

A Chiral Sensor Based on a Peroctylated α -Cyclodextrin

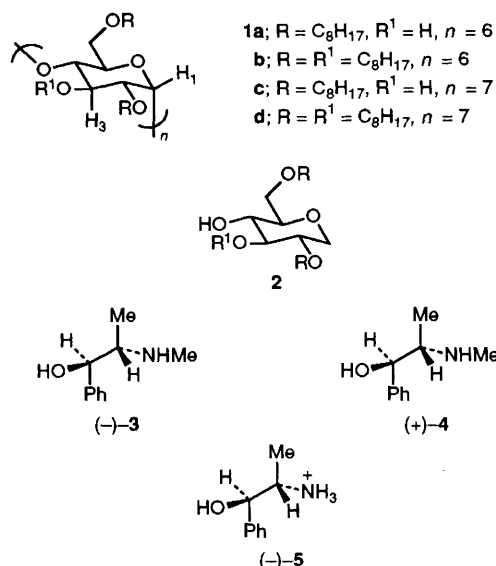
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A peroctylated α -cyclodextrin is used in a potentiometric ion-selective electrode to measure the enantiomeric purity of ephedrine in the presence of serum cations.

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, Me₂SO, C₈H₁₇Br, 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 (Et₃SiH, BF₃, CH₂Cl₂), 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-Ph)₄B-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

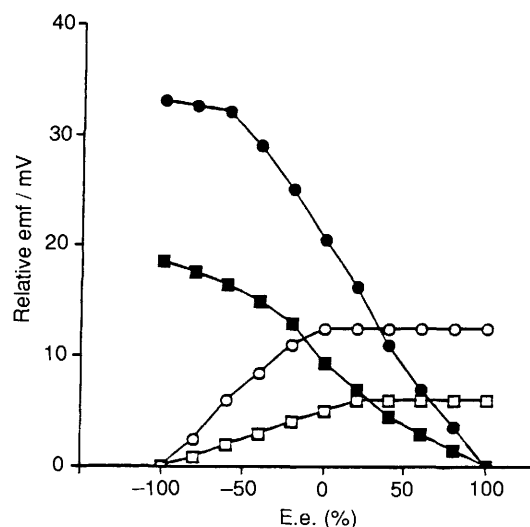


Fig. 1 Behaviour of the electrodes in solutions of varying enantiomeric purity [electroactive membrane peroctyl α -CD/BBPA or peroctyl α -CD/*o*-NPOE; 310 K; conditioned in 0.1 mol dm⁻³ (+) or (-) **3**]. □: +/BBPA; ■: -/BBPA; ○: +/*o*-NPOE; ●: -/*o*-NPOE.

Table 1 Electrode characteristics of membrane electrodes at 310 K

| Analyte | Plasticiser | Slope (mV/decade) | Limit of detection -log[C] | Overall ^b selectivity -logK _{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 | <i>o</i> -NPOE | 56.0 | 5.25 | — |
| (-)- 3 -HCl | <i>o</i> -NPOE | — | — | — |
| (+)- 3 -HCl ^a | <i>o</i> -NPOE | 58.0 | 4.70 | 3.91 |
| (-)- 5 -HCl | <i>o</i> -NPOE | 58.0 | 4.73 | — |
| (+)- 5 -HCl | <i>o</i> -NPOE | 60.0 | 5.19 | — |
| (-)- 5 -HCl ^a | <i>o</i> -NPOE | 60.0 | 3.95 | 3.13 |
| (+)- 5 -HCl ^a | <i>o</i> -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), Ca²⁺ (1.26 mmol dm⁻³). ^b The overall selectivity coefficient gives a measure of the interference from serum levels of Na⁺, K⁺ and Ca²⁺. $K_{ij}^{\text{POT}} = a_i/(a_j)^{z_i/z_j}$ where a_i = primary ion, a_j = interfering ion, z_i , z_j is the charge on ion.

[†] NMR spectral assignments were confirmed by ¹³C-¹H and ¹H-¹H 2D-COSY experiments. Selected data: **1c** (m/z FD) 2706 (M+2), 2705, 2704, δ_{H} (CDCl₃) 0.85 (42H, t, Me), 1.14 (140H, mult, CH₂C), 1.55 (28H, mult, OCH₂CH₂), 3.31 (7H, dd, J 3.6, 9.6 Hz, H-2), 3.41 (14H, brt, CH₂O-C₂), 3.40, 3.89 (14H, m, H-4, H-3), 3.56, 3.68 (14H, m, C-6CH₂O), 3.58, 3.93 (14H, m, C-6-OCH₂), 3.70 (7H, m, H-5), 4.87 (7H, d, H-1, J 3.6 Hz), 5.50 (7H, brs, OH). δ_{C} (CDCl₃) 14.00 (Me), 22.58, 25.70, 26.08, 29.17, 29.27, 29.32, 29.43, 29.59, 29.65, 31.79 (CH₂C); 69.00 (C-6, CH₂O), 70.35 (C-5, CHO), 71.52 (C-2-O-CH₂R), 72.95 (C-6-O-CH₂R), 73.37 (CHOH), 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+CH₂O), 1.52 (42H, m, CH₂C), 1.34 (210H, m, CH₂C), 0.81 (63H, t, Me).

1b δ_{H} (CDCl₃) 0.83 (54H, t, Me), 1.33 (180H, m, CH₂C), 1.51 (36 H, m, CH₂CH₂O), 3.29 (6H, dd, J 3.3, 9.65 Hz, H-2), 3.32 (12H, t, CH₂OCH₂CH₂), 3.40 (189H mult, H-4 + CHOCH₂), 3.57–3.59 (18H, mult, CHCH₂O + CHOCH₂), 3.80 (6H, br, mult, H-5), 3.87 (6H, mult, CHOCH₂), 4.01 (6H, dd, H-3), 4.83 (6H, d, J 3.3 Hz, H-1).

(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⁺, Ca²⁺ (150 mmol dm⁻³, 4.3 mmol dm⁻³ and 1.26 mmol dm⁻³, respectively) giving an overall selectivity coefficient, -logK_{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.

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). Moreover, since the diastereoisomeric (+)- or (-)-pseudoephedrine, **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.

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