Redox Enzyme Models. Catalysis of the Cathodic Cleavage of Benzyl Esters *via* Complexation with a Substituted β-Cyclodextrin

By CARMEN Z. SMITH and JAMES H. P. UTLEY*
(*Department of Chemistry, Queen Mary College, Mile End Road, London* E1 4NS)

Summary β-Cyclodextrin substituted at the 6-position with an electrophore (*o*-benzoylbenzoate) complexes with benzyl esters and promotes their cleavage at the relatively modest reduction potential of the electrophore.

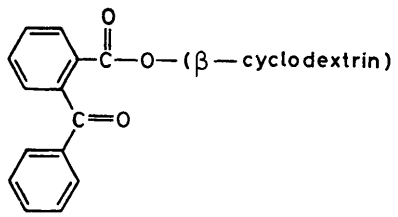
β-CYCLODEXTRIN is a macrocycle which consists of seven glucose units joined by α-(1,4)-glycosidic linkages. A variety of organic compounds may be included within the torus and, for esters, such complexation may result in catalysis of hydrolysis reactions. The peripheral hydroxy-groups are involved in such catalysis and consequently the guest–host complexes have often been used as models for hydrolytic enzymes.[1] We have shown[2] recently that complexation may profoundly alter the course of the reaction of electroactive substrates complexed with β-cyclodextrin. Osa and his co-workers[3] have described an example of enhancement of charge-transfer complexation between species included with γ-cyclodextrin. We are prompted to report on experiments which show that benzyl esters included within a modified β-cyclodextrin may be cleaved electrochemically at the modest potential associated with an electron-accepting group (electrophore) chemically bonded to the periphery. The net process corresponds to catalysis of cleavage and is a consequence of complexation; this is the first observation of such an effect.

Three electrophores, *o*-benzoylbenzoate, *p*-benzoylbenzoate, and anthracene-9-carboxylate, were attached *via* ester linkages to the 6-position of β-cyclodextrin by reaction in pyridine between the relevant acid chloride and β-cyclodextrin. The modified β-cyclodextrins were isolated as solids and recrystallised from water. I.r. spectroscopy indicated the formation of the esters and in each case the attachment of only one substituent per β-cyclodextrin molecule was established by integration of the ^{1}H n.m.r. spectra.

Cyclic voltammetry at a mercury cathode in *NN*-dimethylformamide (DMF) –Bu_4NBF_4 (0·1 M), at 500 mV s^{-1}, showed that the electrochemical properties of the modified β-cyclodextrins were essentially those of the attached electrophores. The *o*- and *p*-benzoylbenzoate substituted β-cyclodextrins gave one-electron quasi-reversible reduction at −1·25 V (*vs.* Ag/AgI) and −1·14 V, respectively. Reduction of the corresponding methyl esters and of the ethylene glycol monoesters was reversible, with E_p (*ortho*) −1·12 V. The reduction peak potential for the anthracene-9-carboxylic ester of β-cyclodextrin was the same, −1·30 V, as that of the corresponding methyl ester; in the latter case one-electron reduction was observed which was irreversible at scan rates of up to 300 V s^{-1}.

The benzoylbenzoate substituted cyclodextrins are of particular interest because their reduction is quasi-reversible and interaction with complexed 'guest' molecules may be monitored by changes in cyclic voltammetric behaviour.

β-Cyclodextrin formed 1 : 1 complexes with benzyl formate and benzyl acetate; the complexes were characterised by



(1)

^{1}H n.m.r. spectroscopy as previously described.[2] Benzyl s-butyrate formed a 2 : 1 complex (β-cyclodextrin : ester) and benzyl *trans*-4-t-butylcyclohexanecarboxylate did not complex. Benzyl formate and benzyl acetate were not easily reduced; cyclic voltammetry in DMF or dimethyl sulphoxide (DMSO) showed reduction to be irreversible, with E_p −1·63 V (*vs.* Ag/AgI) and −2·2 V, respectively. However, the addition of benzyl formate or benzyl acetate caused a significant change in the cyclic voltammetric behaviour of the *o*-benzoylbenzoate substituted β-cyclodextrin (**1**). The experiment which involved benzyl formate is detailed in the Figure; benzyl acetate caused similar changes. The key

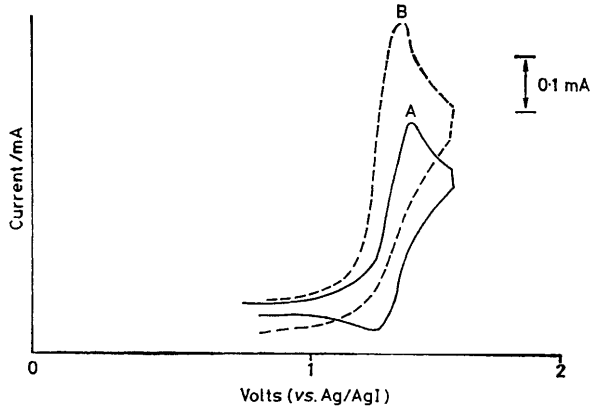


FIGURE. Cyclic voltammetry of *o*-benzoylbenzoate modified β-cyclodextrin (**1**) [DMSO–Bu_4NBF_4 (0·1 M), 0·3 V s^{-1}]; A, *ca.* 10^{-3} M; B, with benzyl formate.

feature is that as further amounts of benzyl ester were added reduction of the electrophore became irreversible and the peak current increased to *ca.* twice the initial value; about a fourfold molar excess of benzyl ester was needed to achieve this. This is compelling evidence for either reaction or electron-transfer between the reduced electrophore and the complexed benzyl ester. Control experiments with benzyl esters and the methyl- or ethylene-glycol monoesters of *o*-benzoylbenzoic acid, with and without added 'free' cyclodextrin, showed that attachment of the electrophore to the cyclodextrin was necessary for the observation of the interaction described above. β-Cyclodextrin itself was found to act as an efficient proton donor and, in its presence,

methyl *o*-benzoylbenzoate gave two-electron irreversible reduction. Furthermore, the benzyl esters with bulky carboxylate functions (s-butyl- and *trans*-4-t-butylcyclohexanecarboxylate), did not complex well and did not cause changes in the voltammetric behaviour of the modified cyclodextrins.

Whatever the nature of the interaction (reaction or electron-transfer) the steric requirements are relatively precise because the cyclic voltammetric behaviour of the *p*-benzoylbenzoate substituted cyclodextrin is essentially unchanged on addition of benzyl formate or benzyl acetate.

Controlled potential electrolysis, in DMF at $-1{\cdot}3$ V, of the *o*-benzoylbenzoate substituted cyclodextrin (8×10^{-2} M) in the presence of a slight excess of benzyl formate or benzyl acetate gave 1 F mol^{-1} reduction (based on the cyclodextrin). When benzyl formate or benzyl acetate was added to a solution of the modified cyclodextrin under electrolysis the current increased to *ca.* twice the initial value, as for the cyclic voltammetric experiment, but eventually only *ca.* 1 F mol^{-1} was consumed. Acetic acid was added at intervals to maintain neutral pH.

The products, identified by g.c.–m.s. and by g.c. comparison with authentic samples, were, in each case, benzyl alcohol (20% and 76% current yield from, respectively, benzyl acetate and benzyl formate) and 3-phenylphthalide (*ca.* 20% and 26%, respectively). These yields assume that the products are formed by 1e reduction; for 2e reduction they would be halved. The phthalide is the product of cathodic reduction of *o*-benzoylbenzoate esters and is the result of lactonisation of the first formed alcohol. Separate electrolysis of the modified β-cyclodextrin gave the phthalide in 75% yield after 2 F mol^{-1} reduction. For the modified β-cyclodextrin–benzyl ester system the difference in behaviour in the controlled potential electrolysis and the cyclic voltammetry experiments (reaction proceeded to 1 F mol^{-1} in the former case) may be a consequence of the different time scales required for reaction. In the longer time scale of preparative reduction, cleavage of the electrophore competes with reaction with the benzyl ester.

Several pathways have been observed for the reduction of esters[4] and reductive cleavage to alcohol and aldehyde is one of them; cathodic reduction of benzylic esters usually results in cleavage to benzylic radicals and carboxylate anion, so the reactions described here are unusual in that respect. Accelerated hydrolysis, promoted by the basicity of the radical anion of the electrophore, is a possibility, but is unlikely in view of the fact that the *p*-benzoylbenzoate substituted cyclodextrin does not catalyse cleavage of complexed benzyl acetate in voltammetric or preparative experiments. Furthermore, reduction of methyl *o*-benzoylbenzoate in the presence of β-cyclodextrin and benzyl acetate did not yield benzyl alcohol. A complete description of the mechanism requires information about the orientation of the substrate within the cavity of the cyclodextrin, but it must take into account the necessary proximity of the electroactive group and the ester, and the fact that cleavage is not catalysed for those esters which, for steric reasons, complex poorly or not at all.

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