Selective Binding and Detection of Onium Ions by Lipophilic Neutral Cyclodextrins

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Lipophilic peroctylated α-, β- and γ-cyclodextrins exhibit good selectivity and cation discrimination in the binding of NH_4^+, NMe_4^+ and NEt_4^+ ions respectively; sensors based on peroctyl β-CD show excellent sensitivity and selectivity for NMe_4^+ over metal cations, and may be used for the selective detection of acetyl choline and cationic surfactants.

Although there are several reported examples of the selective binding of tetraalkylammonium ions involving receptors incorporating attractive coulombic interactions,[1] evidence for the binding of such cationic species by neutral ionophores is restricted to systems involving electron-rich aryl groups where there is a well defined ion–dipole interaction between the onium ion and the aromatic π-system.[2,3] A recent report of the size-selective binding of ammonium ions by neutral cryptophanes has been mentioned, and an ion-selective electrode has been developed.[3b] The well documented binding of arylalkylammonium ions (where charge is generally delocalised over the aryl framework) by electron-rich crown ethers may also involve a certain degree of solvation of quaternary nitrogen alkyl groups by ether oxygens ($^+$N–C–H···O <) although the dominant binding interaction in these cases involves edge–face and face–face π-stacking interactions.[4] We report that the cavity of lipophilic cyclodextrins apparently affords a pocket for the binding and detection of tetrahedral ammonium ions. Such lipophilic cyclodextrins have previously been studied as chiral sensors for aryl β-amino alcohols in which the aryl moiety is believed to be included and which show excellent discrimination against group Ia and IIa cations.[5]

Peroctylation of α-, β- and γ-cyclodextrin to give **1**, **2** and **3** was effected as reported earlier[5,6] in a two-step process (NaOH, DMSO, $C_8H_{17}Br$; then $C_8H_{17}Br$–NaH–THF)† For the evaluation of these ionophores, an electroactive membrane was prepared incorporating 1 mol % cyclodextrin, 33% PVC, 65.6% of the plasticiser *ortho*-nitrophenyl octyl ether (*o*NPOE) or bis(butylpentyl) adipate (BBPA) and 0.4% of $(p\text{-}ClC_6H_4)_4B^-K^+$ (TKB). Results of electrode response studies in the absence and presence of interferent ions are given in Tables 1 and 2. The peroctyl α-CD **1** responds well to NH_4^+, although interference from potassium is severe. The related β-CD **2** is a very good ionophore for the $^+NMe_4$ ion, showing a Nernstian response down to *ca.* 10^{-5} mol dm^{-3} with excellent selectivity over Na^+, K^+, Ca^{2+}, Mg^{2+} and NH_4^+ (Table 2). The larger 'cavity' in per-octyl γ-CD **3** responded

† This procedure typically gives an average of 16, 18 and 21 octyl groups per α-, β- or γ-CD as revealed by electrospray mass spectrometry (see following communication) and reductive depolymerisation (Et_3SiH, BF_3, CH_2Cl_2). Residual OH groups (in the 3-position) can be 'capped' by methylation with MeI–THF–NaH, or converted into acetyl groups (CH_2Cl_2–AcCl–Et_3N). THF = tetrahydrofuran; DMSO = dimethyl sulfoxide).

Table 1 Electrode characteristics [slopes (mV per decade) with limits of detection (n in 10^{-n} mol dm^{-3}) in parentheses] for onium ion sensors[a] (310 K, NH_4Cl 0.001 mol dm^{-3} as inner filling solution)

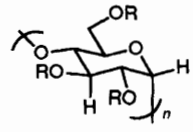
	Electrode					
	α-CD-**1**		β-CD-**2**		γ-CD-**3**	
Analyte	*o*NPOE	BBPA	*o*NPOE	BBPA	*o*NPOE	BBPA
NH_4Cl	57(4.9)	—	No response		No response	
Me_2NH_2Cl	—	2.0	52(4.0)	35(3.4)	No response	
Me_4NCl		10(1.9)	61(4.7)[a,b]	48(4.0)	12.5(2.1)	2.5(2.1)
Et_4NCl	22(3.0)	—	28(3.6)	—	42.0(4.0)	37.5(2.9)
Dopamine HCl	61(4.5)	61(5.4)[d]	60(4.4)	—	—	—
Acetyl choline Cl^{-}[c]	—	—	60(5.0)	52(3.1)	—	—
Choline Cl^{-}[c]	—	—	60(3.0)	No Response	—	—

[a] A 'blank' electrode, without any CD added, consisting of *o*NPOE–PVC–TKB with 0.01 mol dm^{-3} $Me_4N^+Cl^-$ inner filling solution showed no response to $Me_4N^+Cl^-$. [b] With 0.001 $N^+Me_4Cl^-$ as inner filling solution in place of NH_4Cl, the slope was 58 mV with a limit of detection of $10^{-5.7}$ mol dm^{-3}. [c] Inner filling solution was 0.01 mol dm^{-3} of acetyl choline chloride or choline chloride. [d] $MeNH_3Cl$ as analyte gives a poor response, with a slope of 11 mV per decade and a limit of detection of 10^{-2} mol dm^{-3} indicative of the importance of aryl inclusion with the α-CD ionophore **1**.

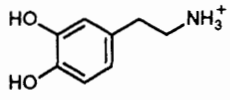
Table 2 Selectivity coefficients ($-\log K_{ij}^{pot}$, 0.1 mol dm^{-3} interferent, 310 K) for detection of ammonium ions

		Interferent					
Electrode	Analyte[a]	K^+	Na^+	Ca^{2+}	Mg^{2+}	NH_4^+	Choline$^+$
1–BBPA	Dopamine	1.5	1.8	3.3	3.2	—	—
1–*o*NPOE	NH_4^+	0.1	1.9	—	—	—	—
2–*o*NPOE	NMe_4^+	3.2	3.8	4.7	4.7	3.5	—
2–*o*NPOE	Acetyl[b] choline	3.5	4.2	4.5	—	3.2	1.8

[a] As chloride salt in MilliQ water. [b] For choline chloride, using an electrode based on **2**–*o*NPOE, $-\log k_{clin}^{pot}$ = 3.4 ('clin' is a simulated background of clinical ions (*c*/mmol dm^{-3} Na^+ 150; K^+ 4.3; Ca^{2+} 1.26; Mg^{2+} 0.9). With acetyl choline as analyte under these conditions, $-\log K_{clin}^{pot}$ = 4.2 (60 mV slope).



1; n = 6, R = octyl
2; n = 7, R = octyl
3; n = 8, R = octyl



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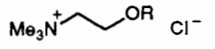
5



6a; R = COMe
6b; R = H

best to the bulkier $^+NEt_4$ ion. With the per-octyl-β-CD sensor for $^+NMe_4$, an electrode prepared without any ionophore gave no response.

The response of the electrode based on **2**–*o*NPOE towards the neurotransmitter acetyl choline **6a** was also evaluated. A Nernstian response was obtained down to 10 μmol dm^{-3} concentrations, and interference from a simulated background of clinical ions (150 mmol dm^{-3} Na^+, 4.3 mmol dm^{-3} K^+, 1.26 mmol dm^{-3} Ca^{2+}, 0.9 mmol dm^{-3} Mg^{2+}) was minimal; an overall selectivity coefficient of log K^{pot} = −4.2 was observed. Reasonable selectivity over the more hydrophilic analyte choline **6b** was also observed (log K^{pot} = −1.8) so that this sensor for acetyl choline could in principle be used to monitor esterase activity in a biological system. In addition the sensor based on **2** is sensitive to the presence of the cationic detergent myristyltrimethylammonium bromide **4** (slope 58 mV at 19 °C, limit of detection $10^{-6.5}$ mol dm^{-3}) at concentrations below its critical micelle concentration, while the sensor based on **1** is able to detect the neurotransmitter dopamine **5**, although there is more marked interference from potassium and sodium.

Further evidence for onium ion inclusion has come from measurements of the ^1H NMR relaxation time of the methyl hydrogens in $^+NMe_4$, and of the methylene group in $^+NEt_4$ in the absence and presence of the cyclodextrin.‡ Binding of the small ion by the relatively bulky ($M_r \geq 3000$) ionophore should lead to a reduction in the effective correlation time, τ_c, and a reduction in T_1. The measured T_1 for $^+NMe_4$ was 1.273 (±0.014) s, and reduced to 1.120 (±0.008) s in the presence of 1 equivalent of **1**. A larger reduction was noted in the presence of 1 equivalent of **2** [T_1 = 1.067 (±0.009) s]. The measured T_1 increased in the presence of **3** [T_1 = 1.413 (±0.004) s].§ No reduction in the T_1 of the methylene hydrogens was observed with $^+NEt_4$ in the presence of either **1** or **2**.

Parallel observations of the ^{14}N linewidth for $^+NMe_4$ in the absence and presence of **2** supported this observation. The linewidth of $^+NMe_4CF_3CO_2^-$ (90% $CDCl_3$, 10% MeCN used as internal reference) in the absence of cyclodextrin was 0.6 Hz, (36.1 MHz) and increased consecutively to 0.8, 0.9 and 1.4 Hz on the addition of 1, 2 and 5 equivalents of **2**, and was too broad to observe after the addition of ≥ 12 equivalents of **2**. In the complex [$^+NMe_4$·**2**], not only is the nitrogen nucleus potentially in a less symmetrical local electronic environment,¶ but also it has increased its volume by a factor of approximately 400 from the 'free' state with a concomitant

‡ Measurements of ^1H NMR T_1 were carried out at 250 MHz in degassed 0.001 mol dm^{-3} solutions (90% $CDCl_3$, 10% CD_3CN) containing the ionophore and $^+NR_4CF_3CO_2^-$. The mean value of eight determinations is given for three separate experiments.

§ This may be associated with inclusion of the $CF_3CO_2^-$ by the γ-cyclodextrin derivative. Measurements of ^{19}F relaxation times showed an increase in ^{19}F T_1 for $^+NMe_4CF_3CO_2^-$ in the presence of the β-cyclodextrin **2** (ΔT_1 = + 0.46 s), but a decrease in the presence of the γ-cyclodextrin derivative **3** (ΔT_1 = −0.06 s).

¶ Free and bound $^+NMe_4$ will be in fast exchange on the NMR time-scale, and the $^+NMe_4$ ion may also be expected to be relatively freely rotating in the bound state.

reduction in the correlation time, τ_c‖. Both factors may contribute to the observed line-broadening in the complex.

Finally direct observation of the selective inclusion of $^+NMe_4$ by **2** using electrospray ionisation mass spectrometry[7] (see accompanying communication) confirms that complexation is occurring. It is likely that the binding of $^+NMe_4$ involves solvation of the ions by the cyclodextrin oxygen lone pairs, *i.e.* an [N–C–H····O] interaction. Presumably at least one of the octyl chains of **2** may be included in the cyclodextrin cavity prior to ion-binding and there is a favourable enthalpy term associated with octyl exclusion when they are more free to interact hydrophobically with other octyl groups. Further experiments are in progress to test this hypothesis.

‖ In ^{14}N NMR: $\pi\omega_{\frac{1}{2}} = 1/T_q = (3/8)\chi^2(1 + \eta^2/3)\tau_q$, where T_q is the quadrupolar relaxation time, and for mobile species corresponding to extreme narrowing conditions $\omega^2\tau^2 << 1$, and $\tau_q = \tau_c$, the effective rotational correlation time of the nuclear quadrupole. An estimate of the reorientational correlation time may also be made from the Stokes–Einstein–Debye equation: $\tau_c = 4\pi r^3\eta/(3kT)$ where r is the 'radius' of the approximate spherical molecule. Assuming that r is *ca.* 3.5 Å for free $^+NMe_4$ and 25 Å in the cyclodextrin complex, the large change in τ_c is evident. For a discussion in related 'bouquet-shaped' molecules see: J. Canceill, L. Julian, L. Lacombe and J-M. Lehn, *Helv. Chim. Acta*, 1992, **75**, 791.

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References

1 H. J. Schneider, D. Güttes and U. Schneider, *J. Am. Chem. Soc.*, 1988, **110**, 6449; F. Vögtle, T. Merz and H. Wirtz, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 221; R. Meric, J-P. Vigneron and J-M. Lehn, *J. Chem. Soc., Chem. Commun.*, 1993, 129.

2 M. A. Petit, T. J. Shepodd, R. E. Barrass and D. A. Dougherty, *J. Am. Chem. Soc.*, 1988, **110**, 6825; S. K. Burley and G. A. Petsko, *FEBS Lett.*, 1986, **203**, 139.

3 (*a*) D. A. Stauffer and D. A. Dougherty, *Tetrahedron Lett.*, 1988, **29**, 6039; see also A. Maelicke, *Trends Biol. Sci*, 1991, **16**, 355; (*b*) A. Collet, J-P. Dutasta, B. Lozach and J-P. Chauvet, *Abstr. Int. Symp. Macrocyclic Chem.*, 1991, **16**, KL21.

4 P. L. Anelli, P. R. Ashton, R. Ballardini, V. Balzani, M. Delgado, M. T. Gandolfi, T. T. Goodnow, A. E. Kaifer, D. Philp, M. Pietrazkiewicz, L. Prodi, M. V. Reddington, A. M. Z. Slawin, N. Spencer, J. F. Stoddart, C. Vicent and D. J. Williams, *J. Am. Chem. Soc.*, 1992, **114**, 193.

5 P. S. Bates, R. Kataky and D. Parker, *J. Chem. Soc., Chem. Commun.*, 1992, 153; *Analyst (London)*, 1992, **117**, 1313.

6 W. A. Konig, *Carbohydr. Res.*, 1989, 51; W. A. Konig, S. Lutz and G. Wenz, *Angew. Chem., Int. Ed. Engl.*, 1989, **27**, 979; G. Wenz, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 783.

7 P. S. Bates, B. N. Green and D. Parker, *J. Chem. Soc., Chem. Commun.*, following communication.