Temperature dependent reversal of enantiomer selectivity in the complexation of optically active phenolic crown ethers with chiral amines

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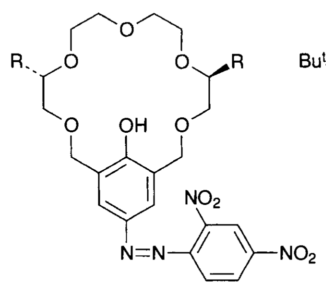
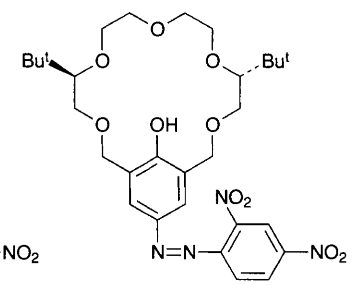
Phenolic crown ethers (*S,S*)-1, (*R,R*)-2, (*S,S*)-3 and (*S,S*)-4 were prepared in enantiomerically pure forms; the enantiomer selectivities of crown ethers (*S,S*)-1 and (*R,R*)-2 in complexation with 2-aminopropan-1-ol reversed at *ca.* 6 °C and increased with increasing temperature above the isoenantioselective temperature.

Enantiomer recognition has been widely studied in various types of the chemical reaction[1] and it is the generally accepted view that lower temperatures enhance the enantiomer selectivity in chiral processes. However, a few papers have recently reported an increase in the enantiomeric selectivity of a chiral process with increasing temperature; the enhancement of the optical purities of compounds resolved by GLC using a chiral stationary phase with increasing column temperature[2] and improvement of the optical yield of the photochemically induced enantiomeric isomerization with increasing irradiation temperature.[3] Enantiomer recognition in the complexation of optically active crown ethers with chiral guests has been well examined,[4] but as far as we know there has been no report of temperature dependent reversal of the enantiomer selectivity in complexation of a crown ether with a chiral amine in solution. We have prepared optically active phenolic crown ethers (*S,S*)-**1**,(*R,R*)-**2**, (*S,S*)-**3** and (*S,S*)-**4** and investigated the temperature dependence of their enantiomer selectivity in complexation with chiral 2-aminoethanol derivatives in solution. The temperature dependent reversal of the enantiomer selectivity was found in the complexation of crown ethers (*S,S*)-**1** and (*R,R*)-**2** with 2-aminopropan-1-ol.

The crown ethers (*S,S*)-**1** (mp 89.0–90.0 °C), (*R,R*)-**2** (mp 65.0–66.5 °C), (*S,S*)-**3** (mp 73.0–75.0 °C) and (*S,S*)-**4** (mp 42.0–42.5 °C) were prepared in enantiomerically pure forms by using (*S*)-1-adamantylethane-1,2-diol,[5] (*R*)-3,3-dimethylbutane-1,2-diol,[6] (*S*)-1-phenylethane-1,2-diol[7] and (*S*)-propane-1,2-diol,[8] respectively, as chiral subunits.† The association constants for the complexes of (*S,S*)-**1** and (*R,R*)-**2** with chiral amines 2-aminopropan-1-ol **5** and 1-aminopropan-2-ol **6** in $CDCl_3$ were determined by the ^1H NMR method at various temperatures (−40 to 30 °C). As K_a values for the complexes of (*S,S*)-**3** and (*S,S*)-**4** with these amines were so large at lower temperature that it was difficult to get accurate data by ^1H NMR titration below 10 °C, those were measured by the UV–VIS spectroscopic method in $CHCl_3$ over the temperature range 15 to 45 °C. The observed association constants for the complexes and the thermodynamic parameters calculated on the basis of ΔG values are given in Table 1.

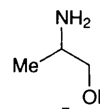
The data given in Table 1 show that K_a values of all complexes increased with decreasing temperature but that the K_a^R/K_a^S values were made to vary by changes in temperature. Figs. 1 and 2 show plots of the $\Delta\Delta G$ values ($\Delta G_S - \Delta G_R$) of complexation of crown ethers (*S,S*)-**1**, (*S,S*)-**2**,‡ (*S,S*)-**3** and (*S,S*)-**4** with 2-aminopropan-1-ol and with 1-aminopropan-2-ol as a function of temperature. The most important feature shown





(*S,S*)-**1** R = 1-adamantyl
(*S,S*)-**3** R = Ph
(*S,S*)-**4** R = Me

(*R,R*)-**2**



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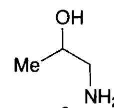

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Table 1 Association constants for the complexes and thermodynamic parameters for complexation of crown ethers with chiral amines

Crown ether	Amine[a]	Solvent	K_a/mol^{-1} (T/°C)			ΔH/kJ mol^{-1}	ΔS/JK^{-1} mol^{-1}
(*S,S*)-**1**	(*R*)-**5**	$CDCl_3$	2.4 × 10^4 (−40)	9.6 × 10^2 (0)	4.2 × 10^1 (30)	−66.6	−188
(*S,S*)-**1**	(*S*)-**5**	$CDCl_3$	6.7 × 10^3 (−40)	9.2 × 10^2 (0)	6.5 × 10^1 (30)	−48.6	−124
(*R,R*)-**2**	(*S*)-**5**	$CDCl_3$	1.3 × 10^4 (−40)	7.8 × 10^2 (0)	5.8 × 10^1 (30)	−57.0	−154
(*R,R*)-**2**	(*R*)-**5**	$CDCl_3$	7.5 × 10^4 (−40)	7.6 × 10^2 (0)	8.0 × 10^1 (30)	−48.0	−122
(*S,S*)-**3**	(*R*)-**5**	$CHCl_3$	1.7 × 10^5 (15)	3.5 × 10^4 (25)	2.0 × 10^3 (45)	−99.4	−247
(*S,S*)-**3**	(*S*)-**5**	$CHCl_3$	2.8 × 10^4 (15)	7.6 × 10^3 (25)	6.7 × 10^2 (45)	−82.6	−203
(*S,S*)-**4**	(*R*)-**5**	$CHCl_3$	2.0 × 10^4 (15)	7.0 × 10^3 (25)	1.1 × 10^3 (45)	−73.9	−174
(*S,S*)-**4**	(*S*)-**5**	$CHCl_3$	7.3 × 10^3 (15)	3.1 × 10^3 (25)	5.6 × 10^2 (45)	−66.0	−155
(*S,S*)-**1**	(*R*)-**6**	$CDCl_3$	1.3 × 10^4 (−40)	1.0 × 10^3 (0)	4.2 × 10^1 (30)	−60.4	−167
(*S,S*)-**1**	(*S*)-**6**	$CDCl_3$	2.7 × 10^3 (−40)	3.5 × 10^2 (0)	2.5 × 10^1 (30)	−48.4	−131
(*R,R*)-**2**	(*S*)-**6**	$CDCl_3$	4.6 × 10^3 (−40)	5.8 × 10^1 (0)	3.4 × 10^1 (30)	−51.6	−139
(*R,R*)-**2**	(*R*)-**6**	$CDCl_3$	3.5 × 10^3 (−40)	3.6 × 10^2 (0)	2.6 × 10^1 (30)	−50.9	−140
(*S,S*)-**3**	(*R*)-**6**	$CHCl_3$	8.4 × 10^4 (15)	1.5 × 10^4 (25)	1.4 × 10^3 (45)	−89.4	−219
(*S,S*)-**3**	(*S*)-**6**	$CHCl_3$	3.1 × 10^4 (15)	6.0 × 10^3 (25)	7.2 × 10^2 (45)	−81.8	−200
(*S,S*)-**4**	(*R*)-**6**	$CHCl_3$	1.4 × 10^4 (15)	5.2 × 10^3 (25)	9.0 × 10^2 (45)	−70.1	−164
(*S,S*)-**4**	(*S*)-**6**	$CHCl_3$	7.8 × 10^3 (15)	3.1 × 10^3 (25)	6.1 × 10^2 (45)	−64.9	−151

[a] 2-Aminopropan-1-ol **5**, 1-aminopropan-2-ol **6**.

in Fig. 1 is that the sign of the $\Delta\Delta G$ values for the complexation of crown ethers (*S*,*S*)-**1** and (*S*,*S*)-**2** reverses at *ca.* 6 °C; the isoenantioselective temperature (T_{iso}) and the *S*-selectivity increased with increasing temperature above T_{iso}. The plots in Fig. 2 show that the temperature dependence of the enantiomer selectivity of (*S*,*S*)-**1** was rather large and the extrapolation predicts that the chirality of the enantiomer of 1-aminopropan-2-ol bound predominantly to (*S*,*S*)-**1** will change at about 60 °C. Complexation of crown ethers (*S*,*S*)-**3** and (*S*,*S*)-**4** with both amines showed an unambiguous temperature dependent enantiomer selectivity; reversal of the selectivity was not observed because of high T_{iso} values, which are calculated to be above 110 °C on the basis of ΔH and ΔS values. The enantiomer selectivity of (*S*,*S*)-**2** towards 1-aminopropan-2-ol scarcely changed during the experiment.

The enantiomer selectivities governed by $-\Delta_{R,S}\ \Delta H$ are interpreted from steric repulsions between the ligands of the amine and the steric barriers of the crown ether in the complex. Using the assumption described in a previous paper,[9] the predicted geometries of **7** and **8**, respectively, are illustrated in Fig. 3 for the complexes of (*S*,*S*)-crown ethers with 2-aminopropan-1-ol and with 1-aminopropan-2-ol on the basis of CPK molecular model examination of the diastereoisomeric complexes. In the case of the complexes with 2-aminopropan-1-ol, judging from CPK molecular model examination and the observed enantiomer selectivities, we infer that the pseudo-equatorial substituent at C-5 (open circle in **7**) makes the methylene group at C-4 the effective steric barrier on the β-face of the crown ring and so a steric repulsion between the ligand R^2 [for the (*S*)-amine R^2 = Me, and for the (*R*)-amine R^2 = H] and the methylene group destabilized the complexes with (*S*)-2-aminopropan-1-ol. The enantiomer selectivity towards 1-aminopropan-2-ol is straightforwardly interpreted in terms of a steric repulsion between the ligand R^1 [for the (*S*)-amine R^1 = Me, and for the (*R*)-amine R^1 = H] and the chiral barrier at C-13 (shade circle in **8**), making the complexes with (*S*)-1-aminopropan-2-ol less stable than their diastereoisomeric complexes.

The *R*-selectivity of (*S*,*S*)-crown ethers **1**–**4** below T_{iso} is rationalized from CPK molecular model examination as mentioned above, but complexation of crown ethers (*S*,*S*)-**1** and (*S*,*S*)-**2** with 2-aminopropan-1-ol showed *S*-selectivity above T_{iso}. Such a reversal of the sign of enantiomer selectivity dependent upon temperature is predictable since the enthalpy change and the entropy change compensate each other, as can be seen in Table 1, and the entropy change contributes to the stability of the complex.[10] The present results demonstrate the first observed example of the temperature dependent reversal of the enantiomer selectivity in complexation of a crown ether with an amine in solution.

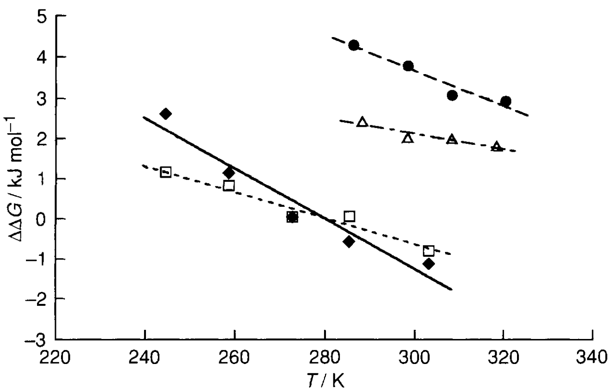


Fig. 1 Temperature dependence of $\Delta\Delta G$ ($\Delta G_S - \Delta G_R$) for the complexation of crown ethers **1**–**4** with 2-aminopropan-1-ol in chloroform; (◆) (*S*,*S*)-**1**, (□) (*S*,*S*)-**2**, (●) (*S*,*S*)-**3** and (△) (*S*,*S*)-**4**

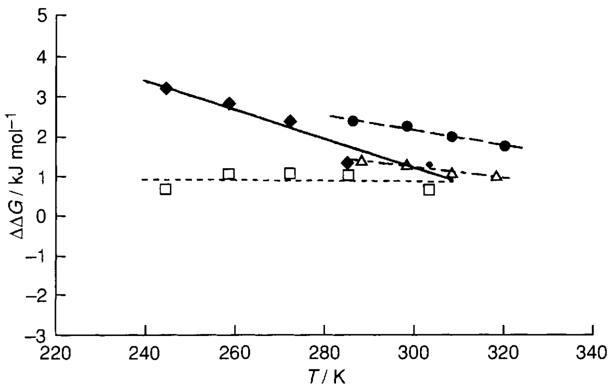
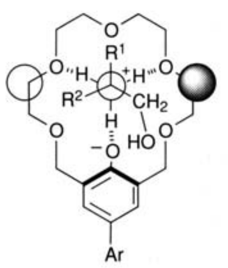


Fig. 2 Temperature dependence of $\Delta\Delta G$ ($\Delta G_S - \Delta G_R$) for the complexation of crown ethers **1**–**4** with 1-aminopropan-2-ol in chloroform; (◆) (*S*,*S*)-**1**, (□) (*S*,*S*)-**2**, (●) (*S*,*S*)-**3** and (△) (*S*,*S*)-**4**



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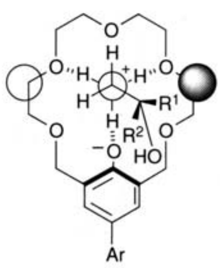

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Footnotes

† The details of the preparation of the phenolic crown ethers (*S*,*S*)-**1**, (*R*,*R*)-**2**, (*S*,*S*)-**3** and (*S*,*S*)-**4** will be reported elsewhere.

‡ In Fig. 1 and 2, $\Delta\Delta G$ values of complexation of crown ether **2** with amines are plotted as (*S*,*S*)-**2**.

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