EPR spectroscopic characterisation of transient organic radicals included in cyclodextrins

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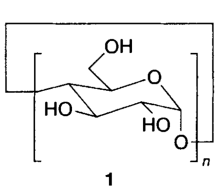
Short-lived organic radicals, generated in aqueous solution using rapid-mixing continuous-flow techniques, form inclusion complexes with cyclodextrins; significant conformational changes accompany inclusion.

α-, β- and γ-Cyclodextrins (CDs) **1** are cyclic oligosaccharides that are made up of 6, 7 or 8 D-glucose units, respectively, bonded through α-(1,4)-linkages. The oligosaccharide ring forms a torus, with the primary OH groups of the glucose residues positioned at the narrower end of these tub-shaped molecules (see **2**), while the secondary glucopyranose OH groups are located around the wider opening. The chiral inner cavity of a CD is hydrophobic, whereas the outer surface of the torus is hydrophilic. In aqueous solution, CDs form a wide range of inclusion complexes when a guest molecule fits, at least partially, into the hydrophobic cavity and these complexes have been investigated by a variety of techniques.[1,2]

The inclusion of organic radicals by CDs has been studied intermittently by EPR spectroscopy during the last 25 years, but all reports have been concerned with very persistent radicals such as sterically-protected nitroxides, nitroarene radical anions and semidiones.[3] We describe here the characterisation by EPR spectroscopy of CD inclusion complexes **2** of short-lived radicals generated in aqueous solution using the flow technique developed by Norman and Gilbert,[4] in which the solution passes through the microwave cavity *ca.* 60 ms after mixing of the reagents.

Many chemically-modified CDs are available[5] and most experiments involved 2-hydroxypropyl-β-cyclodextrin† (Hp-β-CD), which is much more water-soluble than β-CD itself. The radical **3** was generated in a three-stream flow system by the reaction of $HPO_2^{\bullet -}$ with 2-bromo-3-phenylpropanoic acid at pH 8–9, as described previously for similar α-bromoacids.[6,7] The EPR spectroscopic parameters for **3** in aqueous solution (see Table 1) are in accord with those reported previously.[7] The spectrum was unaffected by the presence of methyl-α-D-glucopyranoside (MGP), apart from some additional signals from radicals that result from attack of $HO^{\bullet}$ on the MGP [see Fig. 1(*a*)]. However, in the presence of Hp-β-CD (1.1×10^{-2} mol dm^{-3} in each stream), the spectrum [Fig. 1(*b*)] shows additional signals which we assign to the radical **3** included bimodally in the CD, although the detailed modes of inclusion remain to be established. When the concentration of Hp-β-CD in each stream is increased to 4.0×10^{-2} mol dm^{-3}, the spectra of the included radicals become dominant [Fig. 1(*c*)]. The value of $a(1H_{\alpha})$ is essentially unaffected by inclusion, while that of $a(2H_{\beta})$ increases. The magnitude of the latter splitting constant will depend on the time-average value of $\cos^2 \theta$, where θ is the dihedral angle between a β-C–H bond and the axis of the $2p_{\pi}$ orbital on C_{α}, according to the well-known Heller–McConnell relationship.[8] We attribute the two spectra of included radicals to different conformations of **3**, which interconvert on the EPR timescale at 293 K giving rise to the pronounced linewidth



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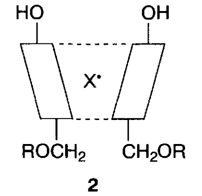

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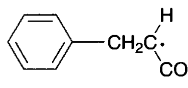
β-CD, R = H
Hp-β-CD, R = CH$_2$CH(OH)Me



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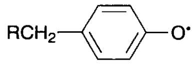

4 R = Me
5 R = Ph

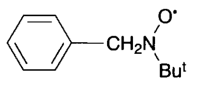

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Table 1 EPR parameters for unbound and included radicals in aqueous media at 293 K

Radical	Additive	Additive conc./ 10^{-2} mol dm^{-3}	g-Factor[a]	Hyperfine splittings[a,b]/G
3	None	—	2.0033	20.28 ($1H_{\alpha}$), 23.08 ($2H_{\beta}$)
	MGP	8.5	2.0033	20.29 ($1H_{\alpha}$), 23.1 ($2H_{\beta}$)
	Hp-β-CD	1.1–4.0	**2.0033**	**20.3 ($1H_{\alpha}$), 26.2 ($2H_{\beta}$)**
			2.0033	**20.2 ($1H_{\alpha}$), 27.9 ($2H_{\beta}$)**
			2.0033	20.28 ($1H_{\alpha}$), 23.08 ($2H_{\beta}$)
4	None	—	2.0044	10.33 (2H), 6.13 ($2H_{o}$), 1.39 ($2H_{m}$)
	MGP	6.8	2.0044	10.33 (2H), 6.11 ($2H_{o}$), 1.37 ($2H_{m}$)
	Hp-β-CD	0.6–2.4	**2.0045**	**9.7 (2H), 6.2 ($2H_{o}$), 1.5 ($2H_{m}$)**
			2.0044	10.23 (2H), 6.13 ($2H_{o}$), 1.38 ($2H_{m}$)
5[c]	None	—	2.0044	9.71 (2H)[d], 6.19 ($2H_{o}$) 1.46 ($2H_{m}$)
	MGP	6.8	2.0044	9.71 (2H), 6.19 ($2H_{o}$), 1.47 ($2H_{m}$)
	Hp-β-CD	0.6–2.4	**2.0045**	**10.3 (2H), 6.3 ($2H_{o}$), 1.6 ($2H_{m}$)**
			2.0044	9.68 (2H), 6.21 ($2H_{o}$), 1.47 ($2H_{m}$)
6	None	—	2.0056	16.66 (N), 10.63 ($2H_{\beta}$)
	MGP	62	2.0056	16.68 (N), 10.59 ($2H_{\beta}$)
	Hp-β-CD	1.5–10	**2.0057**	**15.9 (N), 7.7 ($2H_{\beta}$)**
			2.0056	16.70 (N), 10.60 ($2H_{\beta}$)
	β-CD	1.5	**2.0057**	**15.9 (N), 7.7 ($2H_{\beta}$)**

[a] In the presence of cyclodextrin, the values given in bold type refer to the included radical. [b] Nuclei indicated in parentheses; ±0.05 G for unbound radicals, ±0.1 G for included radicals. [c] Methanol (10% *v*/*v*) present in the phenol stream to improve solubility. [d] Ref. 9*b* gives 8.7 G, which appears to be a typographical error.

effects evident in Fig. 1. Thus, the wing lines of each β-proton triplet $[M_I(2H_\beta) = \pm 1]$ are significantly broader than the central lines, as would result from in-phase modulation of $a(2H_\beta)$ arising from exchange between two conformations which differ in the average values of $\cos^2 \theta$. In accord with this interpretation, the selective line broadening became more pronounced when the temperature was increased to 313 K.

The short-lived aryloxyl radicals **4** and **5**, chosen because the value of $a(p\text{-}CH_2R)$ will be an indicator of conformation about the ring-CH_2R bond, were generated using a two-stream flow system by the reaction of ceric ammonium nitrate with the corresponding phenol.[9] In the presence of Hp-β-CD (2.4×10^{-2} mol dm^{-3} in both streams), computer simulation of the composite spectrum showed that 57% of the radical **4** was included while 43% remained unbound. The aryloxyl radical **5** was included to a similar extent by Hp-β-CD, but now the value of $a(p\text{-}CH_2R)$ increases upon inclusion, whereas for **4** a decrease is observed.

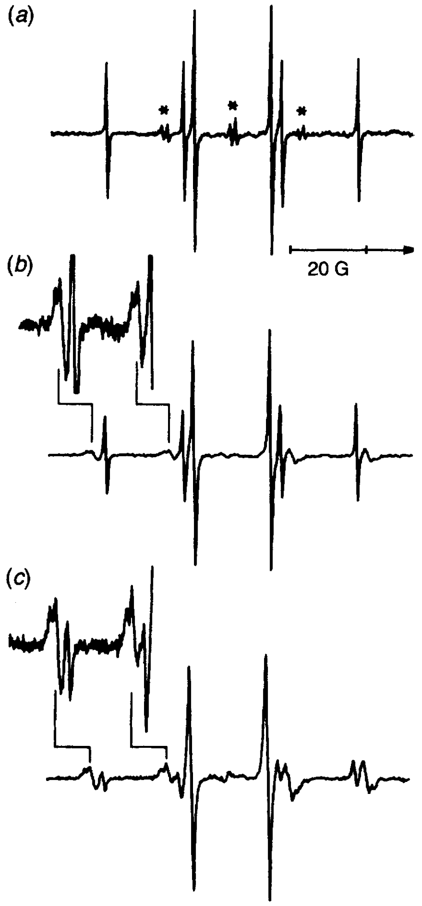

Fig. 1 EPR spectra of the radical **3** in aqueous media at 293 K. In addition to the specified additive, the three reactant streams contained (i) H_2O_2 (1.5×10^{-2} mol dm^{-3}), (ii) $TiCl_3$ (1.0×10^{-2} mol dm^{-3}), α-bromoacid (1.0×10^{-3} mol dm^{-3}), the disodium salt of ethylenediaminetetraacetic acid (3.0×10^{-2} mol dm^{-3}) and ammonia to give a pH of *ca.* 9, and iii) monosodium hypophosphite [0.1, 0.2 and 0.3 mol dm^{-3} in (*a*), (*b*) and (*c*), respectively]. (*a*) Additive was MGP (8.5×10^{-2} mol dm^{-3}); the lines indicated with asterisks arise from MGP-derived radicals. (*b*) Additive was Hp-β-CD (1.1×10^{-2} mol dm^{-3}). (*c*) Additive was Hp-β-CD (4.0×10^{-2} mol dm^{-3}).

Although longer-lived than the radicals **3**–**5**, benzyl *tert*-butyl nitroxide[10] **6** still decays quite rapidly in aqueous solution. However, continuous-flow methods were not necessary for its generation and an adequate steady-state concentration could be obtained for some time after mixing a deoxygenated solution of *N*-benzyl-*tert*-butylamine with a solution of the magnesium salt of monoperoxyphthalic acid. For initial concentrations of amine and peroxycarboxylate equal to 1.0×10^{-2} and 5.0×10^{-3} mol dm^{-3}, respectively, the nitroxide **6** was partially included when [Hp-β-CD] was 1.5×10^{-2} mol dm^{-3}, but only the included radical was detected when [Hp-β-CD] was increased to 0.1 mol dm^{-3}.‡ Similar effects, with rather narrower lines for the included nitroxide, were observed using unmodified β-CD. While the value of $a(N)$ for **6** decreases only slightly upon inclusion into the less polar environment of the Hp-β-CD host cavity, the conformationally-sensitive value of $a(2H_\beta)$ decreases markedly (by 27%) on inclusion.

In general, the changes in conformation and unpaired-electron distribution that accompany inclusion of transient radicals could have significant effects on the regio- and stereochemistry of intramolecular reactions of the guests, as compared with the same reactions of unbound radicals.[11]

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Footnotes

† Commercially-available (Aldrich) Hp-β-CD of average RMM = 1500 was used. In this material, about six of the seven primary OH groups of β-CD have been converted to $OCH_2CH(OH)Me$ groups.

‡ In general under our conditions, there will be a competition between the radical and its parent substrate for inclusion in the CD, as evidenced by the dependence of the extent of inclusion on substrate concentration.

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