Enantiomer discrimination using lipophilic cyclodextrins studied by electrode response, pulsed-gradient spin-echo (PGSE) NMR and relaxation rate measurements

Ayelet Gafni,[a] Yoram Cohen,*[,a] Ritu Kataky,[b] Simon Palmer[b] and David Parker*[,b]

[a] *School of Chemistry, Sackler Faculty of Exact Sciences, Tel-Aviv University, Ramat Aviv, Tel Aviv 69978, Israel*
[b] *Department of Chemistry, University of Durham, South Road, Durham, UK DH1 3LE*

The diastereoisomeric complexes formed between 2,6-di-*O*-alkyl-α- and β-cyclodextrins and the arylammonium ions propranolol, ephedrine and amphetamine have been studied by electrode response and NMR methods. Enantioselectivity in binding propranolol is 3.3 : 1 with 2,6-di-*O*-dodecyl-β-cyclodextrin in favour of the (+)-enantiomer as revealed by measurement of the association constant using pulsed-gradient spin-echo (PGSE) NMR methods. In all of the cases of enantiodifferentiation studied here, the (+)-enantiomer is more strongly bound by the cyclodextrin. Relaxation rate measurements of the host and guest proton NMR resonances highlight the importance of hydrogen-bonding in enantiomer discrimination.

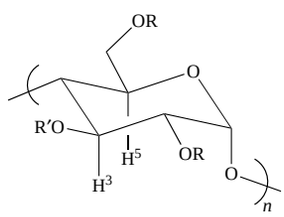
The behaviour of selectively alkylated cyclodextrin derivatives as ionophores in ion-selective electrodes (ISEs) has been the focus of considerable activity in the past few years. Not only do these receptors act as chiral ionophores in potentiometric devices for the enantiodifferentiation of size-matched aryl-ammonium ions[1,2] but also they serve as size-selective receptors for complementary 'onium ions.[3,4] Recent examples include the development of voltammetric sensors for tricyclic anti-depressants such as imipramine,[5] and the definition of a robust biosensor for acetyl choline.[6] Alkylated and acylated cyclo-dextrin derivatives have also been studied in detail as chiral stationary phases in enantiomer analysis by HPLC[7,8] and GC methods.[9,10] The origins of enantiodifferentiation in such systems have focused the attention of many groups,[7a,2b,11–14] but generally work has been undertaken on comparisons of elution orders and separation factors with computations of the relative stability of the diastereoisomeric complexes, for example using Monte Carlo and molecular dynamics simulations.[14] In an attempt to understand better the origins of chiral discrimination in the solution phase, we have carried out some further experiments correlating electrode response studies—which define the most strongly bound enantiomer and give an estimate of the free energy difference between diastereoisomeric complexes in the membrane used—with NMR measurements. Association constants for selected cyclodextrin–arylammonium ion complexes have been determined using NMR diffusion measurements and information on the degree of hydrogen-bonding gleaned from ^{1}H NMR shift and relaxation rate determinations.

Results and discussion

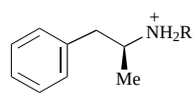
Pulsed-gradient spin-echo measurements of complex stability

Measurements of diffusion coefficients using the pulsed-gradient spin-echo (PGSE) technique[15] have proved to be very useful in studying the degree of association of complementary organic host–guest systems.[16,17] This NMR method is particularly useful when the host has a much bigger molecular volume than the guest. In this situation, there is a large difference in their diffusion coefficients: when conditions of slow-exchange on the NMR timescale prevail, the bound guest will possess a diffusion coefficient that matches that of the host. Under fast exchange, the guest's measured diffusion coefficient will be a weighted average of free and bound species and thereby reports on the equilibrium constant for complex formation.

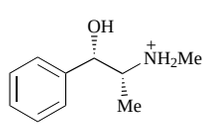
Association constants for 1 : 1 complex formation† between the trifluoroacetate salts of the enantiomers of amphetamine **4a**, ephedrine **5** and propranolol **6** with 2,6-di-*O*-dodecyl-α-cyclodextrin **1**, and the β analogue **3a** have been measured. A representative data set is shown in Fig. 1 showing the decay of the normalised echo intensity as a function of the square of the pulsed gradient strength for free ephedrine (**5**) and for the ephedrine and 2,6-di-*O*-dodecyl-α-cyclodextrin (**1**) in a 1 : 1



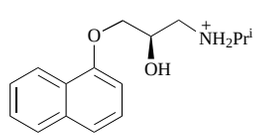
1 R = $C_{12}H_{25}$, R′ = H, *n* = 6
2a R = C_8H_{17}, R′ = H or C_8H_{17}, *n* = 6
b R = C_8H_{17}, R′ = C_8H_{17} or Me
3a R = $C_{12}H_{25}$, R′ = H, *n* = 7
b R = C_8H_{17}, R′ = C_8H_{17} or H



(*S*)-(+)- **4a** R = H
b R = Me



(1*S*,2*R*)-(+)-**5**



(*R*)-(+)-**6**

† Confirmation of a 1 : 1 binding stoichiometry was provided by electrospray mass spectrometry where singly charged adducts were detected at the appropriate mass in each case with observed and calculated isotope patterns showing good agreement.

Table 1 Diffusion coefficients (D/cm^2 s^{-1}) of the chiral ammonium salts [a] and of the cyclodextrin systems studied in the free state and in 1:1 solutions along with the association constants (K_a/dm^3 mol^{-1}) derived from these data [b–d]

System	Cyclodextrin/ 10^{-5} cm^2 s^{-1}	Ammonium salts/10^{-5} cm^2 s^{-1}	K_a/dm^3 mol^{-1}	$K_{(+)}/K_{(-)}$
1 —	0.32 ± 0.01	—	—	—
— (*S*)-(−)-**5**	—	0.66 ± 0.02	—	—
— (*R*)-(+)-**5**	—	0.66 ± 0.02	—	—
1 (*R*)-(+)-**5**	0.28 ± 0.01	0.51 ± 0.01	142 ± 21	1.25 ± 0.25
1 (*S*)-(−)-**5**	0.28 ± 0.01	0.54 ± 0.01	114 ± 15	
2b —	0.39 ± 0.01	—		—
2b (*S*)-(−)-**5**	0.31 ± 0.01	0.52 ± 0.01	113 ± 19	1.00 ± 0.24
2b (*R*)-(+)-**5**	0.31 ± 0.01	0.52 ± 0.01	113 ± 19	
3a —	0.33 ± 0.01	—	—	—
— (*S*)-(+)-**4a**	—	0.69 ± 0.01	—	—
— (*R*)-(−)-**4a**	—	0.69 ± 0.02	—	—
3a (*S*)-(+)-**4a**	0.31 ± 0.01	0.48 ± 0.01	163 ± 28	1.60 ± 0.37
3a (*R*)-(−)-**4a**	0.31 ± 0.01	0.51 ± 0.01	102 ± 16	
— (*S*)-(−)-**6**	—	0.59 ± 0.02	—	—
— (*R*)-(+)-**6**	—	0.59 ± 0.02	—	—
3a (*S*)-(−)-**6**	0.30 ± 0.01	0.53 ± 0.02	67 ± 17	3.31 ± 1.2
3a (*R*)-(+)-**6**	0.24 ± 0.01	0.45 ± 0.02	222 ± 58	

[a] As a trifluoroacetate salt. [b] All experiments were performed on 5 mmol $CDCl_3$ solutions at 283 K using a 500 MHz NMR spectrometer as described previously, see refs. 16 and 17. [c] Diffusion coefficients are the mean of at least three experiments and the reported values are means ± SD. [d] **1** = 2,6-didodecyl-α-cyclodextrin; **2b** = 2,6-didodecyl-3-*O*-methyl-α-cyclodextrin; **3a** = 2,6-didodecyl-β-cyclodextrin; **5** = ephedrine; **4a** = amphetamine; **6** = propranolol.

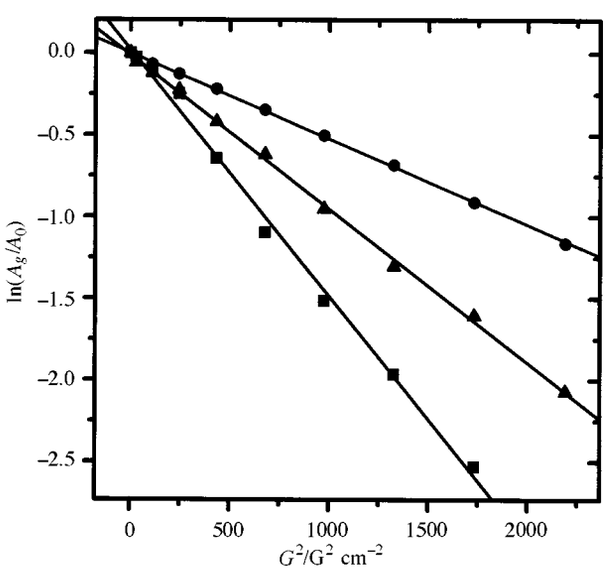


Fig. 1 Normalised ^{1}H NMR signal attenuation (ln A_g/A_0) of free ephedrine (**5**) (■), of bound ephedrine in a 1:1 complex with 2,6-didodecyl-α-cyclodextrin (**1**) (▲) and of the cyclodextrin in the complex (●) as a function of the square of the pulse gradient strength (G^2). The diffusion coefficients were calculated from the slopes of such graphs using eqn. 1.

solution of **5**–**1**. From this data set the diffusion coefficient may be calculated according to eqn. (1)[15] where A_g and A_0 are the

$$\ln\left(\frac{A_g}{A_0}\right) = -(\gamma g \delta^2)^2(\Delta - \delta/3)D \qquad (1)$$

echo intensities in the presence and in the absence of the pulsed gradients, respectively, γ is the gyromagnetic ratio (rad s^{-1} g^{-1}), g is the gradient strength (G cm^{-1}), D is the self diffusion coefficient of the observed spins (cm^2 s^{-1}), δ is the length of the diffusion gradient and Δ is the time-separation between the edges of the diffusion gradients. The most strongly bound complex was formed between **3a** and (*R*)-(+)-propranolol (K_a = 222 ± 58 dm^3 mol^{-1}, 283 K, $CDCl_3$), and the K_a value is of similar magnitude to the reported affinities of β-cyclodextrin for 1-substituted naphthyl derivatives.[18] The (*S*)-enantiomer was bound more weakly (K_a = 67 ± 15 dm^3 mol^{-1}, 283 K, $CDCl_3$) corresponding to a free energy difference in binding of 2.8 (±1.0) kJ mol^{-1}. Both the sense and the magnitude of the measured enantiodifferentiation are in line with values estimated from chiral HPLC methods.[7a] In the other two cases studied (Table 1), more modest selectivity was observed, but in each case it was the (+)-enantiomer which was the more strongly bound. Using the cyclodextrin host **2b**—in which all residual OH groups have been alkylated—no difference was found in the stability of the diastereoisomeric complexes with (*R*) and (*S*)-ephedrine. Alkylation of the 3-OH position in cyclodextrins removes the intramolecular H-bonding network, ([3]OH · · · O[2]), that determines the conformational rigidity of the host molecule. It had previously been noted, in electrode response studies, that complete alkylation of the 3-OH group in α-cyclodextrin derivatives removed the enantioselectivity in binding ephedrine and its stereoisomers.[1,2b]

Electrode response studies

The behaviour of selected lipophilic cyclodextrin derivatives as ionophores in a standard plasticised PVC membrane electrode[1,2] was assessed. The response of an electrode incorporating 2,6-di-*O*-dodecyl-β-cyclodextrin towards (*R*)-(+)-propranolol and its enantiomer was compared in the absence and presence of potential interferent ions (Table 2). Differences in the cell electrode potential ($E_{initial}$) were noted and give a measure of the difference in free energy of complexation of the propranolol guest by the immobilised cyclodextrin ionophore. In the presence of Na^+, K^+ or in a simulated clinical background, the difference in measured electrode potential (*ca.* 30 mV) for (+) and (−)-propranolol corresponded to a free energy difference of 2.9 (±0.4) kJ mol^{-1} which is similar to the value measured by the PGSE method in chloroform solution. The most strongly bound enantiomer (giving rise to the largest $E_{initial}$ value) was the (*R*)-(+) isomer, also in agreement with the sense observed in solution by NMR. Similar correlations were noted in the response of electrodes based on **2a**, **2b**, **3a** and **3b** towards the protonated salts of ephedrine and amphetamine, (Table 3). In each case the (+)-enantiomer was the more strongly bound ($E_{initial}$ value) and the magnitude of the enantioselectivity was dependent upon the nature of the cyclodextrin used. For

Table 2 Response of ISEs incorporating 2,6-di-*O*-dodecyl β-cyclodextrin to *R*-(+)-propranolol [(*S*) enantiomer values are in parentheses] in the absence and presence of interfering ions at 310 K. Selectivity coefficients for interferent ions are given as $-\log K_{i,j}^{pot}$; for individual ions the interferent concentration is 0.1 mol dm^{-3}

Interferent	$E_{initial}$/mV[b]	Limit of detection/ 10^{-5} mol dm^{-3}	Slope/mV	$-\log K_{i,j}^{pot}$
Calibration	251 (239)	2.9 (1.1)	58 (57)	—
Clinical background[a]	301 (270)	1.4 (0.8)	56 (61.5)	4.0 (4.3)
Na^+	258 (239)	0.9 (0.7)	56 (57)	4.0 (4.2)
K^+	293 (261)	1.7 (1.6)	61 (62)	3.8 (3.8)
Ca^{2+}	327 (264)	3.3 (2.3)	33 (31)	3.5 (3.6)

[a] Clinical background is a simulated background of clinical ions as chloride salts (*c*/mmol dm^{-3}: Na^+ 145; K^+ 4.3; Ca^{2+} 1.26; Mg^{2+} 0.9). [b] Relative to an external Ag/AgCl double junction reference electrode connected by a saturated aqueous KCl salt bridge.

Table 3 Response of ISEs incorporating 2,6-di-*O*-dodecyl-β-cyclodextrin **3a** or the poly-*O*-octyl-α-cyclodextrins **2a** and **2b** to chiral amine salts at 310 K

Entry	Analyte	Ionophore	Enantioselectivity ΔE/mV	Slope/mV (+)	Slope/mV (−)
1	ephedrine	**1**	9(3)	55	54
2	ephedrine[a]	**2a**	26(2)	60	50
3	ephedrine[b]	**2b**	3	43	40
4	amphetamine	**3a**	39	61.5	62.5
5	ephedrine[b]	**3b**	8	56	51
6	amphetamine[a]	**2a**	(88.5)	50	37

[a] Similar behaviour was deserved with ionophore **1**; the electrode response with (*R*)-(−) amphetamine was unstable, so the quoted ΔE value is unreliable. Unstable electrode responses were also obtained with methamphetamine and **1** or **2a**. [b] Data from ref. 2*b*.

example with (+)-ephedrine as the analyte, the ΔE value was 26 mV with 'poly'-*O*-octyl-α-cyclodextrin, **2a** (containing 15.4 octyl groups and 2.6 OH groups, on average[2a]), but reduced to 9 (±3) mV with 2,6-di-*O*-dodecyl-α-cyclodextrin as the sensing ionophore (Table 3). In addition when the residual 3-OH groups in **2a** were capped by methyls, there was little or no enantioselectivity in binding ephedrine (entry 3 compared to 2, Table 3), and use of a larger β-cyclodextrin ionophore (entry 5) also diminished the measured enantioselectivity. With amphetamine and methamphetamine as analytes, super-Nernstian or unstable (in time) electrode responses were observed when using any of the available α-cyclodextrin ionophores (*e.g.* entry 6). Only with amphetamine and 2,6-di-*O*-dodecyl-β-cyclodextrin was near Nernstian behaviour observed and in this case, while the sense of the enantioselective response was in line with the NMR measurements, the size of the discrimination was larger (3.8 kJ mol^{-1} in favour of (*S*)-(+)-amphetamine, *cf.* 0.9 kJ mol^{-1} from the PGSE data).

Solution NMR Studies of Hydrogen Bonding

(a) Chemical shift effects. Complex formation was monitored by ^{1}H NMR spectroscopy in $CDCl_3$ solution, using the trifluoroacetate salts of the chiral β-arylammonium ions in the presence (and absence) of **1** and **3a**. Earlier studies had reported the behaviour of the complexes of ephedrine with **2a**,[2b] and IR and NMR experiments had identified a strong intramolecular NH···OH interaction in the free and bound state. The diastereotopic NH_2 hydrogens in ephedrinium trifluoroacetate are highly anisochronous in $CDCl_3$ ($\Delta\delta$ = 1.03 ppm) consistent with the preferential population of a single conformer in which the two hydrogens are in distinct local magnetic environments. Upon addition of **2a** to (+)-ephedrine (in molar ratio 1:2.5 at 293 K) there was an increase in the chemical shift non-equivalence of the NH protons to 1.17 ppm and the higher frequency NH (resonating at 9.42 ppm in the 'free' state) shifted to higher frequency in the bound form (δ_{NH_a} = 9.53 ppm; NH_a is denoted as resonating to higher frequency of NH_b). A similar pattern of behaviour was observed with propranolol both before and after addition of **3**. In the free state, the shift non-equivalence of the NH protons was 1.07 ppm, and the presence of an intramolecular hydrogen bond was also suggested by

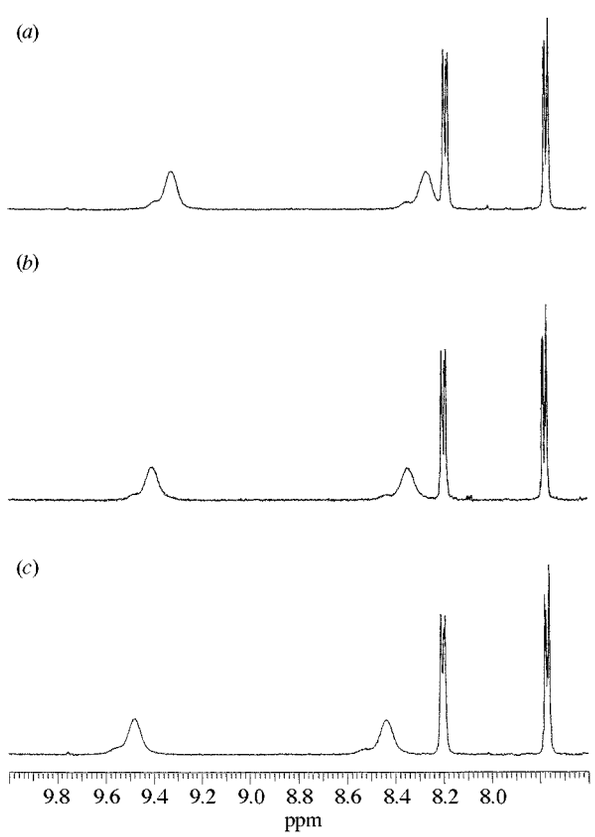


Fig. 2 Changes in the ^{1}H NMR spectra of protonated propranolol in the presence of **3a**: (*a*) (*S*)-propranolol; (*b*) no cyclodextrin; (*c*) (*R*)-propranolol; 293 K, $CDCl_3$, [propranolol] = 33 mM, [**3a**] = 13 mM

the presence of a weak band at 3590 cm^{-1} in the solution FTIR spectrum (293 K, 10^{-1} mol dm^{-3}) whose position was independent of concentration upon dilution by a factor of fifty. In the presence of **3a** ([propranolol] = 33 mmol dm^{-3}, [**3a**] = 13 mmol dm^{-3}, $CDCl_3$, 293 K), the NH_2 shift non-equivalence was 1.04 ± 0.01) ppm for both enantiomers, but in the case of (*R*)-(+)-propranolol, the complexation shifts were 0.08 and 0.09 ppm to higher frequency whereas with (*S*)-(−)-propranolol

Table 4 Comparative relaxation rates (s^{-1}) for chiral arylammonium ions in the presence of 2,6-di-*O*-dodecyl-α- and β-cyclodextrin (293 K, $CDCl_3$, 500 MHz)

Chiral complex	Observed proton[a]	Free (+)	Bound (+)	ΔR_1	Free (−)	Bound (−)	ΔR_1	$\Delta\Delta R_1$
3a–**4a**	NH_3	12.7	3.4	−9.3	12.7	4.7	−8.0	1.3
	H_3	0.64	0.78	+0.14	0.64	0.84	+0.2	0.06
3a–**6**	NH_a	8.6	9.6	+1.0	8.6	5.5	−3.1	4.1
	NH_b	8.8	8.6	−0.2	8.8	5.4	−3.4	3.2
1–**5**	NH_a	7.9	3.5	−4.4	7.9	4.6	−3.3	1.1
	NH_b	7.4	4.5	−2.9	7.4	5.3	−2.1	0.8
	H_3	0.60	0.75	+0.15	0.60	0.80	+0.2	0.05
1–**4b**	NH_a	11.9	6.6	−5.3	11.9	5.3	−6.6	1.3
	NH_b	11.6	6.6	−5.0	11.6	5.4	−6.2	1.2
	H_3	0.61	0.78	+0.17	0.61	0.76	+0.15	0.02
1–**4a**	NH_3	11.2	1.9	−9.3	11.2	3.5	−7.7	1.6

[a] In each case, H_a resonates to higher frequency of H_b. Measurements were made on degassed samples in 5 nm tubes sealed under argon. The proton H_3 is the cyclodextrin hydrogen which is directed into the cavity.

shifts of 0.01 and 0.05 ppm to lower frequency were observed for the NH_a and NH_b protons (Fig. 2). Comparative behaviour of this type is consistent with the formation of a more well-defined hydrogen-bonded structure in the complex for the (+)-enantiomer, with respect to that formed with the (−)-isomer. Although it is not possible to infer any definitive conclusions in the case of methamphetamine, (*S*)-(+)-**4b**, in the presence of **1**, (again at a ratio of 1:2.5, $CDCl_3$, 293 K) the shift difference on inclusion was 0.38 and 0.32 ppm to higher frequency for NH_a and NH_b and with the (−)-enantiomer the corresponding values were +0.28 and +0.32 ppm respectively.

(b) Relaxation rate measurements. Measurements of the proton relaxation rates ($R_1 = T_1^{-1}$) using standard inversion recovery methods were carried out on the complexes of **1** with **5**, **4a** or **4b** and on the complexes of **3a** with **4a** or **6** under identical conditions in an effort to define further structural differences in the diastereoisomeric complexes. It is well known that measured relaxation rates are particularly sensitive to many factors including solvent, temperature, relative conformational population, exchange dynamics and intermolecular distances. In this short study the intention was to compare R_1 data for the diastereoisomeric complexes under controlled conditions, seeking out differences in behaviour and paying attention to the NH protons (Table 4).

The relaxation rates of both NH_2 protons in the more weakly bound (*S*)-(−)-propranolol (**6**), guest decreased markedly upon complexation. With the (*R*)-(+)-enantiomer the R_1 value increased by 1.0 s^{-1} for NH_a (the one resonating to higher frequency) while NH_b remained more or less unchanged. For the complexes of ephedrine **5** and the amphetamines **4a** and **4b**, there was a large drop in the NH R_1 values but in none of these cases was the difference in the change in R_1 ($\Delta\Delta R_1$) as marked as was found with propranolol. In all of these cases complex formation may be associated with the suppression of at least one dipolar relaxation pathway whose effect is to decrease the local reorientational correlation time through an increase in local motional mobility. Such a process may be tentatively linked to NH···O hydrogen-bond formation in the complex. The large change may be related to the change in hydrogen-bonding state of the $\overset{+}{N}H_3$ and NH_2^+ protons associated with the presence of residual water (from the solvent or the salt): complex formation may be linked to a decrease in the extent of hydrogen-bonding to these water molecules, as hydrogen bonding to the cyclodextrin host becomes competitive. Counteracting this tendency is the general increase in R_1 values expected when a small guest associates with a large molecule. A general increase in the guest R_1 values is expected as a consequence of the decrease in molecular motion, ω, associated with a more slowly tumbling molecule. Given that these two factors have an opposing effect on the measured R_1 value, the overall differential effect will be a function of the difference in equilibrium constants for formation of the diastereoisomeric complexes and the change in the degree of NH···O hydrogen bonding in these complexes.

Conclusions

Previous work with ephedrine and its congeners as guest, had established that it was the configuration α to the amino group which determined the sense of enantiodifferentiation in cyclodextrin inclusion complexes.[2b] The (2*R*)-(+)-enantiomer was the more strongly bound and in the (2*S*)-(−)-complex it was proposed that there was an unfavourable steric interaction between the 2-Me group and the H_3 proton of the cyclodextrin host that inhibited a favourable NH···O hydrogen bonding interaction. In this work, the NMR measurements of complex formation and the electrode response studies—albeit on a limited set of complexes—all show that the (+)-enantiomer is the more strongly bound. This accords with an increased degree of hydrogen-bonding (involving NH_a) observed selectively upon cyclodextrin complexation for the (+)-enantiomer. The case of the complexation of propranolol is the most clear-cut: the (*R*)-(+)-enantiomer is the more strongly bound (by *ca*. 2.6–2.9 kJ mol^{-1}) and in its complex with 2,6-di-*O*-dodecyl-β-cyclodextrin there is good evidence for a stabilising $\overset{+}{N}H$···O hydrogen-bond that is absent in the weaker isomeric complex. Such energy differences are not out of line with hydrogen-bond matches and mismatches observed in other hydrogen-bonded arrays, where a single H-bonded interaction has been highlighted.[19] Notwithstanding the fact that this interpretation is in accord with the early model proposed for the interaction of the parent β-cyclodextrin with propranolol[7a]—wherein the (+)-enantiomer forms a stabilising NH···O contact with the β-cyclodextrin host that is absent in the isomeric complex—this work lends support to the case for detailed solution experimental studies of complex formation, rather than just relying on conclusions from modelling studies.[13,14]

Experimental

Potentiometric studies: membrane preparation

The electroactive membranes were prepared containing 1.2% ionophore, 65.6% plasticizer (2-nitrophenyloctyl ether), 32.8% PVC (high molecular weight), and 0.4% lipophilic anion {sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate} in distilled tetrahydrofuran. The membranes were cast by a controlled evaporation method reported previously.[2b] The polymer membranes were mounted in Philips IS(561) electrode bodies (Philips Analytical, Eindhoven, The Netherlands) with an inner filling solution of 10^{-3} mol dm^{-3} ammonium chloride. The

electrodes were conditioned for 24 h in 10^{-3} mol dm^{-3} analyte solution.

Constant volume dilution measurements

The ion-selective electrode was held in a small volume (approximately 2.3 cm^3), thermostatted double walled glass cell with inlet and outlet capillaries and a miniature magnetic follower. The reference cell employed was a T-shaped thermostatted liquid junction configuration in which the analyte solution flowed over a capillary containing a saturated KCl salt bridge solution in contact with a saturated calomel reference electrode (Russell pH Ltd.). The solution was drawn through the system by a peristaltic pump (Gilson Minipuls 3). All measurements were made at 310 K, unless otherwise stated.

The ISE and reference electrode were connected to a digital multimeter (Keithley 197) and a chart recorder (Kipp & Zonen) *via* a buffer amplifier. The system was thermostatted using a Techne tempette junior TE-85 thermostat bath.

Solution infrared measurements

The solution infrared measurements on propranolol trifluoroacetate were recorded in the range 0.1–0.001 mol dm^{-3} (in CCl_4) on a Perkin-Elmer 1600 Series FTIR.

NMR Measurements

All the NMR measurements were performed on a Bruker AMX 500 instrument. Measurements of ^{1}H relaxation times (T_1) were made with degassed $CDCl_3$ samples containing 13.2 mmol dm^{-3} host (alkylated cyclodextrin) and 33 mmol dm^{-3} guest (as the trifluoroacetate salt). The changes in the longitudinal relaxation times were measured using standard inversion–recovery methods.

NMR diffusion experiments were performed, at 283 K, on a Bruker ARX500 spectrometer equipped with a BGU pulsed gradient unit on a B-VT-2000 temperature control unit. Data were collected using a commercial 5 mm inverse probe equipped with shelf-shielded *g*-gradients on 5 mmol dm^{-3} samples in $CDCl_3$.

Reagents

(*R*)-(+) and (*S*)-(−)-propranolol hydrochloride, (*R*)-(+) and (*S*)-(−)-ephedrine hydrochloride, (*R*)-(−)-amphetamine sulphate and (*S*)-(+)-amphetamine were all obtained from Sigma. Analar KCl along with ortho-nitrophenyloctyl ether (ONPOE) and polyvinylchloride (PVC, high molecular weight) were obtained from Fluka-Microselect and resublimed NH_4Cl from Fluka. Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (TKB) was synthesised in this laboratory. All standard solutions were prepared using de-ionised water (Milli Q, Milipore-Waters, Milford, MA, USA).

Acknowledgements

We thank Durham University, EPSRC and the Israel Academy of Sciences and Humanities for support.

References

1 P. S. Bates, R. Kataky and D. Parker, *Analyst*, 1992, **117**, 1313.
2 (*a*) P. S. Bates, A. F. Patti and D. Parker, *J. Chem. Soc.*, *Perkin Trans. 2*, 1994, 657; (*b*) P. S. Bates, R. Kataky and D. Parker, *J. Chem. Soc.*, *Perkin Trans. 2*, 1994, 669.
3 P. M. Kelly, R. Kataky, D. Parker and A. F. Patti, *J. Chem. Soc.*, *Perkin Trans. 2*, 1995, 1955.
4 R. Kataky, P. S. Bates and D. Parker, *Analyst*, 1994, **119**, 181.
5 R. Kataky, S. Palmer and D. Parker, *Electroanalysis*, 1997, in the press.
6 R. Kataky and D. Parker, *Analyst*, 1996, **121**, 1829; R. Kataky and D. Parker, *Chem. Commun.*, 1997, 141.
7 (*a*) D. W. Armstrong, T. J. Ward, R. D. Armstrong and T. E. Beesley, *Science*, 1986, **232**, 1132; (*b*) D. W. Armstrong, T. J. Ward, A. Czech, B. P. Czech and R. A. Bartsch, *J. Org. Chem.*, 1985, **50**, 5556; (*c*) D. W. Armstrong, S. Chen, C. Chang and S. Chang, *J. Liq. Chromatogr.*, 1992, **15**, 545.
8 *Chiral Separations by Liquid Chromatography*, ed. G. Subramaniam, VCH, Weinheim, 1994.
9 V. Schurig and H.-P. Nowotny, *Angew. Chem.*, *Int. Ed. Engl.*, 1990, **29**, 939.
10 W. A. Konig, B. Gehrcke, M. G. Peter and G. D. Prestwich, *Tetrahedron: Asymmetry*, 1993, **4**, 165.
11 K. B. Lipkowitz, S. Ragholhama and J. Young, *J. Am. Chem. Soc.*, 1992, **114**, 1554; K. B. Lipkowitz, *J. Chromatogr. A*, 1995, **694**, 15.
12 C. J. Easton and S. F. Lincoln, *Chem. Soc. Rev.*, 1996, **24**, 163.
13 K. B. Lipkowitz, G. Pearl, B. Coner and M. A. Peterson, *J. Am. Chem. Soc.*, 1997, **119**, 600.
14 Examples of molecular dynamics simulations include: J. E. Kohler, M. Hohla, M. Richters and W. A. Kaing, *Chem. Ber.*, 1994, **127**, 119; A. V. Eliseev, G. A. Iacobucci, N. A. Khanjin and F. M. Menger, *J. Chem. Soc.*, *Chem. Commun.*, 1994, 2051; M. E. Amato, G. M. Lombardo, G. C. Pappalardo and G. Scarlata, *J. Mol. Struct.*, 1995, **350**, 71; see also: D. R. Black, C. G. Parker, S. S. Zimmerman and M. L. Lee, *J. Comput. Chem.*, 1996, **17**, 931.
15 (*a*) E. O Stejskal and J. E. Tanner, *J. Chem. Phys.*, 1965, **42**, 285; (*b*) P. Stilbs, *Progr. Nucl. Magn. Reson. Spectrosc.*, 1987, **19**, 1; (*c*) O. Soderman and P. Stilbs, *Progr. Nucl. Magn. Reson. Spectrosc.*, 1994, **26**, 480.
16 (*a*) O. Mayzel and Y. Cohen, *J. Chem. Soc.*, *Chem. Commun.*, 1994, 1901; (*b*) O. Mayzel, O. Aleksuike, F. Gnynszfan, S. E. Biali and Y. Cohen, *J. Chem. Soc.*, *Chem. Commun.*, 1995, 1183.
17 A. Gafni and Y. Cohen, *J. Org. Chem.*, 1997, **62**, 120.
18 *Cyclodextrins*, ed. J. Szeitli and T. Osa, in *Comprehensive Supramolecular Chemistry*, ed. J. L. Atwood, J. E. D. MacNicol and F. Vogtle, vol. 3, Pergamon, Oxford, 1996.
19 G. C. Best and P. B. Dervan, *J. Am. Chem. Soc.*, 1995, **117**, 1187.

Paper 7/05921C
Received 13*th August* 1997
Accepted 17*th September* 1997