# Modification of Pathways for Cathodic Reduction *via* Complexation with β-Cyclodextrin

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*Summary* Complexation of electroactive substrates with β-cyclodextrin can profoundly alter the course of their reactions; for the cathodic reduction of complexes of ethyl cinnamate, benzaldehyde, and benzophenone protonation of radical-anions is highly efficient whereas a previously unobserved reductive coupling is found for the acetophenone complex.

IMPORTANT factors influencing pathways of cathodic reduction include the rate of mass transport of substrate and intermediates and proton availability; the prediction and control of these factors is usually difficult. We have conducted experiments involving the reduction of electroactive guest molecules included in the torus of a β-cyclodextrin (β-CD) host. Such complexes, much studied as models for enzyme–substrate complexes, are well characterised and therefore we can hypothesise that the guest molecule carries with it, to the cathode, its own 'microenvironment' (the β-cyclodextrin host). The torus of the host molecule is known to be hydrophobic and the peripheral hydroxy-groups, particularly the secondary ones, are known to be efficient proton donors.[1]

Little work has been published on the electrochemistry of cyclodextrin complexes; anodes with attached cyclodextrins cause relatively small changes in the selectivity of anodic chlorination of anisole[2a] and the polarographic reduction potentials of nitrophenols are shifted on complexation.[2b] We herein report the first observations for electro-organic reactions of profound changes in reactivity caused by complexation with a cyclodextrin.

β-Cyclodextrin complexes were prepared by precipitation from methanol solution. Key complexes for this study are those involving guest compounds with a well understood cathodic reduction pathway. In this context 1:1 complexes were isolated containing ethyl cinnamate and acetophenone. Complexes including benzophenone or benzaldehyde were isolated and their stoicheiometry, β-cyclodextrin: carbonyl compound, found to be 2:1. Much information comes from the $^1$H n.m.r. spectra at 400 MHz of $D_2O$ solutions. The ratio of integrated areas for the aromatic: cyclodextrin protons allows calculation of stoicheiometry and the pronounced upfield shift of the inner (3-H and 5-H) protons on complexation indicates that for the 1:1 complexes the aromatic portion of the guest is inside the torus. By contrast, the chemical shifts of the outer (2-H and 4-H) protons are unchanged upon complexation (see the Figure).

The cyclic voltammetry in *NN*-dimethylformamide (DMF) of the guest compounds is changed on complexation in a small but observable fashion (Table 1); shifts in reduction potential are small but whereas reversible or quasi-reversible cyclic voltammetric behaviour is observed in 'free' solution, the anodic peak current on the return scan

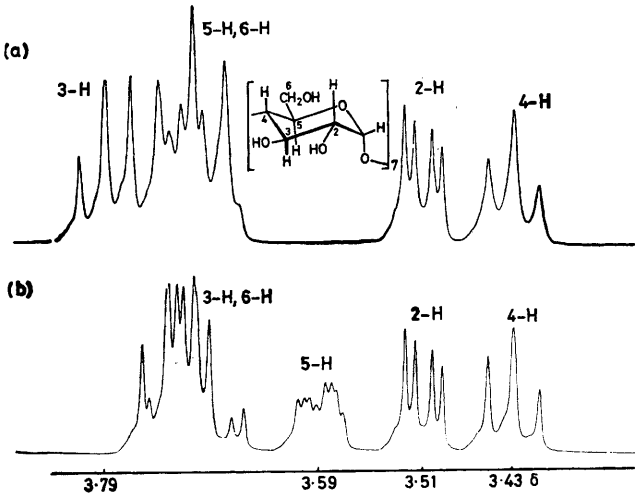



FIGURE. $^1$H n.m.r. spectrum (400 MHz, $D_2O$, 343 K) of (a) β-cyclodextrin and (b) β-cyclodextrin–acetophenone complex.

is greatly diminished by complexation, *i.e.* the host is acting as a proton donor. The reductions are diffusion controlled as shown by linear plots of peak current *vs.* (scan rate)$^{\frac{1}{2}}$.

TABLE 1. Effect of complexation on cyclic voltammetry.[a]

| Substrate | Free $-Ep^b$ | Free $i_p^{red.}/i_p^{ox.}$ | β-Cyclodextrin complex $-Ep^b$ | β-Cyclodextrin complex $i_p^{red.}/i_p^{ox.}$ |
|---|---|---|---|---|
| PhCHO | 1·50 | 1·4, qr.[c] | 1·80 | irr.[c] |
| PhCOMe | 1·49 | 1·8, qr. | 1·47 | irr. |
| $Ph_2CO$ | 1·42 | 1·1, rev.[c] | 1·30 | irr. |
| | 1·69 | irr. | | |
| $PhCH:CHCO_2Et$ | 1·44 | 3·0, qr. | 1·32 | 2·0, qr. |

[a] Hg coated Pt bead cathode, DMF–$Bu_4NBF_4$ (0·1 M), 0·2 V $s^{-1}$; *ca.* 20 °C. [b] V *vs.* Ag/AgI. [c] rev., qr., irr. reversible, quasi-reversible, irreversible, respectively.

Complexation does, however, result in dramatic changes on the course of controlled potential preparative electrolyses. At −1·3 V (*vs.* Ag/AgI) cathodic reduction at mercury, in DMF containing tetra-n-butylammonium iodide (0·1 M), gives for ethyl cinnamate a quantitative yield of the all-*trans* cyclic hydrodimer (**1**). The stereochemistry of this product was elucidated by complete assignment, with coupling constants, of the 400 MHz $^1$H n.m.r. spectrum and this amplifies an earlier report.[3] Complexation with β-cyclodextrin, followed by electroreduction at −1·3 V, gives the dihydro-product (**2**) in 71% yield together with 19% of the linear hydrodimer (**3**) and only 4% of (**1**). The complex may be formed *in situ* and for a series of reductions a plot of the ratio of (**2**) : [(**1**) + (**3**)] *vs.* the ratio of β-cyclodextrin : ethyl cinnamate rises to a plateau at the required ratio of 1 : 1 for *ca.* 70% hydrogenation. These results show that in the complex, protonation is fast compared with the normally rapid dimerisation of the ethyl cinnamate radical-anion. Complexation would also be expected to slow the dimerisation by slowing the diffusion of the intermediates.

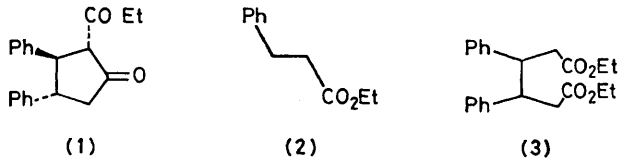
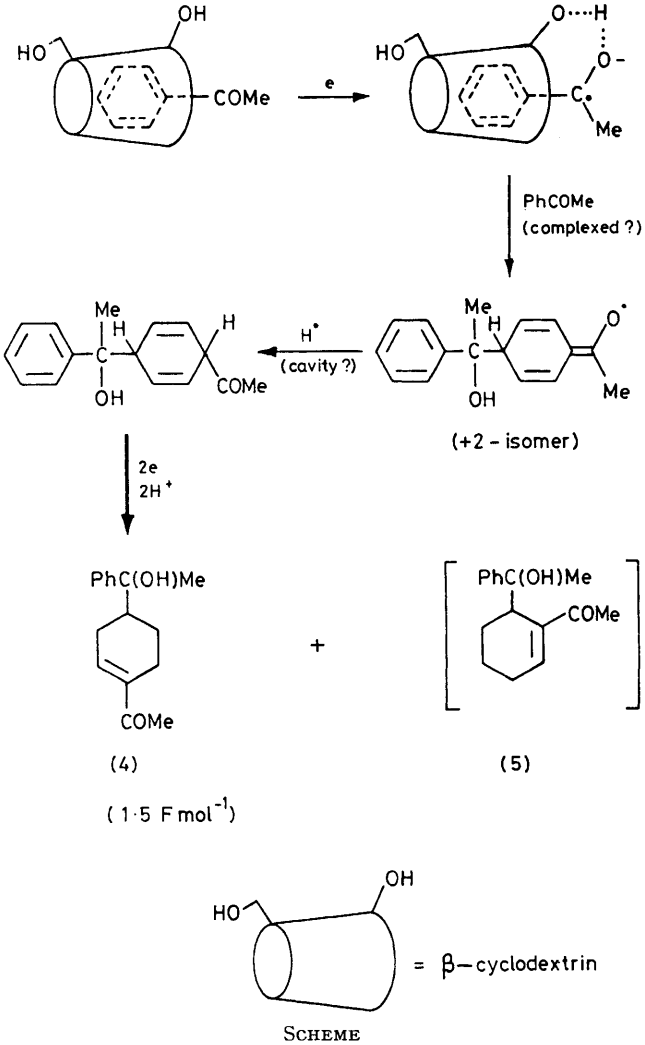



TABLE 2. Proton donation and stereochemistry of pinacolisation.[a]

| Substrate | Proton source | Pinacols (±) : meso | % yield |
|---|---|---|---|
| PhCHO | none[b] | 14 : 1 | 60 |
| | $H_2O$[c] | 3 : 1 | 60 |
| | $CrCl_3.6H_2O$[d] | 1 : 1 | 50 |
| | glucose[e] | 2 : 1 | 85 |
| [PhCHO–β-CD complex] | —[b] | 1 : 3 | 80 |
| $Ph_2CO$ | $H_2O$[c] | diphenyl-methanol only | 80 |
| [$Ph_2CO$–β-CD complex] | —[b] | diphenyl-methanol only | 80 |

[a] Controlled-potential electrolysis, Hg cathode, DMF solution, substrate *ca.* 0·1 mol $dm^{-3}$, *ca.* 20 °C. [b] $Bu_4NBF_4$ (0·15 mol $dm^{-3}$). [c] *Ca.* 0·1 mol $dm^{-3}$. [d] $NaClO_4$ (0·15 mol $dm^{-3}$). [e] *Ca.* 7 mol. equiv.

These concepts are verified and extended in an explanation of the effects of complexation on the electroreduction of benzaldehyde, benzophenone, and acetophenone. The results for reduction of the benzaldehyde and benzophenone







SCHEME

complexes are displayed in Table 2. The predominant effect of β-cyclodextrin is as an efficient proton donor. Benzophenone, which pinacolises only in strongly acidic solution or in the presence[4] of $Cr^{III}$, is reduced cleanly to benzhydrol with and without complexation. The stereochemistry of the benzaldehyde reduction to hydrobenzoin is affected profoundly. The nature of the proton source causes variations in the (±) to *meso* ratio but the (±) isomer always predominates except for reduction at −1·24 V of the β-cyclodextrin complex which gives a high yield of predominantly the *meso* pinacol. It is noteworthy that the benzaldehyde and benzophenone complexes both have a stoicheiometry of 1 : 2 (β-CD). This is an indication that the guest molecules may not inhabit the cavity of a single β-cyclodextrin molecule but may be situated in channels between associated β-cyclodextrins.[5] This type of non-stoicheiometry is often found in the crystalline state. The carbonyl compounds are, nevertheless, in a highly protic environment and, it should be noted, a chiral environment.

Acetophenone, on the other hand, forms in DMF solution a 1 : 1 complex with β-cyclodextrin with the aromatic ring inside the apolar cavity of the torus (see the Figure). Its behaviour on cathodic reduction at −1·34 V is strikingly different; a previously unreported coupling takes place to give, in 90% yield, a 1 : 1 mixture of the isomers (**4**) and (**5**). Similar coupling has been observed[6] for 1-acetylnaphthalene but appears to be unprecedented for acetophenone. Structures (**4**) and (**5**) were satisfactorily characterised by mass spectrometry and i.r. and $^1H$ n.m.r. spectroscopy.

A key observation is that only 1·3 F $mol^{-1}$ are consumed and this prompts the suggestion of a mechanism (formally 1·5 F $mol^{-1}$) in which hydrogen abstraction is involved (Scheme). It is tempting to speculate that abstraction would be promoted in the apolar cavity of complexed intermediates involving either the secondary hydrogen atoms of the torus or hydrogens of co-complexed organic solvent molecules.

We are grateful to the Royal Society and the University of London Central Research Fund for equipment grants and to the S.R.C. for a postdoctoral fellowship (to C. Z. S.). N.m.r. spectra were measured by the ULIRS WH-400 N.M.R. Service at Queen Mary College.

(*Received, 25th February* 1981; *Com.* 218.)

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