The Synthesis of Azophenolic Crown Ethers of C_s Symmetry incorporating cis-1-Phenylcyclohexane-1,2-diol Residues and Diastereotopic Face Selectivity in Complexation of Ethanolamine by their Diastereotopic Faces
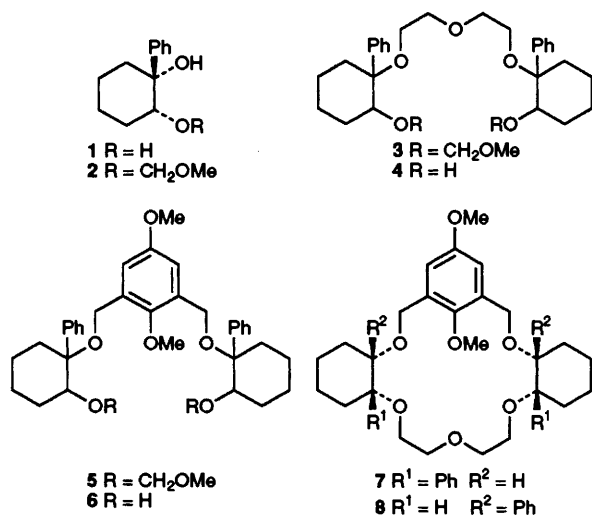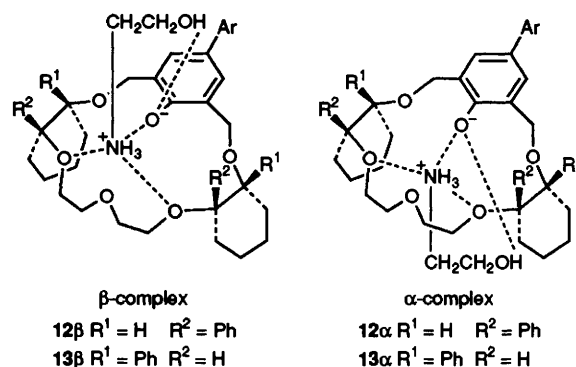
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Azophenolic crown ethers 9 and 10 of C_s symmetry incorporating cis-1-phenylcyclohexane-1,2-diol residues as a steric barrier have been prepared; they bind ethanolamine stereoselectively to one of their diastereotopic faces.

Many reports have described the complexation of ammonium cations with crown ethers having homotopic faces.[1] Some have described the complexation of alkylammonium cations with chiral crown ethers having diastereotopic faces,[2] but, as far as we know, there has been no report of diastereotopic face selectivity in complexation of alkylammonium cation by diastereotopic faces of a crown ether of meso-type. We report the preparation of azophenolic crown ethers of meso-type incorporating cis-1-phenylcyclohexane-1,2-diol residues as a

β-complex
12β R¹ = H　R² = Ph
13β R¹ = Ph　R² = H

α-complex
12α R¹ = H　R² = Ph
13α R¹ = Ph　R² = H

1 R = H
2 R = CH₂OMe

3 R = CH₂OMe
4 R = H

5 R = CH₂OMe
6 R = H

7 R¹ = Ph R² = H
8 R¹ = H　R² = Ph

9

10　11

Table 1 ¹H NMR chemical shifts of selected protons of 9 and 10 (at 35 °C in CDCl₃; J in Hz)

Proton	9	10
H_a	8.73, d, J 2.2	8.71, d, J 2.2
H_b	8.46, dd, J 8.9, 2.2	8.44, dd, J 8.9, 2.2
H_c	7.80, d, J 8.9	7.76, d, J 8.9
H_d	7.63, s	7.54, s
H_e	4.41, d, J 10.9	4.35, d, J 10.9
H_f	4.89, d, J 10.9	4.52, d, J 10.9

Table 2 ¹H NMR chemical shifts of selected protons of the mixture of the free host 9 and 12α (host 9/ethanolamine = 1.4, at −20 °C in CDCl₃)

Proton	Host 9	Complex 12α
H_a	8.81, d	8.53, d
H_b	8.53, dd	8.40, dd
H_c	7.82, d	8.02, d
H_d	7.59, br	6.70, s
H_e	4.28, br	3.06, d
H_f	4.89, d	5.19, d

Table 3 ¹H NMR chemical shifts of selected protons of 12α and 13β (in CDCl₃)

Proton	12α		13β	
	35 °C	−30 °C	35 °C	−50 °C
H_a	8.58, d	8.65, d	8.59, d	8.69, d
H_b	8.34, dd	8.41, dd	8.29, dd	8.36, dd
H_c	7.95, d	8.04, d	7.93, d	8.09, d
H_d	6.79, s	6.68, s; 6.69, s	7.85, br	7.85, d; 8.05, d
H_e	3.11, d	3.04, d; 3.09, d	4.17, d	4.10, d; 4.12, d
H_f	5.19, d	5.19, d	4.75, d	4.80, d; 4.86, d
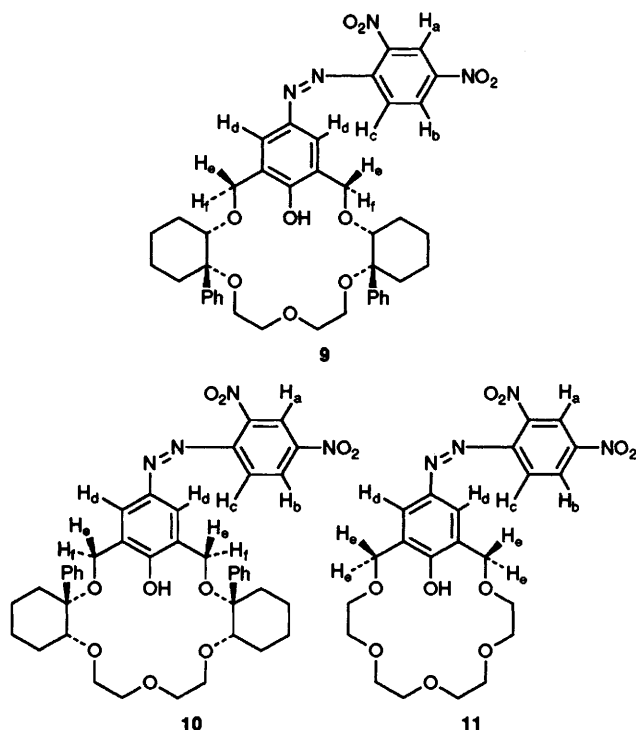
steric barrier and the ability of these crown ethers to form diastereoisomeric complexes with ethanolamine.

Condensation of (±)-2, prepared from (±)-1,[3] with diethylene glycol bis(methanesulfonate) in the presence of NaH in dry (THF) under reflux gave a mixture of diastereoisomers of 3 (35% yield). After hydrolysis of the mixture with conc. HCl–methanol, the resulting diol 4 was treated with 2,6-bis(bromomethyl)-1,4-dimethoxybenzene in the presence of NaH and KBF$_4$ in dry THF under reflux to give the mixture of diastereoisomers of 7, which was chromatographed on silica gel to furnish meso-7† (24% yield, mp 175–176.5 °C) and (±)-7 (25% yield, as a glass). The structure of (±)-7 was unambigously established by comparing its spectral data with those of (+)-7[4] prepared from (−)-1. Similarly, the mixture of diastereoisomers of 5 (59% yield), prepared from (±)-2 and 2,6-bis(bromomethyl)-1,4-dimethoxybenzene, was hydrolysed to give 6, which was condensed with diethylene glycol bis(methanesulfonate) to give a mixture of diastereoisomers of 8. Chromatography of the mixture gave meso-8 (17% yield, as a colourless solid) and (±)-8 (19% yield, as a glass); (±)-8 was identified by comparison of its spectral data with those of (−)-8, [α]$_D$ −41.3 (CHCl$_3$),[5] prepared from (−)-1. Oxidation of meso-7 and meso-8 with cerium(IV) ammonium nitrate in acetonitrile–H$_2$O at 40 °C followed by treatment with 2,4-dinitrophenylhydrazine in conc. H$_2$SO$_4$–ethanol gave the azophenolic crown ethers 9 (25% yield for two steps, as a red powder) and 10 (24% yield for two steps, as a red powder), respectively; their ¹H NMR data are given in Table 1. The azophenolic crown ethers 9 and 10 can form a stable complex with ethanolamine by three-point binding and additional hydrogen bonding between the phenolate oxygen and the alcoholic OH group,[6] and the association constant for their complexes is easily estimated by electronic spectrometry.

meso-Crown ethers 9 and 10 have diastereotopic faces and hence can form diastereoisomeric α- and β-complexes with achiral alkylamines. We examined stereoselectivity in complexation of ethanolamine by the diastereotopic faces of 9 and 10 using the temperature-dependent ¹H NMR technique.

Calculation on the basis of the temperature dependent ¹H NMR spectra of the complexes showed that 9 and 10 were almost quantitatively converted into 12 and 13, respectively, in CDCl$_3$ solution at low temperature. When less than one equivalent of ethanolamine was added to the crown ether, the NMR spectrum of the mixture showed separate signals for the free host and the complex at low temperature (see Table 2). The ¹H NMR spectra of the α-complex 12α and the β-complex 13β (Table 2) provided evidence for the exclusive formation of one diastereoisomeric complex in each case.

In the case of the complex of 9 with ethanolamine, signals for H$_d$ and H$_e$ in 12α were shifted upfield by ca. 0.95 and ca. 1.35 ppm compared with their respective chemical shifts in the spectrum of 9. The upfield shifts observed showed that two

Table 4 ¹H NMR chemical shifts of selected protons of 11 and the complex of 11 with ethanolamine (in CDCl$_3$); J in Hz)

	11		Complex	
Proton	35 °C	−50 °C	35 °C	−50 °C
H$_a$	8.75, d, J 2.2	8.87, d	8.59, d	8.69, d
H$_b$	8.48, dd, J 8.9, 2.2	8.59, dd	8.33, dd	8.42, dd
H$_c$	7.81, d, J 8.9	7.85, d	7.91, d	7.95, d
H$_d$	7.81, s	7.89, s	7.84, s	7.83, s; 7.95, s
H$_e$	4.76, s	4.76, s	4.55, br	5.03, d; 5.19, d[a]

[a] Other two peaks for H$_e$ are overlapping resonances at δ 3.9–4.1.

phenyl substituents were oriented over these protons in 12α; that is, complexation occurred at the α-face of 9. CPK models of the complexes show that the aromatic protons H$_d$ and benzylic protons H$_e$ are shielded by phenyl barriers in 12α, but not in 12β. The high α-face selectivity in complexation is assumed to arise from steric repulsions between two cyclohexane residues on the α-face of 12β which make the β-complex less stable than 12α.

In the case of complexation of 10 with ethanolamine, it was concluded that complexation occurred preferentially at the β-face, because no upfield shift of the signals for H$_d$ and H$_e$ was observed in the spectrum of 13β. Aromatic protons H$_d$ and benzylic protons H$_e$ in 13α should be oriented within the shielding zones of the phenyl groups. CPK models suggest that the high stereoselectivity of binding to the β-face may be ascribed to large steric repulsions by two phenyl substituents and the phenol moiety on the β-face of 13α.

A singlet signal for H$_d$ in 12α and 13β at 35 °C showed that the two H$_d$ protons were homotopic because of free rotation about the C–N bond. However, this signal separated into two peaks of equal intensity at low temperature. Similarly, H$_d$ protons in 11 were homotopic even at −50 °C, but their signals in the complex of 11 with ethanolamine separated into two peaks of equal intensity at −50 °C. From these results, we assume that restricted rotation about the C–N bond resulting from a contribution of the quinoid structure of the phenolate moiety in the complex made these protons heterotopic at low temperature.

The association constant, K_a, for 12α and 13β in chloroform, based on their UV and visible absorption spectra‡ at 25 °C, were 2.97 × 10⁴ and 9.88 × 10³ respectively.[7] The ¹H NMR spectroscopic method in CDCl$_3$ at 25 °C gave K_a = 1.9 × 10⁴ dm³ mol⁻¹ for 12α.

Footnotes

† All new compounds gave satisfactory analytical and spectral data.
‡ The absorption maxima for 9, 10, 12α and 13β appeared at 414 nm (ε 2.25 × 10⁴), 416 nm (ε 2.31 × 10⁴), 585 nm, and 589 nm, respectively, in the UV and visible spectrum in CHCl$_3$ at 25 °C.

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