Chiral Sensors Based on Lipophilic Cyclodextrins: Interrogation of Enantioselectivity by Combined NMR, Structural Correlation and Electrode Response Studies

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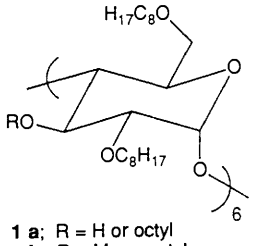
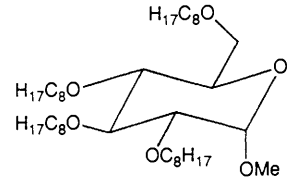
Potentiometric chiral sensors based on 'per'-*O*-octyl-α-cyclodextrin have been devised for the ephedrinium ion. Electrode response studies, varying the structure of the host cyclodextrin and of the guest β-arylammonium ion, combined with NMR measurements on the diastereoisomeric complexes have led to the formulation of a working model defining the structural origins of enantioselection in which the *C*-methyl substituent, β to the aryl ring, acts as a stereo-differentiating group, and residual hydroxy groups in the cyclodextrin† are needed.

Potentiometric ion-selective electrodes that respond in an enantioselective manner to chiral arylammonium ions have been reported.[1-3] In each of these systems, the sensing ionophore was an enantiopure, neutral, lipophilic crown ether derivative in which the primary binding interaction involved hydrogen-bonding between the $-\overset{+}{N}H_3$ group of the analyte and the ring oxygens of the crown ether. Accordingly, these chiral sensors were of rather limited use because either alkylation of the analyte at nitrogen (*i.e.*, 2°/3° ammonium ions) or analysis in the presence of alkali/alkaline-earth metal cations led to much reduced limits of detection and sensitivity as a result of poor binding or competitive cation binding, respectively. An alternative approach is to consider binding the chiral ammonium ion not only by hydrogen-bonding interactions but also by Van der Waals' interactions between the aryl ring and a complementary host, *i.e.*, one with an appropriate aryl binding pocket. Accordingly cyclodextrin† hosts were considered as they are well known to bind aryl species with a selectivity and stability that is determined by the match between the steric bulk of the aryl moiety and the size of the hydrophobic cavity of the α-, β- or γ-cyclodextrin (with 6, 7 or 8 glucopyranose subunits engendering a cavity of approximate internal diameter 5.7, 7.8 and 9.5 Å, respectively). Alkylated cyclodextrins were required (these possess a slightly expanded cavity compared with the water-soluble parent systems) as a lipophilic ionophore was needed for membrane electrode studies. The intention was, therefore, to study these ionophores for the chemoselective and enantioselective potentiometric detection of suitable chiral arylammonium ions. The effect of varying the structure of the host ionophore and of the guest substrate on the membrane electrode response has been studied in parallel with NMR measurements of the complex in non-polar solvents. The preparation of the various cyclodextrin derivatives discussed here, **1**–**4**, is reported in the accompanying paper[5] and some of the detailed analytical electrode response studies have been described previously.[6,7]



1 a; R = H or octyl
b; R = Me or octyl
c; R = H
d; R = Ac
e; R = Me



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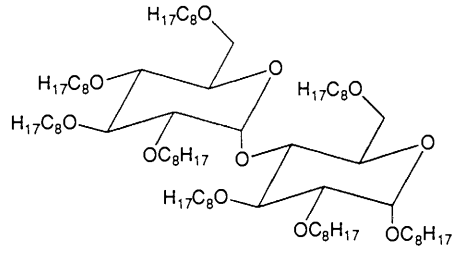

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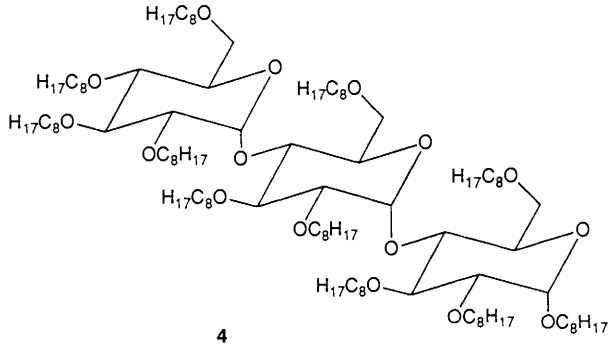

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Results and Discussion

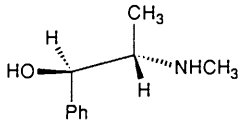
It has previously been shown[6,7] that 'poly'-*O*-octyl-α-cyclodextrin, **1a** (containing an average of 15.4 octyl groups per cyclodextrin)[5,8] when incorporated into a PVC membrane electrode, plasticised with either *o*-nitrophenyl octyl ether (oNPOE) or bis(butylpentyl) adipate (BBPA), gave an ion-selective electrode that showed a different response towards (−)-(1*R*,2*S*)-ephedrine, **5**, than that exhibited in the presence of its three stereoisomers (+)-ephedrine **6**, and (−)- and (+)-pseudoephedrine **7** and **8**. The (−)-ephedrine electrode showed a slope 10 mV per decade less than the diastereoisomeric (+)-ephedrine electrode and there was a difference in electrode

† α-cyclodextrin = cyclomaltohexaose; β-cyclodextrin = cyclomaltoheptaose, γ-cyclodextrin = cyclomaltooctaose, according to IUPAC recommendations.

potentials (*E vs.* SCE) of 26 mV (Table 1). Working in a cell with no liquid junctions, the bias potential of the two electrodes [one in 0.1 mol dm^{-3} (+)-ephedrinium hydrochloride, the other in an 0.1 mol dm^{-3} solution of the (−)-enantiomer] was measured to be 25 mV (*E vs.* Ag/AgCl) corresponding to a difference in free energy for the two diastereoisomeric cells (and hence the cyclodextrin complexes) of 2.4 kJ mol^{-1}. This electrode could be calibrated therefore to measure the enantiomeric purity of (−)-ephedrine, even in mixtures containing its two pseudo-ephedrine diastereoisomers.[6,7] Furthermore, the electrode response was not significantly impaired by the presence of a simulated background of serum ions (Na^+ 150 mmol dm^{-3} Na^+; 4.3 mmol dm^{-3} K^+; 1.26 mmol dm^{-3} Ca^+; 0.9 mmol dm^{-3} Mg^{2+}) and an 'overall' selectivity coefficient $-\log K^{POT}$ of 3.7 was determined.

Formation of a 1:1 complex between (+)-ephedrinium trifluoroacetate and 'poly'-*O*-octyl-α-cyclodextrin, **1a**, was confirmed by electrospray ionisation mass spectrometry.[8] Admixture of isopropyl alcohol solutions of **1a** (50 pmol mm^{-3}) and (+)-ephedrinium trifluoroacetate (0.2 mmol dm^{-3}) gave a mass spectrum (Fig.1), in which only peaks due to a singly charged 1:1 complex were observed, *i.e.*, at lower source potentials no multiple charged ions were evident. Repeating this experiment in the presence of 10 mmol dm^{-3} ammonium acetate gave the ephedrinium complex spectrum selectively (250:1 with respect to the NH_4^+ complex from peak heights and ignoring relative ionisation efficiencies) showing the preference for ephedrinium inclusion.

In seeking further to understand the detailed mechanism by which enantiomer discrimination occurs in these systems, a systematic variation of both the structure of the chiral β-aminoaryl substrate and of the cyclodextrin host was undertaken. Similar such analyses have been made in the study of cyclodextrin chiral stationary phases in the gas chromatographic analysis of structurally related substrates.[9,10]



(1*R*, 2*S*)-(−)-ephedrine

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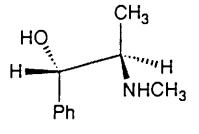

(1*S*, 2*R*)-(+)-ephedrine

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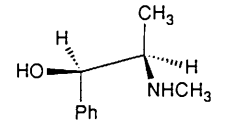

(1*R*, 2*R*)-(−)-pseudoephedrine

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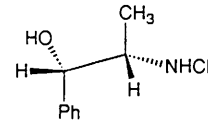


(1*S*, 2*S*)-(+)-pseudoephedrine

8

Electrode Response Studies.—(*a*) *Variation of ionophore structure.* The behaviour of different α-cyclodextrin derivatives as ionophores in a standard membrane electrode was compared, examining the response to the (−)-(1*R*,2*S*)- and (+)-(1*S*,2*R*)-ephedrinium ions. These cyclodextrin derivatives included systems both with (**1a, 1c**) and without a 3-OH group (**1b, 1d, 1e**). For purposes of comparison the peroctylated mono-, di- and tri-saccharides **2**, **3** and **4** were examined in parallel, (Table 1). Differences in the cell electrode potential when analysing (+)- or (−)-ephedrinium were noted, (ΔE in Table 1), giving a measure of the enantioselectivity of the system. In addition the slopes and limits of detection for each cell were noted in order to define the sensitivity and range of a given cell.

From an examination of the data in Table 1, several conclusions can be drawn. The capping of the residual OH group (**1a** *vs.* **1b**; **1a** *vs.* **1e**) markedly reduces the enantioselective response of the electrode and also its sensitivity suggesting that residual 3-OH groups in **1a** may be involved in complexation of the ephedrinium analyte. The acyclic ionophores based on glucose, maltose and maltotriose also showed reduced enantioselectivity although per-*O*-octyl maltose was a reasonably good 'achiral' ionophore for the ephedrinium cation (ΔE = 1 mV

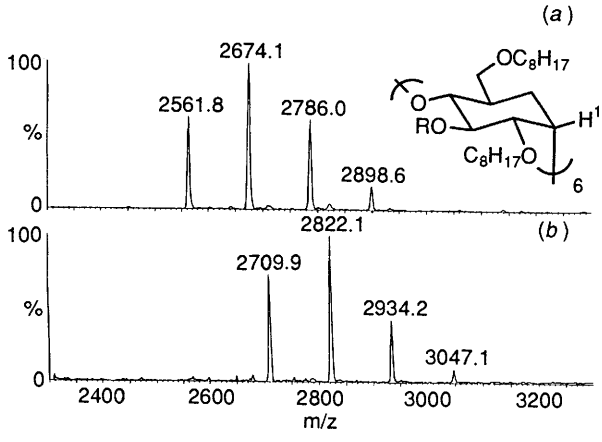


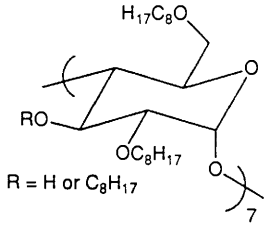
Fig. 1 ES–MS spectrum of **1a** (mean degree of octylation = 15.4; [all M + NH_4^+] in the presence of ammonium acetate (10 mmol dm^{-3}); (*a*) and (+)-ephedrinium trifluoroacetate (0.2 mmol dm^{-3}; all [M^+ + ephedrinium$^+$] (*b*). Calculated values 2710.1 (14 octyls), 2822.3 (15 octyls), 2934.5 (16 octyls) and 3046.8 (17 octyls).

Table 1 Response of the (+)-(1*S*,2*R*)- and (−)-(1*R*,2*S*)-ephedrinium ion to variations in ionophore functionalities

		Enantioselectivity		Sensitivity slope/mV decade^{-1} [c–e]		Limit of detection −log[C]	
Ionophore	Plasticiser	ΔE/mV	$K^{pot}_{+/-}$ [b]	(+)-1*S*,2*R*	(−)-1*R*,2*S*	(+)-1*S*,2*R*	(−)-1*R*,2*S*
1a	*o*NPOE	−25.0	2.54	56.0	[c]SN	5.3	—
1a	BBPA	−26.0	2.64	60.0	50.0	6.6	6.3
1b	BBPA	−3.0	1.12	42.5	39.5	2.0	2.0
1c	BBPA	−24.0	2.45	24.0	[d]#	—	—
1d	BBPA	−29.0	2.96	58.0	50.0	3.2	3.0
1e	BBPA	—	—	49.0	[e]#	2.5	2.5
2	*o*NPOE	−6.0	1.25	50.0	50.0	2.0	2.0
3[f]	*n*NPOE	−1.0	1.04	60.0	SN	5.6	—
4	*o*NPOE	−10.0	1.45	50.0	SN	3.7	—
9	BBPA	−8.0	1.0	56.0	51.0	4.0	3.9

[a] Measurements at 310 K. [b] $\log K^{pot}_{+/-} = (E_- - E_+)/61.54$; 61.54 = theoretical slope at 310 K. [c] SN: super-Nernstian slopes. [d] # Slope 59.0 mV down to 1.0 mmol dm^{-3}; reversal of slope on further dilution. [e] # (−)-(1*R*,2*S*) electrode unstable. [f] Per-*O*-octylsucrose (a glucofuranoside) showed no response at all to either enantiomer.

only, but the limit of detection was $10^{-5.6}$ mol dm^{-3}). With 2,6-di-*O*-octyl-α-cyclodextrin, **1c**, good enantiomer selection was evident but the limit of detection was poor and the response time rather slow. Thus while 3-OH groups may be helpful for a good enantioselective response, too many (*i.e.*, 6 not 3 in **1c** *vs.* **1a**) may slow down the rate of exchange of the guest ion, inhibiting establishment of equilibrium. An interesting observation was made with 3-*O*-acetyl-2,6-di-*O*-octyl-α-cyclodextrin (**1d**) in that a good enantioselective response occurred ($\Delta E_{+/-}$ = 29 mV) but the electrode showed a relatively poor sensitivity (the limit of detection was only *ca.* 10^{-3} mol dm^{-3} compared with $< 10^{-6}$ mol dm^{-3} for **1a**). Finally when 'poly'-*O*-octyl-β-cyclodextrin, **9**, was examined, modest enantioselectivity was



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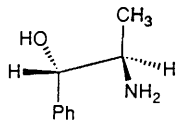
found ($\Delta E_{+/-}$ = 8 mV) again with reduced sensitivity compared with **1a**. Although ephedrine forms a weak 1:1 inclusion complex with the parent β-cyclodextrin,[11,12] (K = 177 dm^3 mol^{-1}; H_2O; 293 K), it is possible that the substituted α-cyclodextrin derivatives possess a cavity for inclusion of a monosubstituted phenyl species that matches the size of the aryl ion more closely.

(*b*) *Variation of arylammonium ion structure.* Several structurally similar β-arylammonium ions were examined as analytes using an electrode based on **1a**, 'poly'-*O*-octyl-α-cyclodextrin. These included the four stereoisomers of ephedrine **5**, **6**, **7** and **8**, (+)-(1*S*,2*R*)- and (−)-(1*R*,2*S*)-norephedrine **10** and **11**, and three sets of arylammonium ions lacking an α-hydroxy group, *i.e.*, (−)- and (+)-deoxyephedrine **12** and **13**, (−)- and (+)-amphetamine **14** and **15** and the achiral neurotransmitter, dopamine, **16**.

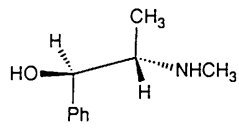
In the ephedrine series, (+)- and (−)-pseudoephedrine **8** and **7** were detected in a similar manner to (+)-ephedrine **5**, with a near-Nernstian response and similar limits of detection. The pharmacologically active isomer, (−)-ephedrine, behaved uniquely with a lower slope and a reduced limit of detection (Table 2). Parallel behaviour was observed with the two enantiomeric norephedrine substrates examined: (−)-norephedrine exhibited a reduced slope and limit of detection. Evidently the *N*-methyl group is not a critical feature in enantiomeric discrimination. Clear evidence that it was the configuration of the chiral centre β to the aryl-ring that was most important in defining enantioselectivity was provided by examination of **12**, **13**, **14** and **15** which lack the α-hydroxy group (*i.e.*, no chiral centre in the 1-position). A marked increase in enantioselectivity was found (Table 3) for deoxyephedrine (also called methamphetamine) and amphetamine, although the electrode response characteristics were rather poor (low slopes, modest detection limits).

Solution NMR Studies.—Complex formation was studied by ^{1}H NMR spectroscopy in deuteriochloroform solution using the trifluoroacetate salts of the chiral β-arylammonium ions in the presence (and absence) of 'poly'-*O*-octyl-α-cyclodextrin, **1a**. In $CDCl_3$, ephedrinium trifluoroacetate (0.1 mmol dm^{-3}; 293 K) gives a ^{1}H NMR spectrum in which the two diastereotopic ammonium hydrogens are highly anisochronous ($\Delta\delta_H$ = 1.03) suggesting that a single conformer is preferentially



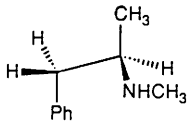
(1*S*, 2*R*)-(+)-norephedrine

10



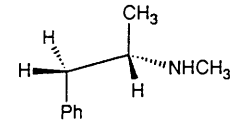
(1*R*, 2*S*)-(−)-norephedrine

11



(*R*)-(−)-deoxyephedrine

12



(*S*)-(+)-deoxyephedrine

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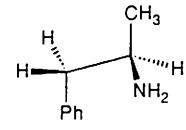

(*R*)-(−)-amphetamine

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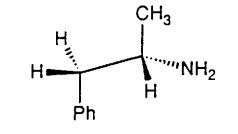

(*S*)-(+)-amphetamine

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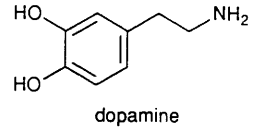

dopamine

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Table 2 Electrode response with 'poly'-*O*-octyl-α-cyclodextrin-based sensors (BBPA plasticiser, 0.01 mol dm^{-3} analyte as inner filling solution; 298 K)

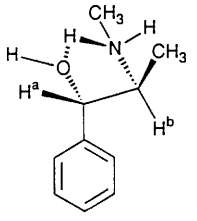
Analyte	Slope (mV decade^{-1})	Limit of detection (−log[C])
(+)-Ephedrinium (1*S*,2*R*)	59	5.10
(−)-Ephedrinium (1*R*,2*S*)	46	5.40
(+)-Pseudoephedrinium (1*S*,2*S*)	56	4.70
(−)Pseudoephedrinium (1*R*,2*R*)	59	5.10
(+)-Norephedrinium (1*S*,2*R*)	58	5.10
(−)-Norephedrinium (1*R*,2*S*)	46	3.80

populated with the two hydrogens in a very distinct local magnetic environments. Infrared measurements, recorded in the concentration range 0.4–0.01 mol dm^{-3} (in CCl_4 and in $CDCl_3$) indicate that there is an OH stretch at 3600 cm^{-1} whose position and shape is independent of concentration owing to an intramolecular hydrogen bond. This is in addition to the broad OH stretch at 3350 cm^{-1} due to intermolecular hydrogen bonding whose relative intensity diminishes on dilution. In a non-polar environment therefore, the ephedrinium ion adopts a relatively rigid conformation, *e.g.*, **17**, due to the strong intramolecule OH • • • $\overset{+}{H}$–N interaction. In the presence of 'poly'-*O*-octyl-α-cyclodextrin, **1a** (in molar ratio 1:2.5), the chemical shift of the diastereotopic ammonium protons changed according to which enantiomer of ephedrine was bound. With (+)-ephedrine, there was an increase in the chemical shift non-equivalence of the NH protons in the presence of cyclodextrin ($\Delta\delta_H$ = 1.17) that was not apparent with (−)-ephedrine,

Table 3 Response of polyoctylated α-CD, **1a**, to variations in analyte functionality[a]

Analyte	Sensitivity (Slope: mV decade^{-1})	Limit of detection −log[C]	Enantioselectivity ΔE/mV	$K^{pot}_{-/+}$[b]
(+)-(1*S*,2*R*)-EphHCl	56.0	5.3	−25.0	2.54
(−)-(1*R*,2*S*)-EphHCl	SN[c]	—		
(+)-(1*S*,2*R*)-norEphHCl	58.0	5.0	−11.0	1.51
(−)-(1*R*,2*S*)-norEphHCl	46.0	3.8		
(+)-(*S*)-Methamphetamine·HCl	12.0	—	164.0	—
(−)(*R*)-Deoxyephedrine·HCl	SN	—		
(+)(*S*)-Amphetamine·HCl	50.0	3.6	88.5	—
(−)-(*R*)-Amphetamine·HCl	37.0	unstable		
Dopamine·HCl	61.0	5.4		

[a] Measured at 310 K, with *o*NPOE as plasticiser in the PVC membrane electrode. [b] $K^{pot}_{-/+} = (E_- - E_+)/61.54$; 61.54 = theoretical slope at 310 K. [c] SN: Super-Nernstian slopes.



17

suggesting that N–H interactions are important in determining the relative structures of the two diastereoisomeric complexes.

A change in the vicinal coupling constant, $J_{H_bH_b}$ in **17**, was also evident when the (+)-enantiomer was complexed by **1a**, with a decrease from 2.4 Hz to 1.6 Hz being observed consistent with a change in the dihedral angle (about HCCH) of about 6°. With the (−)-enantiomer, no change in this coupling constant was noted in the presence of **1a**.

Although these changes are modest, it is plausible that the (+)-ephedrinium ion changes its conformation somewhat upon complexation in order to maximise its interaction with the cyclodextrin, in a manner that is not attainable for the (−)-enantiomer. In addition the resonances due to the ephedrine aromatic protons underwent enantiomer-dependent changes upon complexation. Although it was not possible fully to assign the complex multiplet structure, it was evident that the pairs of *ortho* and *meta* protons were rendered diastereotopic ($\Delta\delta$ = 0.02) by complexation with the cyclodextrin suggestive of phenyl-group participation in the diastereoisomeric complexes. The observed chemical shift non-equivalence between related multiplets in the diastereoisomeric complexes was no more than 0.3 ppm. That the nature of aryl inclusion by an α-cyclodextrin is dependent on the chirality of the guest has been demonstrated previously by Harata[13] when examining the complexation of mandelic acid by per-*O*-methyl-α-cyclodextrin and there are many instances of aryl resonances being shifted in an enantio-dependent manner when α-cyclodextrin binds simple chiral aryl species in D_2O.[14]

Variable-temperature ^{1}H NMR spectra for the complexes of **1a** with (+)- and (−)-ephedrinium trifluoroacetate were acquired in the range 298 to 223 K. Resonances due to the cyclodextrin CHO and octyl CH_2O protons were distinctly different in the diastereoisomeric complexes but were difficult to assign unambiguously. As a result of this, measurements of the changes in proton relaxation rates ($R_1 = T_1^{-1}$) for the host and guest were used comparatively in an effort to define further the structural differences between the diastereoisomeric complexes. It was presumed that complexation would lead to changes in the effective correlation times and in internuclear distances for the host and the guest that might lead to changes in relaxation rate for individual protons.[15]

The changes in the longitudinal relaxation rates for the protons of (+)- and (−)-ephedrinium trifluoroacetate in the presence of 'poly'-*O*-octyl-α-cyclodextrin, **1a**, were measured using standard inversion–recovery methods (Table 4). With the (−)-ephedrinium ion, the observed changes on complexation could be regarded as not being unusual for the association of a small ion with a larger molecule, *i.e.*, a general increase in R_1 as a consequence of the decrease in molecular motion, ω, associated with a more slowly tumbling molecule. For the (+)-ephedrinium ion, more marked changes in R_1 on complexation occurred. Most striking was the difference in the relaxation rates of the two ammonium protons of the (+)-ephedrinium ion, with one having a much faster relaxation rate than the other (6.5 *vs.* 1.15 s^{-1}).

These results are suggestive of a more well-defined host–guest interaction in the complex of the (+)-ephedrinium ion with **1a** than with the (−)-ephedrinium ion. The significant decrease in R_1 for one ammonium proton of the (+)-ephedrinium ion suggests that complexation may reduce the rate of relaxation through the suppression of one (or more) relaxation mechanism(s) thereby decreasing the local reorientational correlation time through an increase in local motional mobility. It is plausible that complexation may weaken the intramolecular hydrogen-bond between the OH and $\overset{+}{N}H_2$ groups.* This hydrogen-bonding may give rise to a rapid relaxation mechanism and it is not unreasonable that its inhibition leads to a significantly dcreased R_1 value. If only one ephedrinium NH is involved in hydrogen bonding to the cyclodextrin host (involving charge-solvating $\overset{+}{N}$–H · · · O interactions with ether or anomeric oxygens of the cyclodextrin) it has an alternative rapid relaxation mechanism and so its R_1 value may not change significantly.

Changes in the relaxation rates of the host cyclodextrin protons when the (+)- or (−)-ephedrinium ion was present were measured (Table 5). The H^3 resonance (see **18** for the numbering system used), certain octyl chain protons and an unassigned resonance at 3.58 ppm (most probably an octyl CH_2O resonance) gave changes in relaxation rate that were strongly dependent upon the enantiomer included. The H^3 proton ($\Delta\Delta R_1$ = 1.4 s^{-1}) is well known to be directed into the cyclodextrin cavity quite near to the secondary hydroxy rim, and it may be experiencing cross dipolar relaxation from the proximate ephedrine phenyl-group hydrogens. There is a

* Similar arguments may be put forward with regard to *inter*molecular hydrogen-bonding: complexation would weaken it and in the complex an intramolecular NH · · · OH bond may occur selectively with one of the NH protons. However it is difficult to correlate this proposal with the large chemical shift non-equivalence of the $\overset{+}{N}H_2$ protons in the absence of cyclodextrin, and with the fact that IR studies reveal that the free ephedrinium ion is significantly intramolecularly hydrogen-bonded.

Table 4 Comparison of relaxation rates ($R_1 = T_1^{-1}$) for (+)- and (−)-ephedrinium trifluoroacetate in the presence of 'poly'-*O*-octyl-α-cyclodextrin, **1a** (293 K; $CDCl_3$)

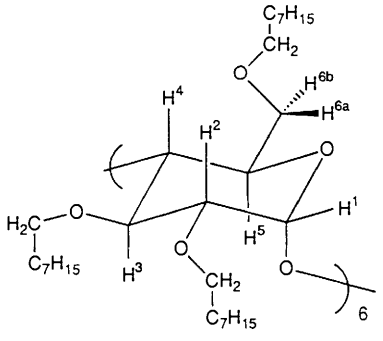
Proton(s)	Free (+)	'Bound' (+)	$\Delta R_1/s^{-1}$	Free (−)	'Bound' (−)	$\Delta R_1/s^{-1}$	$\Delta\Delta R_1/s^{-1}$
NH[a]	4.3	6.5	+2.2	4.3	6.5	+1.8	0.4
NH	5.8	1.15	−4.65	5.8	6.9	+1.1	5.75
Ph	0.9	0.93	+0.03	0.9	0.93	+0.03	0
Ha	3.1	4.8	+1.7	3.1	3.4	+0.3	1.4
NMe	2.5	3.2	+0.7	2.5	2.8	+0.3	0.4
Me	2.1	2.0	−0.1	2.1	2.3	+0.2	0.3

[a] The higher frequency NH resonance at *ca.* 9.2 ppm, compared with 8.2 ppm for the lower frequency resonance.

Table 5 Comparison of changes in relaxation rate (s^{-1}) for 'poly'-*O*-octyl-α-cyclodextrin, **1a**, with (+)- and (−)-ephedrinium trifluoroacetate as the guest[a]

Proton(s)	'Free'	'Bound' (+)	'Bound' (−)	$\Delta\Delta R_1/s^{-1}$
H^1	2.6	3.3	3.3	0
H^3	2.0	3.5	2.1	1.4
H^5	2.6	2.7	2.7	0
H^2	2.3	2.4	2.4	0
CH_2[b]	1.1	1.4	1.1	0.3
CH_3[c]	0.5	0.6	0.5	0.1

[a] An unassigned CH_2O resonance at 3.58 ppm gave values of R_1 as follows: free 3.0 s^{-1}, (+)-bound 3.6 s^{-1}, (−)-bound 3.1 s^{-1}. [b] At 1.25 ppm. [c] At 0.88 ppm.



Proton numbering scheme

18

precedent for such an interaction[17] and in the case of the α-cyclodextrin–tryptophan complex studied in D_2O,[18] it was noted that the rate of relaxation of H^3 increased by 0.17 s^{-1} in the complex with (+)-tryptophan.

Measurements of host and guest relaxation rates were also undertaken for **1a** and (+)- and (−)-*N*-methylephedrine (probing the steric requirement of the ammonium moiety) and for **1a** with (+)- and (−)-pseudoephedrine, **8** and **7**. With *N*-methylephedrine the changes in R_1 for the host and guest showed relatively little dependence on which enantiomer was bound showing that increasing the steric demand at the nitrogen centre has significantly perturbed the marked enantiodifferentiation in ephedrinium complexation.

With (1*S*,2*S*)-pseudoephedrine, changes in R_1 on complexation with **1a** closely paralleled those of (1*R*,2*S*)-ephedrine, *i.e.*, all of the guest proton relaxation rates increased slightly as a result of the slower molecular motions of a larger molecule. With (1*R*,2*R*)-pseudoephedrine changes in R_1 resembled those found for (1*S*,2*R*)-ephedrine but were much less marked (particularly for the NH protons) Table 6. It would seem therefore that an *R*-configuration at the centre β to the aryl ring favours a stronger interaction with the cyclodextrin host.

Attempts were made, using NOESY and ROESY pulse sequences at 500 MHz, to seek intermolecular nOe effects (*e.g.*, between H^3 of **1a** and the aryl protons of the ephedrinium enantiomers). In the ROESY experiments various spin-locking pulses of different duration and power were tried but no reproducible intermolecular cross-peaks could be observed and only the expected intramolecular cross-peaks were found.

A Model for Enantioselective Complexation of the Ephedrinium Ion.—In devising a model for the enantioselective complexation of the ephedrinium guest by the cyclodextrin, it is necessary to correlate all of the information obtained from the electrode response and NMR studies. The observation that methyl-capping of residual OH groups in 'per'-*O*-octyl-α-cyclodextrin almost completely removes enantioselection indicated that these OH groups are required for a 'well-defined' electrochemical response. Their role may either involve a hydrogen-bonding interaction with the hydroxy or amino group of the ephedrinium guest or to lock the conformational mobility of the cyclodextrin glucopyranosyl subunits with respect to each other as a result of 3(OH)···2(O) hydrogen-bonding interactions (which are well-defined in the parent cyclodextrin structures). In this latter case, such interactions would clearly influence the stereochemical hospitality of the host. That β-cyclodextrin hosts are relatively ineffective at enantiomer discrimination indicates that the phenyl moiety should be relatively tightly included by the more compact cavity of the α-cyclodextrin hosts. There is evidence that the ammonium centre has a simple steric requirement: *N*-methylation suppresses enantiomeric discrimination (R_1 results) while norephedrine (lacking any NMe group) behaves well electrochemically with enantioselection comparable to that found for ephedrine itself. The strongly enantiomer-dependent behaviour of the diastereotopic NH_2 protons in the ephedrinium ion ($\Delta\delta_{NH}$ and $\Delta\Delta R_1$ data) highlights the importance of this group in binding.

Upon inclusion within the cyclodextrin cavity the counterion (Cl^- or $CF_3CO_2^-$) is prevented from closely approaching the ephedrinium charge centre. Given that a partial charge of −0.46 (e units) is associated with each cyclodextrin oxygen atom, $\overset{+}{N}$–H···O interactions are quite reasonable and orienting $\overset{+}{N}$CH···O interactions[16,19] are also quite likely. A possible model allowing for both of these interactions between the (+)-ephedrinium ion and the glycosidic region of **1a** may be considered (Fig. 2). This model allows several observations to be rationalised. (*i*) The very different rates of relaxation for the ammonium protons (6.5 *vs.* 1.15 s^{-1}) result from one being involved in $\overset{+}{N}$–H···O interactions whilst the other is directed towards a much less polar environment in the octyl-chain region of O^3 and O^2. (*ii*) In order for such hydrogen-bonding interactions to occur the relative orientation of the ephedrinium phenyl ring, NH_2 and OH groups must change consistent with the observed change in H–C^1–C^2–H dihedral angle [*not* seen for the (−)-enantiomer]. (*iii*) An increase in $\Delta\delta_{NH}$ on

Table 6 Comparison of relaxation rates for (+)- and (−)-pseudoephedrinium trifluoroacetate in the presence of 'poly'-*O*-octyl-α-cyclodextrin, **1a**

Proton(s)	Free (+)	'Bound' (+)	$\Delta R_1/s^{-1}$	Free (−)	'Bound' (−)	$\Delta R_1/s^{-1}$	$\Delta\Delta R_1/s^{-1}$
NH	4.7	4.85	+0.15	4.7	4.5	−0.2	0.35
NH	4.9	4.9	0	4.9	4.9	0	0
Ph	0.63	0.68	+0.05	0.63	0.73	+0.1	0.05
Ha	2.1	2.4	+0.3	2.1	2.4	+0.3	0
NCH_3	1.7	1.9	+0.2	1.7	2.1	+0.4	0.2
CH_3	1.7	1.8	+0.1	1.7	1.8	+0.1	0

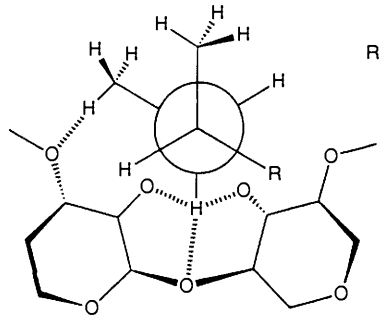


Fig. 2 Proposed interaction between the (+)-ephedrinium ion and 'poly'-*O*-octyl-α-cyclodextrin, **1a** (view down the C–N bond)

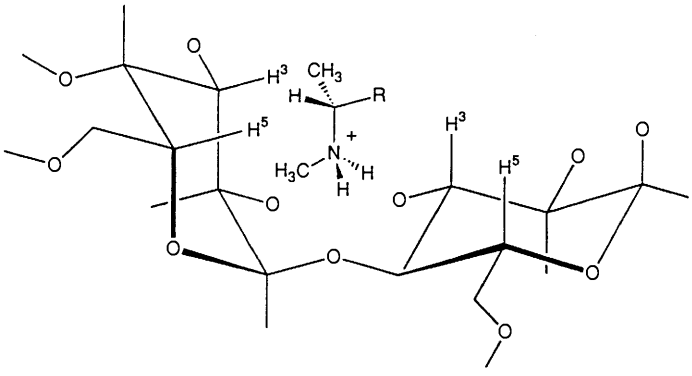


Fig. 3 Model of the binding of the (+)(1*S*,2*R*)-ephedrinium ion per 'poly'-*O*-octyl-α-cyclodextrin

complexation of (+)-ephedrine [not seen with the (−)-enantiomer] may be expected if the intermolecular hydrogen-bonding restricts the rate of rotation about the C(Me)–N bond. (*iv*) *N*-Methylation of ephedrine inhibits the close approach of the ammonium ion to the glycosidic region of the host.

The NMR and electrode response studies highlighted the importance of the absolute configuration of the stereogenic centre β to the aryl ring: an *R*-configuration at this centre seems to give rise to a more well-defined host–guest interaction. Assuming the binding scheme outlined in Fig. 2, then the enantioselective interaction may depend upon the orientation of the *C*-methyl group with respect to the cyclodextrin cavity. In the case of (+)-ephedrinium (Fig. 3), the methyl group is oriented away from the glycosidic region of the host; with (−)-ephedrinium it is oriented towards H^3 and relatively close to H^5 (Fig. 4). Such an unfavourable steric interaction will prevent the close approach of the ammonium ion to the glycosidic region and will tend to inhibit strong hydrogen-bonding interactions. Binding in this manner requires the phenyl ring to be included within the cyclodextrin but inclined at an angle of between 20 and 30° to the mean *z*-axis in a manner similar to that observed in the complexation of (*R*)-mandelic acid by poly-*O*-methyl-α-cyclodextrin.[13] Such an orientation, if absent in complexation of the (−)-enantiomer of ephedrine, may also partly explain the observed enantio-dependent differences in the nature of the ^1H NMR phenyl resonances.

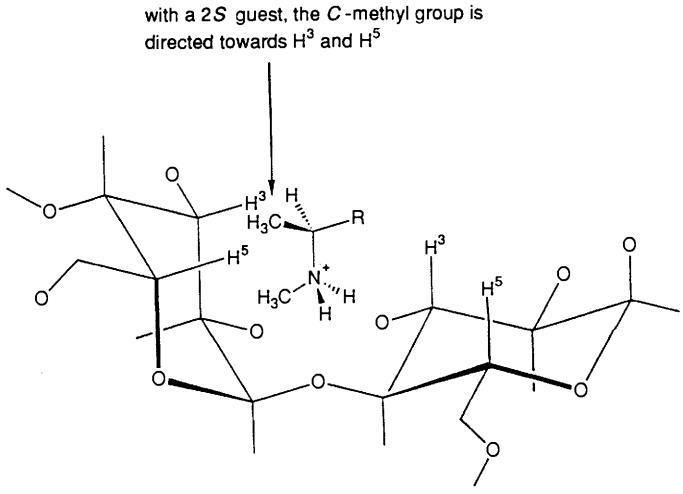


Fig. 4 Model of the unfavourable interactions in complexation of (−)-(1*R*,2*S*)-ephedrinium with 'poly'-*O*-octyl-α-cyclodextrin

Experimental

Proton NMR experiments and electrospray ionisation mass spectroscopic experiments were carried out using instrumentation and methods discussed in ref. 19. Degassed solutions in $CDCl_3$ were used which were 90 μmol dm^{-3} in the cyclodextrin host and 225 μmol dm^{-3} in the β-arylammonium trifluoroacetate guest. Electrode response studies were carried out with the methods and equipment reported previously.[5,6,19]

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