

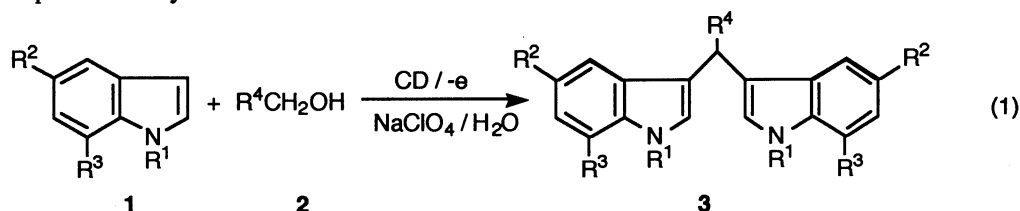
A Novel Electrochemical Oxidation Reactions Utilizing Cyclodextrins.
Anodic Oxidation of Indole–Cyclodextrin–Alcohol System

Kohji SUDA and Toshikatsu TAKANAMI

Meiji College of Pharmacy, Nozawa, Setagaya, Tokyo 154

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.



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 NaClO₄ was placed in one chamber of an H-shaped divided cell equipped with two platinum electrodes (50 × 100 mm), and 0.2 M NaClO₄ (40 ml) was placed in the other chamber. The system was subjected to constant current electrolysis (0.2 mA/cm²) 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 MgSO₄. 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** (R¹ = R² = R³ = H, R⁴ = 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**.

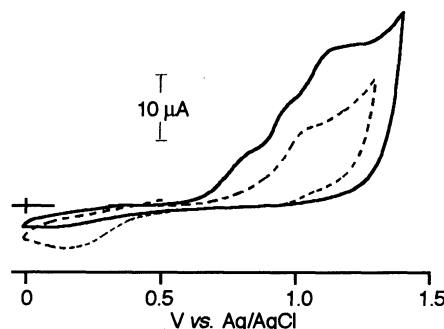
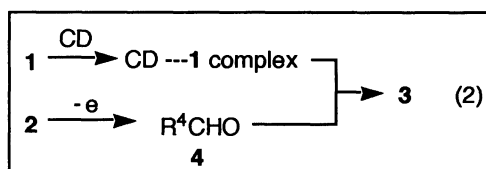


Fig. 1. Cyclic Voltammograms of **1a** (1 mM). (—) in the absence of DMCD, (---) in the presence of DMCD (100 mM). Conditions: solvent, water; supporting electrolyte, NaClO₄ (0.1 M); voltage sweep rate, 100 mV/s; anode, Pt disk electrode.

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.

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

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).

(Received June 24, 1994)