A Chiral Sensor Based on a Peroctylated α-Cyclodextrin

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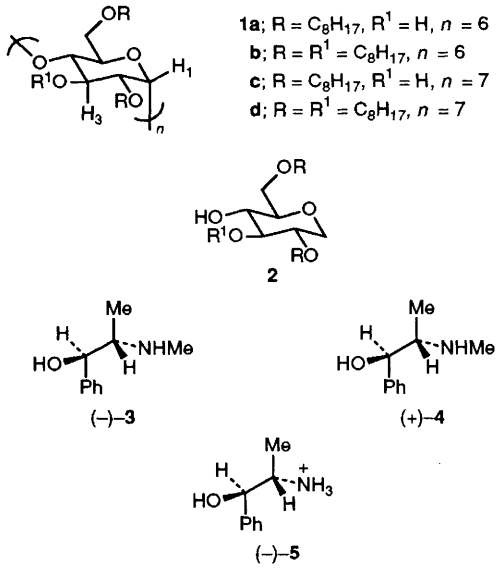
A peroctylated α-cyclodextrin is used in a potentiometric ion-selective electrode to measure the enantiomeric purity of ephedrine in the presence of serum cations.

The development of a potentiometric ion-selective electrode that can be calibrated to read the enantiomeric purity of a chiral analyte is an attractive target. Previous work has concentrated on the interaction of chiral ammonium salts with enantiopure crown ether derivatives.[1,2] Some evidence for enantioselective complexation has been reported although cation interference (Na^+, K^+, Ca^{2+}) in binding the arylammonium ion is severe. Although encouraging chiral recognition is well-defined with certain synthetic receptors,[3] these are most successful in the selective complexation of amino acid



derivatives. Prompted by the use of peralkylated cyclodextrins as gas-chromatographic or HPLC chiral stationary phases,[4] the potential of lipophilic peroctylated cyclodextrins in electrochemical sensors for a range of chiral molecules incorporating aryl rings is being investigated.

Octylation of α-cyclodextrin (NaOH, Me_2SO, $C_8H_{17}Br$, 20 °C) yielded the 2,6-di-*O*-octyl-α-cyclodextrin **1a** (53%) as the major product, characterised by field desorption mass spectrometry (FDMS) (*m*/z 2320, 2319, 2318 [M^+]) and the appearance of a clean doublet in the ^1H NMR spectrum for the anomeric proton H-1 (δ_H 4.90). Further alkylation was achieved under more forcing conditions (NaH, tetrahydrofuran, 60 °C, 4 days) to give the 2,3,6-tri-*O*-octyl derivative **1b** (73%). FDMS revealed the presence of compounds with 15, 16 and 17 octyl groups as well as the desired compound (*m*/*z* = 2990.6, M^+). Confirmation of partial alkylation was provided by reductive depolymerisation (Et_3SiH, BF_3, CH_2Cl_2), which yielded alkylated 1,5-anhydro-D-glucitols, **2**, which were analysed by ^1H NMR and mass spectrometry [DCI (desorption chemical ionisation)] highlight the presence of between 15 and 25% of under-alkylated material. Peroctylation of β-cyclodextrin was effected in a similar stepwise manner, yielding **1c** and **d**.†

Using 1–2 mol% **1b**, an electroactive membrane was prepared [32.8% PVC, 0.4% *p*-$(Cl\text{-}Ph)_4B\text{-}K^+$] using either bis(butylpentyl)adipate (BBPA) or *ortho*-nitrophenyloctyl ether (*o*-NPOE) as plasticiser. With a BBPA plasticiser using 1 mmol dm^{-3} ammonium chloride inner filling solutions, (+)-ephedrinium hydrochloride **3** gave a nernstian response

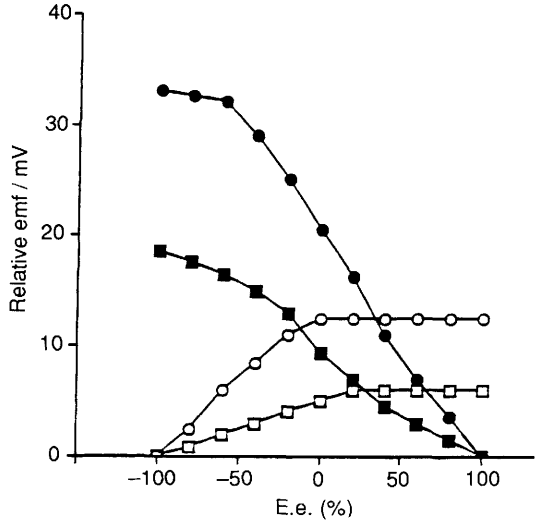


Fig. 1 Behaviour of the electrodes in solutions of varying enantiomeric purity [electroactive membrane peroctyl α-CD/BBPA or peroctyl α-CD/*o*-NPOE; 310 K; conditioned in 0.1 mol dm^{-3} (+) or (−) **3**]. □: +/BBPA; ■: −/BBPA; ○: +/*o*-NPOE; ●: −/*o*-NPOE.

Table 1 Electrode characteristics of membrane electrodes at 310 K

Analyte	Plasticiser	Slope (mV/decade)	Limit of detection −log[C]	Overall[b] selectivity $-\log K_{ij}^{POT}$
(−)**3**·HCl	BBPA	50.0	6.60	—
(+)**3**·HCl	BBPA	60.0	6.30	—
(+)**3**·HCl[a]	BBPA	60.0	4.64	3.90
(−)**3**·HCl[a]	BBPA	—	4.40	3.51
(+)**3**·HCl	*o*-NPOE	56.0	5.25	—
(−)**3**·HCl	*o*-NPOE	—	—	—
(+)**3**·HCl[a]	*o*-NPOE	58.0	4.70	3.91
(−)**5**·HCl	*o*-NPOE	58.0	4.73	—
(+)**5**·HCl	*o*-NPOE	60.0	5.19	—
(−)**5**·HCl[a]	*o*-NPOE	60.0	3.95	3.13
(+)**5**·HCl[a]	*o*-NPOE	59.0	4.14	3.32
(+)**5**·HCl[a]	BBPA	58.0	5.05	—
(−)**5**·HCl	BBPA	46.0	3.80	—
(+)**5**·HCl[a]	BBPA	58.0	2.90	2.1
(−)**4**·HCl	BBPA	59.0	5.90	—
(+)**4**.HCl	BBPA	59.0	6.10	

[a] Background of serum levels of Na^+ (150 mmol dm^{-3}), K^+ (4.3 mmol dm^{-3}), Ca^{2+} (1.26 mmol dm^{-3}). [b] The overall selectivity coefficient gives a measure of the interference from serum levels of Na^+, K^+ and Ca^{2+}. $K_{ij}^{pot} = a_i/(a_j)^{z_i/z_j}$ where a_i = primary ion, a_j = interfering ion, z_i, z_j is the charge on ion.

(60 mV/decade change at 25 °C) with a limit of detection of $10^{-6.3}$ mol dm^{-3}. This sensitivity was only slightly affected by the presence of serum levels of Na^+, K^+, Ca^{2+} (150 mmol dm^{-3}, 4.3 mmol dm^{-3} and 1.26 mmol dm^{-3}, respectively) giving an overall selectivity coefficient, $-\log K_{ij}^{POT}$ = 3.9. With (−)-ephedrinium hydrochloride, a reduced slope was observed (50 mV/decade, limit of detection $10^{-6.6}$). The 'bias' potential of the two electrodes—one conditioned in 0.1 mol dm^{-3} (+)-ephedrinium hydrochloride, the other with the (−)-enantiomer—was measured in a cell with no liquid junctions, giving a value of 24.5 (±0.5) mV, with BBPA as plasticiser, at room temperature, constant over 4 h. This emf (electromotive force) difference may be related to a free-energy difference of 2.4 (±0.05) kJ mol^{-1} for formation of the diastereoisomeric cyclodextrin complexes in this sensor.

† NMR spectral assignments were confirmed by ^{13}C–^1H and ^1H–^1H 2D-COSY experiments. *Selected data*: **1c** (*m*/*z* FD) 2706 (M+2), 2705, 2704, $\delta_H(CDCl_3)$ 0.85 (42H, t, Me), 1.14 (140H, mult, CH_2C), 1.55 (28H, mult, OCH_2CH_2), 3.31 (7H, dd, *J* 3.6, 9.6 Hz, H-2), 3.41 (14H, brt, CH_2O-C_2), 3.40, 3.89 (14H, m, H-4, H-3), 3.56, 3.68 (14H, m, C-6CH_2O), 3.58, 3.93 (14H, m, C-6-OCH_2) 3.70 (7H, m, H-5), 4.87 (7H, d, H-1, *J* 3.6 Hz), 5.50 (7H, brs, OH). $\delta_C(CDCl_3)$ 14.00 (Me), 22.58, 25.70, 26.08, 29.17, 29.27, 29.32, 29.43, 29.59, 29.65, 31.79 (CH_2C); 69.00 (C-6, CH_2O), 70.35 (C-5, CHO), 71.52 (C-2-O-CH_2R), 72.95 (C-6-O-CH_2R), 73.37 (*C*HOH), 80.34 (C-2, CHOR), 83.44 (C-4, CHO⁻), 101.79 (C-1, CHO).

1d (*m*/*z* FD) 3491 (M+2), 3490, 3489, δ_H 4.91 (1H, d, H-1), 4.09–3.31 (91H, m, CHO+CH_2O), 1.52 (42H, m, CH_2C), 1.34 (210H, m, CH_2C), 0.81 (63H, t, Me).

1b $\delta_H(CDCl_3)$ 0.83 (54H, t, Me), 1.33 (180H, m, CH_2C), 1.51 (36 H, m, CH_2CH_2O), 3.29 (6H, dd, *J* 3.3, 9.65 Hz, H-2), 3.32 (12H, t, $CH_2OCH_2CH_2$), 3.40 (189H mult, H-4 + $CHOCH_2$), 3.57–3.59 (18H, mult, $CHCH_2O$ + $CHOCH_2$), 3.80 (6H, br, mult, H-5), 3.87 (6H, mult, $CHOCH_2$), 4.01 (6H, dd, H-3), 4.83 (6H, d, *J* 3.3 Hz, H-1).

Using *o*-NPOE as plasticiser, the response to (+)-ephedrine hydrochloride was good (Table 1), but with (−)-ephedrine hydrochloride a reversal of slope was observed in solutions more dilute than $10^{-2.8}$ mol dm^{-3}. Since *ortho*-nitrophenol is known to bind to α-cyclodextrin,[5] a likely explanation of this effect is related to the competitive binding of the plasticiser by the peroctyl-α-cyclodextrin.

Using solutions of predetermined enantiomeric purity, the electrode response was measured, and the electrode could be calibrated (and used over a period of at least 3 months) to measure directly the enantiomeric purity of the ephedrinium salt (Fig. 1). Moreoever, since the diastereoisomeric (+)- or (−)-pseudoephedrines, **4**, responded in a nernstian manner like (+)-ephedrine (Table 1) the presence of varying amounts of (−)-ephedrine (one of the 4-stereoisomers in this series) may be selectively discerned with this sensor. The enantiomeric purity of the related β-aminoalcohol norephedrine, **5**, may also be measured with the (−)-enantiomer again giving a reduced slope (Table 1, slope difference of 12 mV).

Clearly, peroctylated cyclodextrin-based electrodes in which the aryl moiety is matched to the size of the hydrophobic binding pocket, show considerable promise as simple chiral sensors.

We thank the SERC for support and Professor A. K. Covington for stimulating discussions and for the cell assembly to measure bias potentials.

Received, 11th October 1991; Com. 1/05175J

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