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A Novel Electrochemical Oxidation Reactions Utilizing Cyclodextrins. Anodic Oxidation of Indole–Cyclodextrin–Alcohol System

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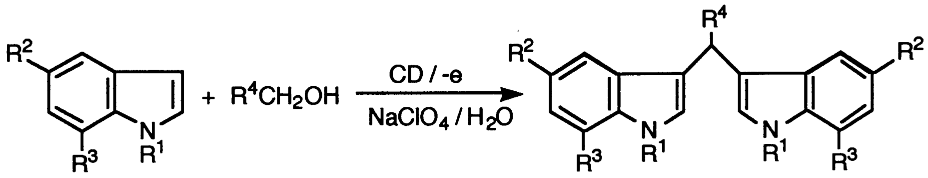
The anodic oxidation of indoles (**1**) and alcohols (**2**) in the presence of cyclodextrins gave diindolylmethanes in good yields. Cyclic voltammetry and macro scale electrolyses showed that the reaction was initiated by the oxidation of **2** with an oxidation potential higher than that of **1**.

Electrochemistry is a powerful and convenient tool for the inversion of polarity (Umpolung) of organic molecules, and a variety of reactions which can not be realized by conventional organic chemistry such as reactions between two nucleophiles or two electrophiles have been developed with this tool.[1)] In most of the electrochemical reactions, the initial step is an anodic oxidation (cathodic reduction) of a substrate having a more negative (positive) potential and the resulting electrophile (nucleophile) reacts with the other substrate with a less negative (positive) potential to give products. However, reports on the electrochemical reactions where the initial oxidation (reduction) of substrates having a less negative (positive) oxidation (reduction) potential appears to occur are rare.[2)] We now report the anodic oxidation of indoles (**1**) and alcohols (**2**) to give diindolylmethane derivatives (**3**) in the presence of cyclodextrins (CD) (eq 1).[3)] Under this situation, more labile substrates **1** are stabilized by inclusion into CDs and the oxidation of the more stable substrates **2** takes place preferentially.



(1)

1 **2** **3**

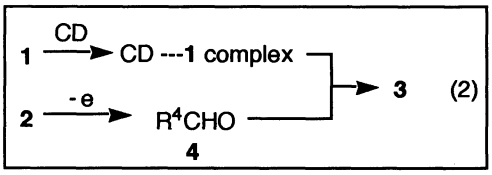
We first examined the effect of added CDs in the anodic oxidation of indole **1a** and ethanol **2b**. Typical procedure for the electrolysis is as follows: A mixture of **1a** (1 mmol), **2b** (5 ml), and a CD (1.2 mmol) in 35 ml of 0.2 M $NaClO_4$ was placed in one chamber of an H-shaped divided cell equipped with two platinum electrodes (50 × 100 mm), and 0.2 M $NaClO_4$ (40 ml) was placed in the other chamber. The system was subjected to constant current electrolysis (0.2 mA/cm^2) at room temperature. After a 6–8 F of electricity per mol of **1a** had been passed, the reaction mixture in the anodic chamber was extracted with AcOEt (3 × 50 ml), and the combined organic solution was dried over $MgSO_4$. After removal of the solvent, the residue was column-chromatographed on silica-gel with *n*-hexane-EtOAc (4:1) to give a diindolylmethane derivative **3b** ($R^1 = R^2 = R^3 = H$, $R^4 = Me$). The yields of **3b** in the presence of CDs were in the order of 2, 6-di-O-methyl-β-cyclodextrin (DMCD) (86%) > β-CD (72%) > γ-CD (35%) > α-CD (26%). Therefore, the anodic oxidation of various **1** and **2** were carried out under the reaction condition described above with DMCD. In all cases examined, the corresponding diindolylmethanes **3** were obtained in good to excellent yields (Table 1).

In the present reaction the initial step should be the anodic oxidation of **2**, because the products **3** are also available from the addition of **1** and aldehydes (**4**).[4] The cyclic voltammetry showed that the anodic peak current of **1** significantly decreased with increase in the amount of added DMCD (Fig. 1). This indicates that DMCD can incorporate **1** and effectively prevent the anodic oxidation of **1** from occurring. When the electrolysis of **1** and **2** was performed under similar conditions but without CDs, only a tarry material was obtained. The present anodic oxidation process thus can be expressed by eq 2. After the formation of an electrochemically inactive inclusion-complex of **1** with CD, the anodic oxidation of **2** having a less negative potential occurs preferentially, and the resulting aldehydes **4** are attacked by **1** to give the products **3**.

Table 1. Anodic Oxidation of **1**, **2**, and DMCD

	Product	Yield (%)a)
3a	$R^1 = R^2 = R^3 = R^4 = H$	74
3b	$R^4 = Me, R^1 = R^2 = R^3 = H$	86
3c	$R^4 = Et, R^1 = R^2 = R^3 = H$	42
3d	$R^1 = Me, R^2 = R^3 = R^4 = H$	88
3e	$R^2 = Me, R^1 = R^3 = R^4 = H$	70
3f	$R^3 = Me, R^1 = R^2 = R^4 = H$	89

a) Isolated yields based on **1**.



(2)

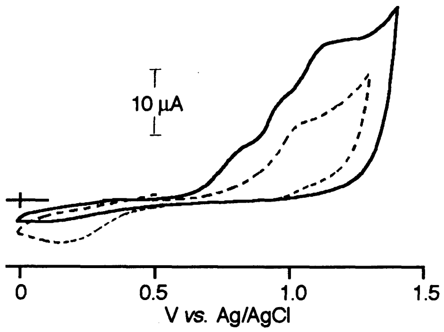


Fig. 1. Cyclic Voltammograms of **1a** (1 mM). (——) in the absence of DMCD, (----) in the presence of DMCD (100 mM). Conditions: solvent, water; supporting electrolyte, $NaClO_4$ (0.1 M); voltage sweep rate, 100 mV/s; anode, Pt disk electrode.

With conventional electrochemical procedures, it is difficult to control the order of the reactivity between two nucleophiles.[2] Therefore, the application of the present inclusion chemistry to the anodic oxidation of other combinations of nucleophiles may enable to promote the development of a new type of electroorganic reaction. Generalization and application of this unique electrochemical method with CD systems are a matter of continuing concern in this laboratory.

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References

1) T. Shono, "Electroorganic Chemistry as a New Tool in Organic Synthesis," Springer-Verlag, Berlin (1984).
2) To our knowledge, two methods for such reactions have been developed so far: one is the utilization of the difference in the adsorptivity between aromatic compounds and non-aromatic compounds on an anode (see Ref. 2a), and the other is silylation of a substrate, which can lower the oxidation potential (see Ref. 2b). These methods, however, are highly substrate-dependent. a) L. Eberson and K. Nyberg, *Tetrahedron*, **32**, 2185 (1976); T. Takanami, A. Abe, K. Suda, H. Ohmori, and M. Masui, *Chem. Pharm. Bull.*, **38**, 2698 (1990); b) J. Yoshida, T. Maekawa, T. Murata, S. Matsunaga, and S. Isoe, *J. Am. Chem. Soc.*, **112**, 1962 (1990); K. Suda, K. Hotoda, J. Watanabe, K. Shiozawa, and T. Takanami, *J. Chem. Soc., Perkin Trans. 1*, **1992**, 1283.
3) Several electrochemical reactions utilizing cyclodextrin systems have been reported: T. Matsue, C. Tasaki, M. Fujihira, and T. Osa, *Bull. Chem. Soc. Jpn.*, **56**, 1305 (1983); K. Kano, K. Mori, B. Uno, M. Goto, and T. Kubota, *J. Am. Chem. Soc.*, **112**, 8645 (1990); and references cited therein.
4) A. Kamal and A. A. Qureshi, *Tetrahedron*, **19**, 513 (1963).

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