Chiral Recognition of 1-(4-Quinolyl)ethanol by Permethylated α-Cyclodextrin

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^{1}H NMR studies on enantioselective complexation of 1-(4-quinolyl)ethanol (4QE) with hexakis(tri-*O*-methyl)-α-cyclodextrin reveal the formation of the equatorial and axial inclusion complexes of (*R*)- and (*S*)-4QEs, respectively.

Cyclodextrins (CDs) have extensively been used as chiral selectors which can separate guest enantiomers in HPLC, GLC and capillary zone electrophoresis (CZE).[1] In spite of numerous examples of enantiomer separation by these analytical methods, CDs have generally been known as poor hosts to discriminate between optical isomers of guests in aqueous solutions.[2] Indeed, several studies show small differences in free energy changes ($\Delta\Delta G$) for complexation between the enantiomers of guests having central chirality.[8] Most of these studies, however, lack in clarification of the mechanisms for chiral recognition. In this work, we chose the 1-arylethanols, especially 4QE (see Fig. 1), as the typical guests with central chirality and studied the mechanism for their enantioselective complexation with CDs by means of ^{1}H NMR spectroscopy.

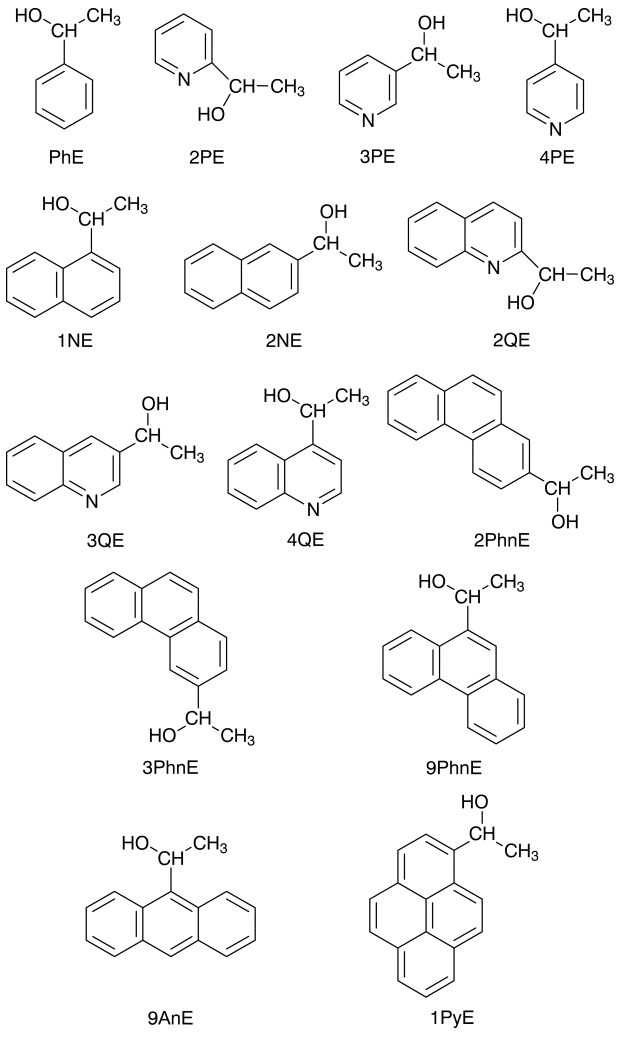

Fig. 1 Chiral 1-arylethanols used in the present study

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Table 3 Binding constants (K) and enantioselectivities ($\Delta\Delta G$) for complexation of (*R*)- and (*S*)-4QEs with various CDs in D_2O at pD 9.0 and 25 °C[a]

Host	K [(*R*)-4QE]/ dm^3 mol^{-1}	K [(*S*)-4QE]/ dm^3 mol^{-1}	$\Delta\Delta G$/kJ mol^{-1} [b]
α-CD	—[c]	—[c]	—
β-CD	65 ± 11	55 ± 5	—[d]
γ-CD	88 ± 6	73 ± 4	0.46 ± 0.31
TMe-α-CD	51 ± 3	41 ± 1	0.54 ± 0.21
TMe-β-CD	23 ± 3	27 ± 4	—[d]

[a]The K values were determined from ^{1}H NMR titrations of the enantiomers of 4QE (2×10^{-3} mol dm^{-3}) in D_2O. [b]$\Delta\Delta G = \Delta G_S - \Delta G_R$. [c]The K values for the α-CD complexes could not be determined because of very small CIS. [d]The $\Delta\Delta G$ values for these systems were not calculated because the differences in the K values between the enantiomers were in the range of the standard deviations.

The binding constants (K) determined from the NMR titrations for complexation with hexakis(tri-*O*-methyl)-α-cyclodextrin (TMe-α-CD) are 51 ± 3 and 41 ± 1 dm^3 mol^{-1} for (*R*)- and (*S*)-4QEs, respectively (Table 3). Similar enantioselective complexation was observed for 1NE and 1PyE whose molecular sizes are too large to be incorporated wholly into the TMe-α-CD cavity (Table 4). In contrast, no chiral discrimination between the enantiomers occurs with PhE, 3PE and 4PE whose molecular sizes are significantly smaller than those of 4QE, 1NE and 1PyE. The ROESY spectra as well as the molecular mechanics-molecular dynamics calculations suggest the formation of the equatorial and axial inclusion complexes of (*R*)- and (*S*)-4QEs, respectively (Fig. 7). The chiral discrimination might occur at the secondary OCH_3 group side of TMe-α-CD where the guest molecule is bound shallowly to the asymmetrically twisted cavity of the host.

Table 4 Binding constants (K) and enantioselectivities ($\Delta\Delta G$) for complexation of (*R*)- and (*S*)-1-arylethanols with TMe-α-CD in D_2O at pD 9.0 and 25 °C[a]

Guest	K_1/ dm^3 mol^{-1}	K_2/ dm^3 mol^{-1}	$\Delta\Delta G$/ kJ mol^{-1} [b]
(*R*)- and (*S*)-PhE	128 ± 22		0
(*R*)- and (*S*)-4PE	34 ± 2		0
(*R*)-1NE	277 ± 14	41 ± 3	
(*S*)-1NE	239 ± 15	28 ± 5	0.37 ± 0.28
(*R*)-4QE	51 ± 3		
(*S*)-4QE	41 ± 1		0.54 ± 0.20
(*R*)-1PyE	565 ± 57		
(*S*)-1PyE	421 ± 43		0.73 ± 0.51

[a]The K values were determined from ^{1}H NMR titrations of 1-arylethanols (2×10^{-3} mol dm^{-3}) in D_2O except for 1PyE. In the case of 1PyE, the K values were determined by means of UV–VIS absorption spectroscopy in 0.033 mol dm^{-3} phosphate buffer at pH 9.0. [b]$\Delta\Delta G = \Delta G_S - \Delta G_R$. The $\Delta\Delta G$ for K_1 is exhibited for the 1NE complexes.

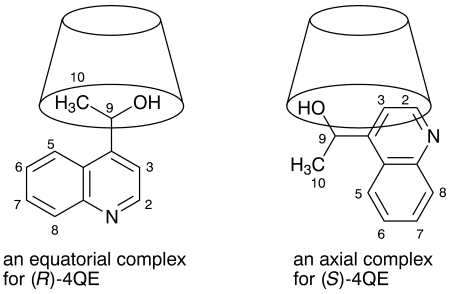

Fig. 7 Structures of the (*R*)- and (*S*)-4QE complexes of TMe-α-CD deduced from the ROESY spectral measurements

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Techniques used: ^{1}H NMR, molecular dynamics–molecular mechanics calculations

Appendix: NMR titration curves for determining the *K* values

Table 1: Results on ^{1}H NMR measurements of 1-arylethanols (2×10^{-3} mol dm^{-3}) in D_2O at pD 9.0 in the presence of various CDs at 25 °C

Table 2: Results on ^{1}H NMR measurements of 1-arylethanols (2×10^{-3} mol dm^{-3}) in D_2O at pD 9.0 in the presence of TMe-α-CD (1×10^{-2} mol dm^{-3}) at 25 °C

Fig. 2: ^{1}H NMR spectra of ($\pm$)-4QE (2×10^{-3} mol dm^{-3}) in D_2O at pD 9.0 in the absence and the presence of various CDs at 25 °C

Fig. 3: ^{1}H NMR spectra of ($\pm$)-9AnE (2×10^{-3} mol dm^{-3}) in $CDCl_3$ and D_2O at pD 9.0 in the presence of TMe-α-CD (1×10^{-2} mol dm^{-3}) at 25 °C

Fig. 4: Changes in the chemical shifts of TMe-α-CD (2×10^{-3} mol dm^{-3}) in D_2O at pD 9.0 and 25 °C upon addition of (*R*)- and (*S*)-4QEs and 1NEs (2×10^{-3} mol dm^{-3})

Fig. 5: ROESY spectrum of the (*R*)-4QE–TMe-α-CD system at 25 °C. The sample was the mixture of (*R*)-4QE (4×10^{-3} mol dm^{-3}) and TMe-α-CD (1×10^{-2} mol dm^{-3}) in D_2O at pD 9.0 and 25 °C

Fig. 6: ROESY spectrum of the (*S*)-4QE–TMe-α-CD system at 25 °C. The sample was the mixture of (*S*)-4QE (4×10^{-3} mol dm^{-3}) and TMe-α-CD (1×10^{-2} mol dm^{-3}) in D_2O at pD 9.0 and 25 °C

Fig. 8: Structures of the (*R*)-4QE– and (*S*)-4QE–TMe-α-CD complexes in water calculated from the MM–MD calculations

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