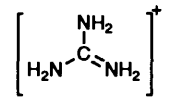
Selective Binding and Sensing of Guanidinium Ions by Lipophilic Cyclodextrins

Ritu Kataky, Patricia M. Kelly, David Parker* and Antonio F. Patti†
Department of Chemistry, University of Durham, South Road, Durham, UK DH1 3LE

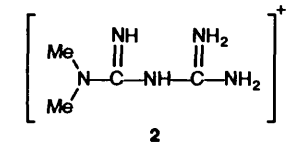
Potentiometric sensors based on lipophilic alkylated cyclodextrins exhibit a good response to the guanidinium ion, with higher selectivity over sodium than previously reported ionophores; 2,6-didodecyl-β-cyclodextrin has also been shown to exhibit selective response to the guanidine derivatives metformin and phenformin in a simulated clinical electrolyte background.

Compounds containing the guanidine group play an important role in biochemistry, thus the guanidinium ion and guanidine derivatives are an attractive analytical goal in the design of chemical sensors. Previous reports of ionophores used in potentiometric sensors for the guanidinium ion include crown ethers,[1] phosphoryl-containing podands,[2] bissulfonamide podands[3,4] and functionalised calixarenes.[5] The latter have also been used in fluorimetric sensors.[6] Of the potentiometric sensors, the latter two showed the highest selectivity over interferent ions, although interference by sodium is considerable. Previous studies have shown that alkylated cyclodextrins possess a suitable cavity to form inclusion complexes with a variety of onium ions.[7,8] Multiple hydrogen-bonding interactions of the type –N–H···O< or –N–C–H···O< are considered to occur between the included ion and the array of oxygen lone pairs of the CD. Such multiple 'ionic hydrogen bond' interactions have been shown to occur in the gas phase using mass spectrometric measurements[9,10] and in crystal structures from analysis of neutron diffraction data.[11,12] We report that alkylated cyclodextrins apparently form complexes with guanidinium ions (**1**) and the protonated forms of the guanidine derivatives, metformin (**2**) and phenformin (**3**), which may be detected potentiometrically.

The syntheses of the cyclodextrins used in this study (**4**–**8**) have been reported previously,[13] they include fully alkylated derivatives (**4** and **8**) which possess no OH groups and partially alkylated derivatives (**5**–**7**). The electroactive membranes tested contained, by weight, 1.2% CD, 65.6% 2-nitrophenyl octyl ether, 32.8% high molecular weight poly(vinyl chloride) and 0.4% sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate. They were mounted in standard electrode bodies supplied by Fluka, with 10^{-3} mol dm^{-3} NH_4Cl internal filling solution, and conditioned in 10^{-2} mol dm^{-3} analyte. Calibration and selectivity data were obtained at 37 °C using the constant volume dilution method, the selectivity coefficients being measured by the fixed interferent (mixed solution) method (FIM). Results of the response of electrodes to the guanidinium ion in the absence and presence of interferent ions are given in Table 1. All the cyclodextrins tested showed Nernstian response and good limits of detection. The similarity of response by all the cyclodextrins tested implies that (i) the binding is non-specific, with no size selectivity apparent between α (**6**–**8**) and β (**4** and **5**) cyclodextrins, suggesting that the ion is too small to interact peripherally with the entire ring and probably multi –N–H···O< interactions with the 2,6-oxygen lone pairs of the cyclodextrin take place, (ii) the interaction involves –N–H donation to the 2,6-ring oxygens as there is no significant difference in response between cyclodextrins with (**5**–**7**) and without (**4** and **8**) residual –OH groups.



1



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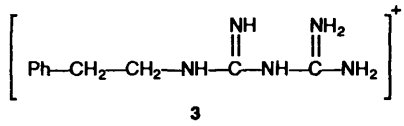

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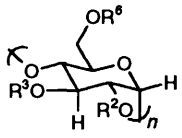

4 n = 7, R^2 = R^3 = R^6 = octyl
5 n = 7, R^2 = R^6 = dodecyl, R^3 = OH
6 n = 6, R^2 = R^6 = octyl, R^3 = OH
7 n = 6, R^2 = R^6 = octyl, R^3 = octyl/OH
8 n = 6, R^2 = R^6 = octyl, R^3 = octyl/methyl

The selectivities in the presence of interferent cations are also very similar for all the cyclodextrins tested and are poorer than for ions with a more specific binding interaction with CDs, such as NMe_4^+ and acetyl choline.[7] The cyclodextrins appear to show preferential binding to larger cations with diffuse charge, which afford multiple hydrogen-bonding interactions with the cyclodextrin oxygen lone pairs. They show a lesser affinity to more charge dense cations. Pertinent to clinical applications, this imparts selectivity over the ions of highest concentration in blood, of which sodium is the most significant. The CD based sensors are significantly more selective to guanidinium over sodium than the sensor based on a derivative of calix[6]arene[5] (Table 1). Urea, which is isoelectronic with guanidinium but uncharged at neutral pH, did not significantly interfere ([urea] = 5×10^{-3} mol dm^{-3}) with the response of an electrode based on **7** (slope = 61.0 mV, $c_{limit} = 10^{-5.4}$ mol dm^{-3}).

Certain simple N-substituted guanidine derivatives (*e.g.* metformin) are used clinically. The response of a sensor based on **5** to the protonated forms of metformin (**2**), a drug used to treat diabetes mellitus, and phenformin (**3**) has been evaluated (Table 2). Higher selectivity in a clinical background is exhibited than for the parent guanidinium ion.

Electrospray mass spectrometry has been used to provide additional evidence for the formation of a 1 : 1 inclusion complex

† *Permanent address:* School of Applied Science, Monash University, Churchill Campus, Victoria, Australia.

Table 1 Response of ISEs incorporating alkylated α- and β-cyclodextrins to guanidine H^+ in the absence and presence of interfering ions at 310 K. Selectivity coefficients for interferent ions are given as $-\log K^{pot}_{i,j}$, 0.1 mol dm^{-3} interferent.

	Calibration		Interferent[b]				
Electrode	Slope/mV	Limit of detection/ mol dm^{-3}	Clinical background[a]	Na^+	K^+	NH_4^+	Ca^{2+}
β-CD-**4**	61.5	$10^{-5.8}$	2.5	2.9	1.3	1.6	3.5
β-CD-**5**	60.2	$10^{-5.7}$	2.7	2.9	1.3	1.7	3.9
α-CD-**6**	61.5	$10^{-5.9}$	2.6	2.8	1.4	1.7	4.1
α-CD-**7**[c]	61.2	$10^{-6.2}$	2.6	2.9	1.4	1.7	3.8
α-CD-**8**[c]	61.7	$10^{-5.7}$	2.6	2.9	1.4	1.7	3.9

[a] Clinical background is a simulated background of clinical ions (c/mmol dm^{-3} Na^+ 145; K^+ 4.3; Ca^{2+} 1.26). [b] $-\log K^{pot}_{i,j}$ for the sensor based on a calix[6]arene derivative,[5] for comparison: Na^+ 1.85; K^+ 1.8; NH_4^+ 1.8; Ca^{2+} 2.85 (interferent concentration 0.1 mol dm^{-3}). [c] Compound **7** has 15.4 octyl groups per cyclodextrin ring; [13] in **8** these OH groups have been capped by methyls.

Table 2 Response of 2,6-didodecyl-β-cyclodextrin membrane to metformin and phenformin

	Calibration		
	Slope/mV	Limit of detection/ mol dm^{-3}	Selectivity, $-\log K^{pot}_{i,j}$ clinical background
metformin	61.4	$10^{-5.6}$	3.1
phenformin	55.6	$10^{-4.3}$	3.3

between 2,6-didodecyl-β-CD and the guanidinium ion. The spectrum for a solution of 50 μmol dm^{-3} CD, 100 μmol dm^{-3} guanidinium chloride and 5×10^{-3} mmol dm^{-3} ammonium acetate (molar ratios, respectively, of 1:2:100) in propan-2-ol was measured. A peak corresponding to a 1:1 complex of the 2,6-didodecyl-β-CD with guanidinium ion was observed (calculated mass: 3551.59, mass obtained: 3551.5). No evidence for binding to the ammonium ion was observed even in the presence of a 50-fold excess over guanidinium. Only peaks due to a 1:1 complex were found: no 2:1 species at half the m/z ratio were observed.

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