# Characterisation of the Complexation Behaviour of Lipophilic Cyclodextrins by Electrospray Mass Spectrometry

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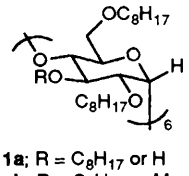
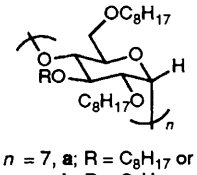
Electrospray ionisation mass spectrometry is well suited to the characterisation of lipophilic cyclodextrins and may be used to study complexation *in situ* and competitively for a range of charged onium ions, including cationic surfactants and acetyl choline.

In the last few years, electrospray-ionisation mass spectrometry (ES-MS) has proved to be a most useful method for the analysis of non-volatile, thermally labile and polar compounds. Most reports have been concerned with the analysis of high molecular mass biomolecules such as proteins[1] and enzymes[2] because of the ease of formation of multiply charged species. However ES-MS is well suited to the analysis of low molecular mass compounds which are difficult to characterise by other methods, *e.g.* radical cations,[3] transition metal complexes[4] and porphyrins.[5] During the course of work aimed at exploring the complexation behaviour of lipophilic peroctylated cyclodextrins towards aryl β-amino alcohols[6] and tetrahedral onium ions,[7] we have sought to use mass spectrometric methods both to characterise the alkylated cyclodextrins and to examine directly complex formation.




**1a**; R = $C_8H_{17}$ or H
**b**; R = $C_8H_{17}$ or Me




**2**, *n* = 7, **a**; R = $C_8H_{17}$ or H
**b**; R = $C_8H_{17}$ or Me
**3**, *n* = 8, **a**; R = $C_8H_{17}$ or H
**b**; R = $C_8H_{17}$ or Me

Per-octylation of α-cyclodextrin (NaOH–DMSO–$C_8H_{17}Br$ then NaH–THF–$C_8H_{17}Br$)[6] (DMSO = dimethyl sulfoxide; THF = tetrahydrofuran) results in incomplete octylation of the 18 sites and there are residual hydroxy groups in the 3-position of each of the six glucose units. Fast atom bombardment mass spectral analysis of **1a** in a variety of matrices yielded only very weak spectra. Field-desorption methods were more encouraging but gave variable intensities for the different alkylated species. Using propan-2-ol solutions of the cyclodextrin in the presence of ammonium acetate, electrospray ionisation† gave reliable and strong

† ES-MS measurements were made on a VG Quattro-BQ, a quadrupole instrument with an atmospheric pressure electrospray source and a mass range for singly charged ions of 4000. Samples, as solutions in propan-2-ol (typically 20–50 pmol $mm^{-3}$) were introduced into the source at a flow rate of 5 $mm^3$ $min^{-1}$. Mass scale calibration employed the ammonium adducts from polypropylene glycols 2000 and 3000 (1 μg $mm^{-3}$) and were introduced into the source at a flow rate of 5 $mm^3$ $min^{-1}$. Ammonium acetate (10 mmol $dm^{-3}$), tetramethylammonium trifluoroacetate (0.2–2 mmol $dm^{-3}$), ephedrinium trifluoroacetate (0.2 mmol $dm^{-3}$) or myristyltrimethylammonium bromide (0.5 mmol $dm^{-3}$) solutions in propan-2-ol were added to the cyclodextrin samples. Agreement between observed and calculated *m/z* values was typically within 0.4.

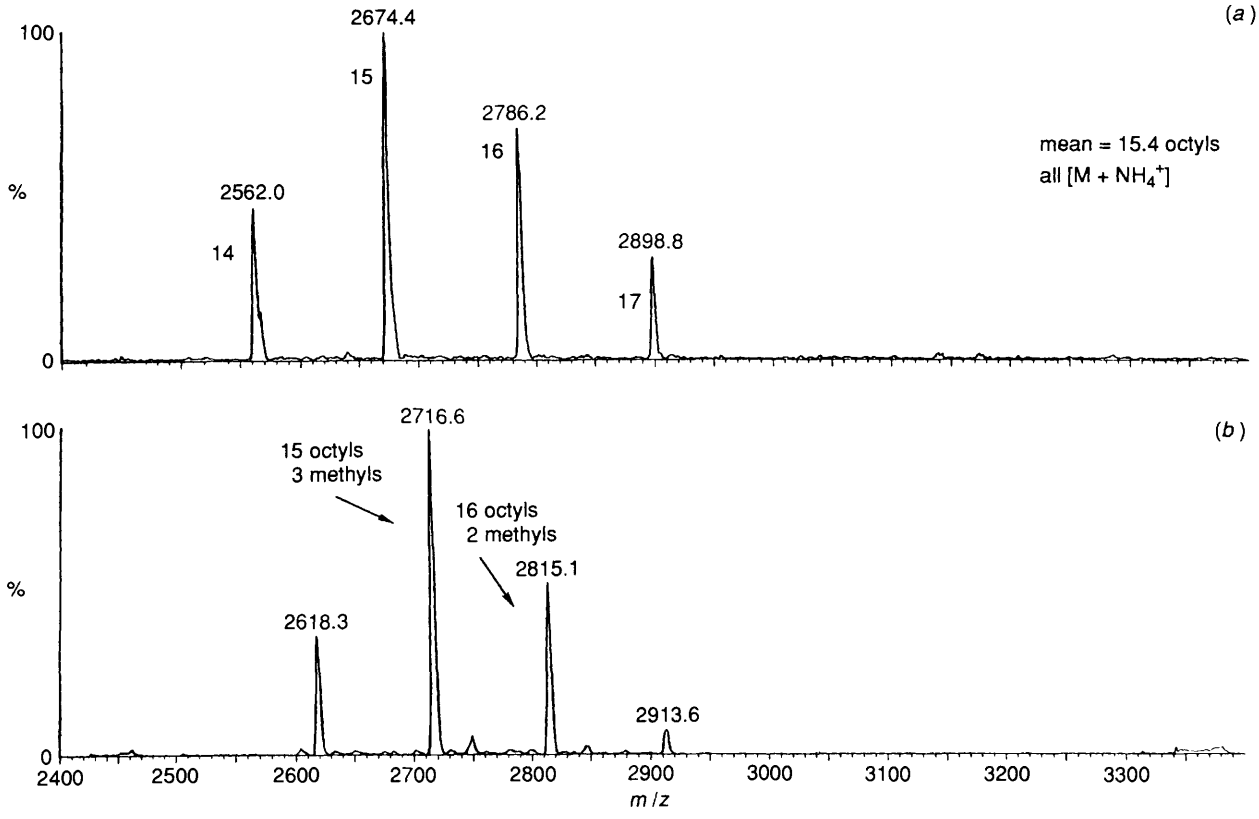



**Fig. 1** ES-MS spectra for (*a*) **1a** and (*b*) **1b** in the presence of 10 mmol $dm^{-3}$ $NH_4OAc$

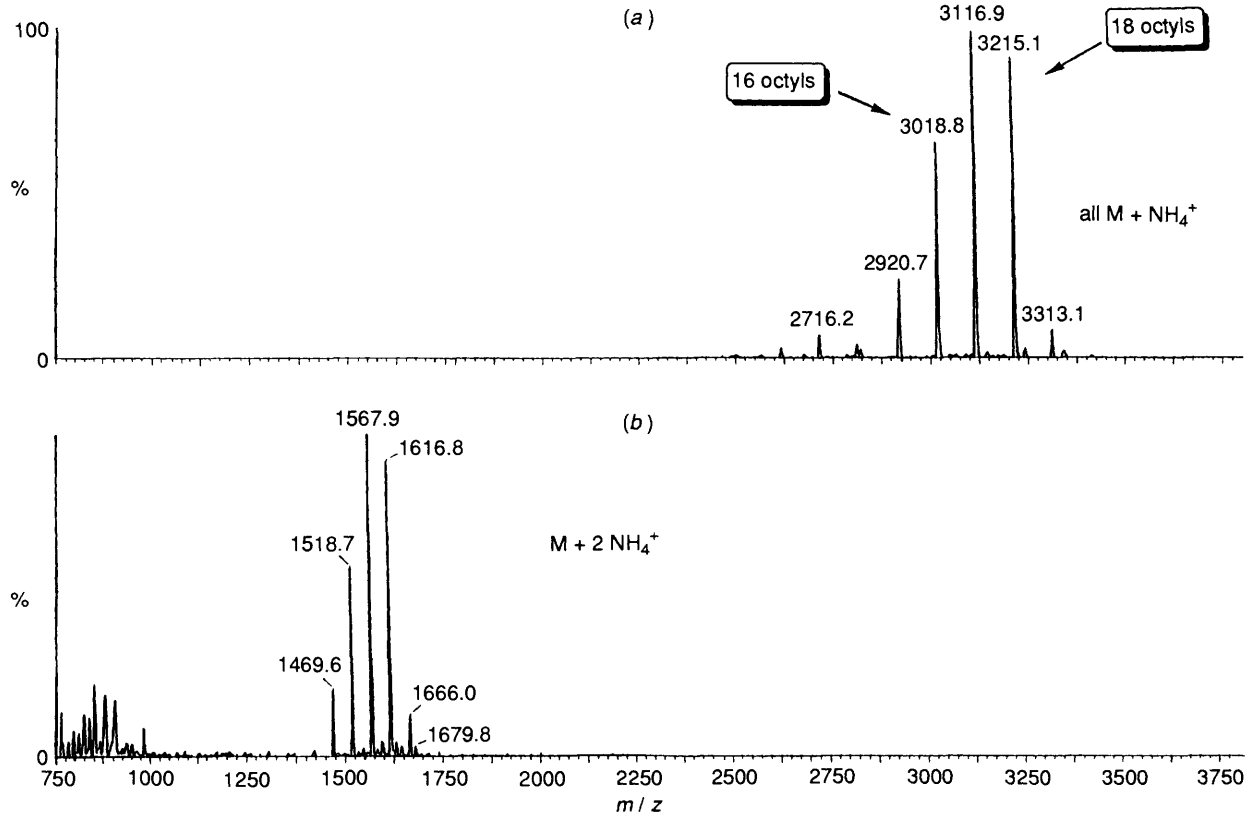



**Fig. 2** ES-MS spectra for **2b** (10 mmol $dm^{-3}$ $NH_4OAc$) showing (*a*) singly and (*b*) doubly charged ions

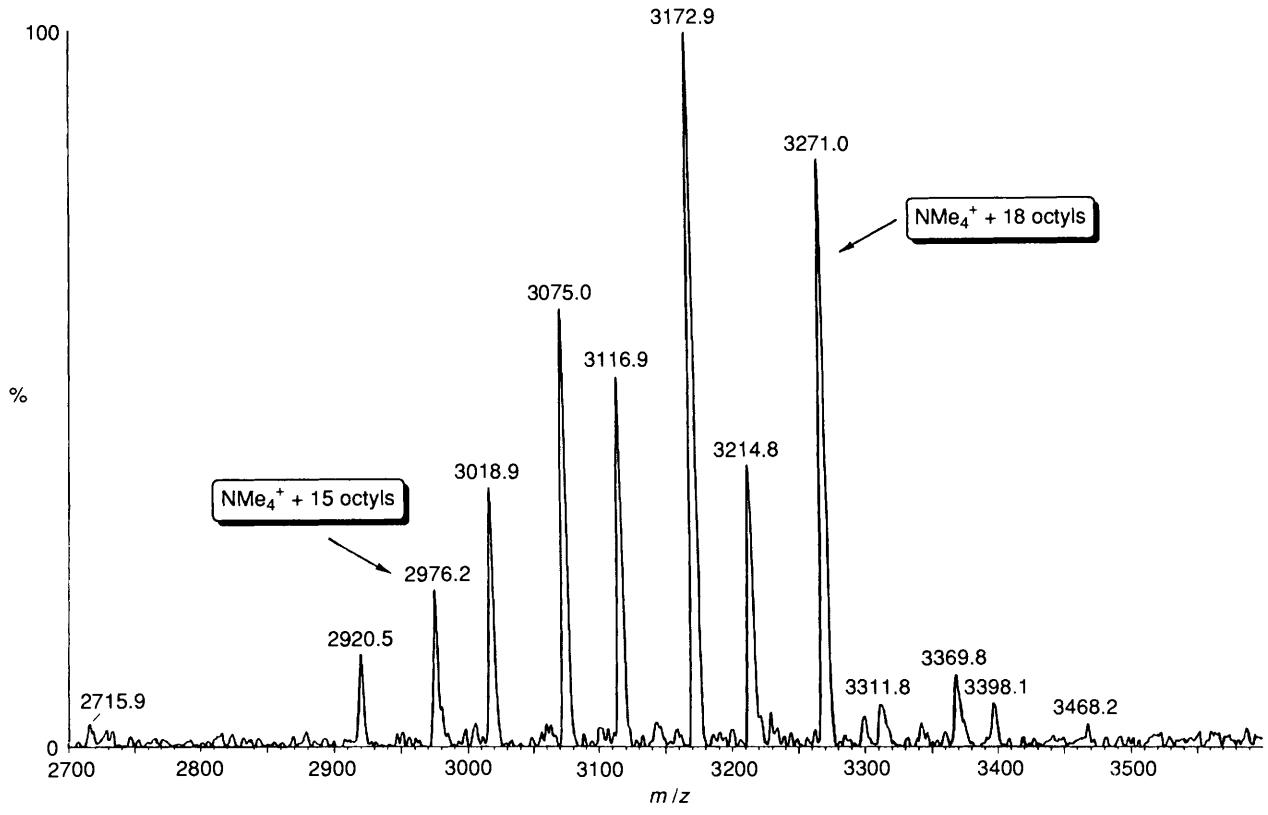



**Fig. 3** ES-MS spectrum for **2b** (10 mmol $dm^{-3}$ $NH_4OAc$, 0.1 mmol $dm^{-3}$ $NMe_4^+$; peaks at 2920.5, 3018.9, 3116.9 and 3214.8 are due to the $NH_4^+$ complex

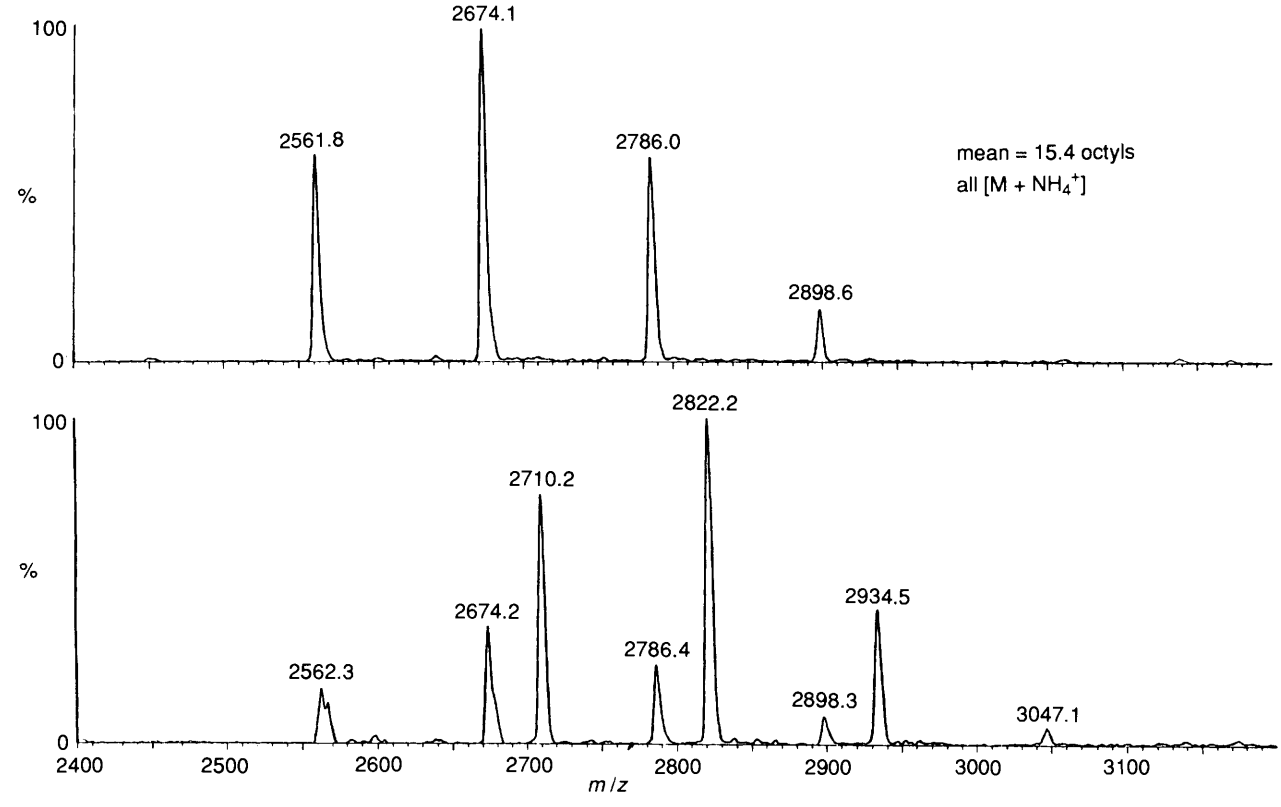



**Fig. 4** ES-MS spectrum of **1a** in the presence of (*a*) $NH_4OAc$ (10 mmol $dm^{-3}$) and (*b*) ephedrinium trifluoroacetate (0.2 mmol $dm^{-3}$) showing selective formation of the ephedrinium complex; peaks at 2710.2, 2822.2 and 2934.5 are due to the ephedrinium complex

**Table 1** Mean number of octyl groups in **1a**, **2a** and **3a**

| Method | **1a** (α) | **2a** (β) | **3a** (γ) |
|---|---|---|---|
| ES-MS[a] | 15.4 | 17.5 | 20.7 |
| NMR[b] | 15.3 | 17.3 | 20.5 |
| GC-MS[a] | 15.5 | 17.4 | 20.4 |

[a] Determined directly from peak sizes. [b] By $^1$H NMR integration of the OMe singlet in the derived 'methyl-capped' compounds **1b–3b**. $^{13}$C NMR analysis of **1b**, **2b** and **3b** [in presence of 0.5 mol % $Cr(acac)_3$] gave similar values (± 0.2).

spectra for the ammonium adduct (Fig. 1).[8] The relative sizes of the peaks for the 14-, 15-, 16- and 17-octylated species were independent of sample and added ammonium concentration and the mean degree of alkylation (15.4) was consistent with values obtained following reductive depolymerisation and GC–MS analysis[6] and also with an NMR method. Analysis by NMR [both $^1$H directly and $^{13}$C following addition of 0.5% $Cr(acac)_3$; Hacac = pentane-2,4-dione] on the 'methyl-capped' derivative **1b**, obtained by the reacting of **1a** with MeI (NaH–THF), gave values for the degree of octylation which were consistent with the two independent mass spectroscopic methods (Table 1). The 'methyl-capped' cyclodextrin **1b** was also characterised by ES-MS (Fig. 1). In a similar manner, per-octylated β- and γ-cyclodextrins **2a** and **3a**, were characterised (Table 1). Doubly charged ions of composition (M + $2NH_4^+$) were also produced from all six cyclodextrins at their expected *m/z* ratios, but at lower source potentials than were optimum for the singly charged species. The spectra of the singly and doubly charged species from **2b**, obtained in separate analyses, are shown in Fig. 2.

Having recently noted that the β-CD derivative **2a** is a very selective ionophore for the $NMe_4^+$ ion [*e.g.* log $K^{pot}$ = −3.5 ($NH_4^+$), −3.8 ($Na^+$), −4.7 ($Ca^{2+}$)],[7] tetramethylammonium trifluoroacetate was used in place of ammonium acetate and large peaks were observed for the $NMe_4^+$ complex of both **2a** and **2b** in the ES mass spectrum. No peaks due to the (M + $2NMe_4^+$) species were observed. In a competition experiment (10 mmol dm$^{-3}$ $NH_4OAc$ *vs.* 0.1 mmol dm$^{-3}$ $NMe_4^+$ $CF_3CO_2^-$ in Pr$^i$OH), the size-selective binding of the $NMe_4^+$ ion was observed (Fig. 3), consistent with selectivities determined in the potentiometric sensor. Given that peroctylated β-CD also forms the basis of a promising sensor for cationic trimethylammonium surfactants,[7] complexation of $C_{14}H_{29}NMe_3^+Br^-$ by **2b** was studied and peaks due to the complex [**2b** + $C_{14}H_{29}NMe_3^+$] at 3256.7 (16 octyls; calc. 3257.1), 3355.2 (17 octyls; calc. 3355.3) and 3453.7 (18 octyls; calc. 3453.7) were clearly observed. Similarly the complex of **2a** with both acetyl choline ($Me_3^+NCH_2CH_2OAc$) and choline could be clearly defined in the ES-MS spectra.

Competition between ammonium acetate (10 mmol dm$^{-3}$) and ephedrinium trifluoroacetate (0.2 mmol dm$^{-3}$) using **1a** was examined and the ephedrinium complex formed in preference (Fig. 4) suggesting that ES-MS may prove to be a valuable technique for quickly assessing complexation preferences in supramolecular chemistry in the same way that FAB-MS is used to screen metal complexation by neutral ionophores.[9]

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