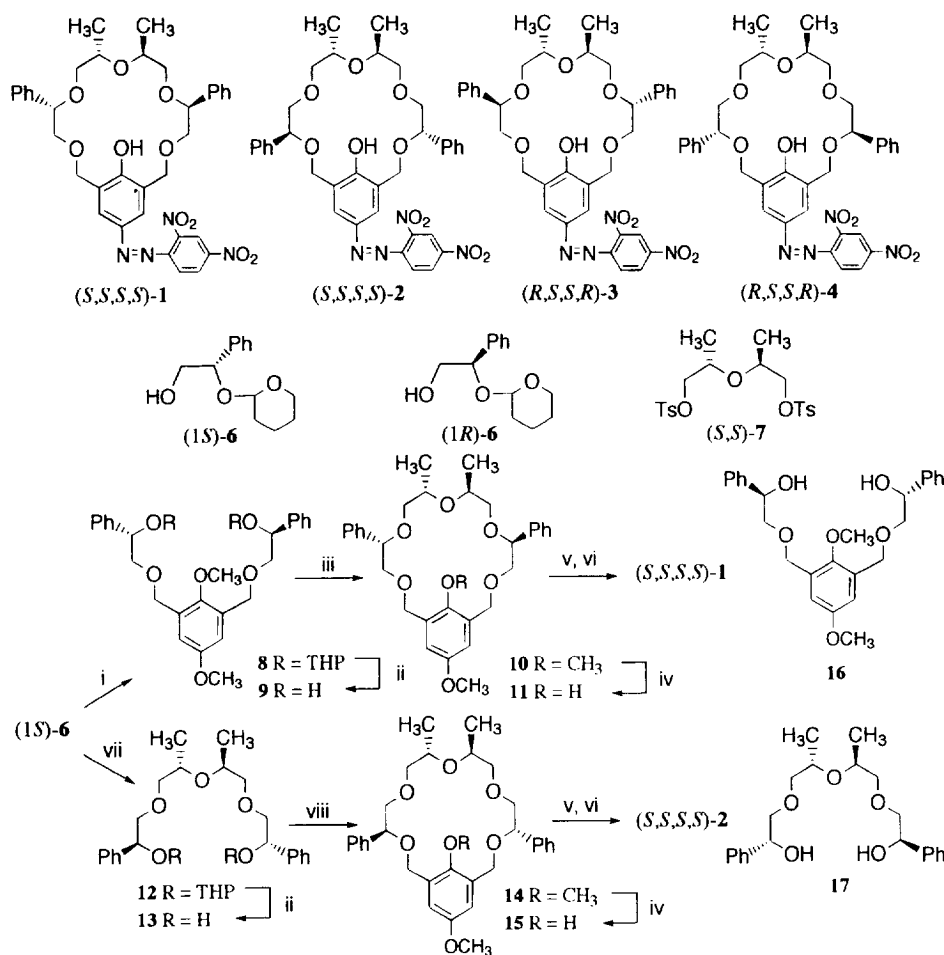
Abstract: Enantiomerically pure azophenolic crown ethers **1–4** containing (*S*)- or (*R*)-1-phenylethane-1,2-diol moieties and (2*S*,4*S*)-2,4-dimethyl-3-oxapentane-1,5-diol moiety as a chiral subunit were prepared; crown ethers (*S,S,S,S*)-**1** showed high chiral recognition behaviour in complexation 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 diastereoisomers³ 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 cm² g⁻¹) (CHCl₃) in 57% overall yield. High-dilution condensation of (*S,S*)-**9** with (*S,S*)-**7**, $[\alpha]_D^{29} +3.40$ (CHCl₃), prepared from ethyl (*S*)-lactate,⁴ in the presence of NaH and KBF₄ in DMF at 100°C gave crown ether (*S,S,S,S*)-**10**, $[\alpha]_D^{22} +143$ (CHCl₃) in 37% yield. Demethylation of (*S,S,S,S*)-**10** with sodium ethanethiolate in DMF at 90°C⁵ gave phenolic crown ether (*S,S,S,S*)-**11**, $[\alpha]_D^{22} +133$ (CHCl₃) in 80% yield. By oxidation with cerium(IV) ammonium nitrate (CAN) in acetonitrile followed by treatment with 2,4-dinitrophenylhydrazine and H₂SO₄ in a mixture of methylene dichloride and ethanol, (*S,S,S,S*)-**11** was converted to azophenolic crown ether (*S,S,S,S*)-**16** 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**, $[\alpha]_D^{25} +94.0$ (CHCl₃) 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**, $[\alpha]_D^{25} +133$ (CHCl₃) 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, KBF₄; iv, C₂H₅SH, NaH; v, CAN; vi, 2,4-dinitrophenylhydrazine; vii, (S,S)-7, NaH; viii, 1,3-bis(bromomethyl)-2,5-dimethoxybenzene, NaH, KBF₄.

+143 (CHCl₃). Azophenolic crown ether (*S,S,S,S*)-2⁶ 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*)-3⁶ and (*R,S,S,R*)-4⁶ were prepared via (*R,R*)-16, [α]_D²⁵ −37.3 (CHCl₃) and (*R,S,S,R*)-17, [α]_D²⁵ −59.6 (CHCl₃), 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 method⁷ on the basis of the absorption in the UV–visible spectrum in chloroform at 25°C. The observed *K*_a-values together with the λ_{max}-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 K_a (M^{-1}) and λ_{\max} for the complexes with chiral amines in $CHCl_3$ at $25^\circ C$

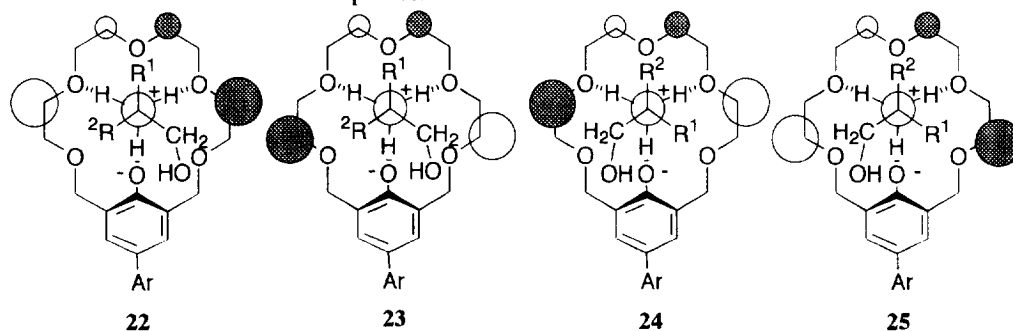
crown ether	amine ^a	K_a^R (λ_{\max}/nm) ^b	K_a^S (λ_{\max}/nm) ^b	K_a^R/K_a^S	$\Delta\Delta G^c$ kcal mol ⁻¹
(<i>S,S,S,S</i>)-1	18	5.95×10^3 (560)	2.54×10^3 (564)	2.3	0.50
(<i>S,S,S,S</i>)-1	19	9.55×10^3 (558)	1.55×10^3 (570)	6.2	1.1
(<i>S,S,S,S</i>)-1	20	1.57×10^3 (564)	3.06×10^2 (569)	5.1	0.97
(<i>S,S,S,S</i>)-1	21	4.76×10^3 (558)	4.10×10^2 (567)	11.6	1.5
(<i>S,S,S,S</i>)-2	18	3.96×10^3 (565)	1.69×10^3 (563)	2.3	0.50
(<i>S,S,S,S</i>)-2	19	4.63×10^3 (561)	2.77×10^3 (565)	1.7	0.30
(<i>S,S,S,S</i>)-2	20	8.66×10^2 (569)	7.30×10^2 (566)	1.2	0.10
(<i>S,S,S,S</i>)-2	21	1.27×10^3 (564)	4.10×10^2 (561)	3.1	0.67
(<i>R,S,S,R</i>)-3	18	1.50×10^3 (565)	3.12×10^3 (562)	0.48	0.43
(<i>R,S,S,R</i>)-3	19	1.68×10^3 (565)	4.70×10^3 (562)	0.36	0.61
(<i>R,S,S,R</i>)-3	20	2.18×10^2 (567)	9.47×10^2 (566)	0.23	0.87
(<i>R,S,S,R</i>)-3	21	4.72×10^2 (573)	2.75×10^3 (559)	0.17	1.0
(<i>R,S,S,R</i>)-4	18	6.08×10^2 (564)	1.42×10^3 (559)	0.43	0.50
(<i>R,S,S,R</i>)-4	19	9.19×10^2 (563)	1.67×10^3 (560)	0.55	0.35
(<i>R,S,S,R</i>)-4	20	1.94×10^2 (563)	3.23×10^2 (564)	0.66	0.30
(<i>R,S,S,R</i>)-4	21	2.69×10^2 (574)	4.17×10^2 (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) K_a^R for the complex with (*R*)-amine and K_a^S for the complex with (*S*)-amine c) $\Delta\Delta G = RT \ln (K_a^{\text{more stable}} / K_a^{\text{less stable}})$ 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 $25^\circ C$ 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.



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**: λ_{\max} (CHCl₃)/nm (ϵ dm³ mol⁻¹ cm⁻¹) 405 (2.34×10^4); δ H (CDCl₃) 1.12(6H, d, *J* 6.6, CH₃), 3.27(2H, dd, *J* 2.5, 9.5, OCH₂), 3.46(2H, dd, *J* 9.1, 9.5, OCH₂), 3.70(2H, t, *J* 10.3, OCH₂), 3.84(2H, dd, *J* 2.6, 10.3, OCH₂), 4.11–4.50(2H, m, CHMe), 4.60 (2H, dd, *J* 2.5, 9.1, CHPh), 4.78(2H, d, *J* 11.1, CH₂Ar), 4.88(2H, d, *J* 11.1, CH₂Ar), 7.28–7.37(10H, m, C₆H₅), 7.83(1H, d, *J* 8.9, HAr(NO₂)₂), 7.85(2H, s, HAr(OH)), 8.49(1H, dd, *J* 2.3, 8.9, HAr(NO₂)₂), 8.75(1H, d, *J* 2.3, HAr(NO₂)₂), 9.45(1H, s, OH); *m/z* (FAB⁺) 687 (M+1)⁺. (*S,S,S,S*)-**2**: λ_{\max} (CHCl₃) 406 (2.38×10^4); δ H (CDCl₃) 1.22(6H, d *J* 6.6, CH₃), 3.40(2H, dd *J* 4.5, 9.6, OCH₂), 3.55(2H dd, *J* 2.7, 10.9, OCH₂), 3.69(2H, t, *J* 9.6, OCH₂), 3.71(2H, dd, *J* 5.8, 10.9, OCH₂), 4.28–4.39(2H, m, CHMe), 4.60(2H, dd, *J* 2.7, 10.9, CHPh), 4.61(2H, d, *J* 11.1, CH₂Ar), 4.71(2H, d, *J* 11.1, CH₂Ar), 7.34–7.47(10H, m, C₆H₅), 7.78(1H, d, *J* 8.9, HAr(NO₂)₂), 7.71(2H, s, HAr(OH)), 8.46(1H, dd, *J* 2.5, 8.9, HAr(NO₂)₂), 8.73(1H, d, *J* 2.5, HAr(NO₂)₂), 9.53(1H, s, OH); *m/z* (FAB⁺) 687 (M+1)⁺. (*R,S,S,R*)-**3**: λ_{\max} (CHCl₃) 400 (2.46×10^4); δ H (CDCl₃) 1.16(6H, d, *J* 6.3, CH₃), 3.28(2H, dd, *J* 7.3, 8.9, OCH₂), 3.54(2H, dd, *J* 4.0, 8.9, OCH₂), 3.70(2H dd, *J* 8.9, 11.2, OCH₂), 3.77(2H, dd, *J* 3.0, 11.2, OCH₂), 4.00–4.70(2H, m, CHMe), 4.68(2H, dd, *J* 3.0, 8.9, CHPh), 4.82(2H, d, *J* 10.6, CH₂Ar), 4.87(2H, d, *J* 10.6, CH₂Ar), 7.29–7.41(10H, m, C₆H₅), 7.81(1H, d, *J* 8.9, HAr(NO₂)₂), 7.84(2H, s, HAr(OH)), 8.48(1H, dd, *J* 2.5, 8.9, HAr(NO₂)₂), 8.75(1H, d, *J* 2.5, HAr(NO₂)₂), 9.53(1H, s, OH); *m/z* (FAB⁺) 687 (M+1)⁺. (*R,S,S,R*)-**4**: λ_{\max} (CHCl₃) 404 (2.23×10^4); δ H (CDCl₃) 1.12(6H, d, *J* 6.4, CH₃), 3.46(2H, dd, *J* 4.9, 9.2, OCH₂), 3.58–3.77(6H, m, OCH₂), 4.07–4.11(2H, m, CHMe), 4.73–4.76(6H, m, CHPh and CH₂Ar), 7.33–7.42(10H, m, C₆H₅), 7.72(2H, s, HAr(OH)), 7.79(1H, d, *J* 8.9, HAr(NO₂)₂), 8.47(1H, dd, *J* 2.5, 8.9, HAr(NO₂)₂), 8.74(1H, d, *J* 2.5, HAr(NO₂)₂), 9.53(1H, s, OH); *m/z* (FAB⁺) 687 (M+1)⁺.
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