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Synthesis of a β-cyclodextrin derivate and its molecular recognition behavior on modified glassy carbon electrode by diazotization

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ABSTRACT

A novel β-cyclodextrin (β-CD) derivative containing mono-phenylamino (MPA-β-CD) was newly synthesized by classical Mitsunobu reaction in good yield, and its structure has been confirmed by ^{1}H NMR, ^{13}C NMR and electrospray ionization mass spectra. The compound MPA-β-CD was immobilized onto glassy carbon electrode (GCE) by diazotization, and with this modified electrode the binding behavior of MPA-β-CD for ferrocene (Fc) was investigated qualitatively, and the comparison of differential pulse voltammetry before and after immersion in ferrocene solution indicated that the MPA-β-CD immobilized GCE exhibited the molecular recognition behavior between β-CD and ferrocene.

1. Introduction

Cyclodextrin(CDs),[1]a class of cyclic oligosaccharides with 6–8 D-glucose units, gained prominence in recent years in diverse fields, such as molecular reactors,[2]drug delivery systems,[3]artificial enzymes,[4]catalysis,[5] molecular machines,[6]or supramolecular sensing.[7] Cyclodextrins, in their native state, are rigid molecules, and offer limited utility in terms of size, shape, and availability of chemically useful functional groups. Cyclodextrins have thus been called structural and functional straightjackets.[8] Consequently, in the past few decades a great deal of effort has been directed toward conversion of hydroxyl groups of cyclodextrins to other useful functional groups.[9–12]

The modification of cyclodextrins offers both enormous opportunities and challenges for chemists. Among all the possible types of modifications, Monomodifications of cyclodextrins to give selectively 2-, 3-, or 6-substituted product is a challenging task because of the number of hydroxyl groups that can potentially react with the incoming reagent.[13,14] Many researchers have been accustomed to prepare monosubstituted cyclodextrins derivatives by the tosylation of native cyclodextrins extensively,[10,15,16,17] However, by this method, the desired products are painstakingly separated out from other isomers and homologues by chromatographic methods and always in the poor yield. A way to overcome this problem is to protect the primary side of CDs by reversible silylation, because the protected compounds can be readily purified by flash chromatography. Consequently, here, we report a monosubstituted β-Cyclodextrin derivative with mono-phenylamino group by Mitsunobu reaction in good yield.

In the former work, the studies on the abilities of native or modified cyclodextrin were extensively carried out in some special kind of solutions by differential circular dichroism spectroscopy or spectrofluorometric titration in combination with computational methods.[15,18,19] Simultaneously, The functionalization of surfaces is of considerable interest in applications, such as sensors and biocompatible surfaces. Consequently, many researchers have successfully prepared a variety of mercaptocyclodextrin derivatives and studied the host-guest molecular recognition through their immobilization on gold surfaces, which was achieved by the oxidative adsorption of thiols covalent S–Au bond.[20–23]Recent reports showed that the electrochemical reduction of aryl diazonium salts is proven to be an excellent method to irreversibly attach molecules to some special conducting substrates.[24] Firstly, it avoids the use of oxidative conditions, which can lead to the detrimental oxidation of the carbon substrate, moreover because it allows the presence of selected functional groups on the aryl groups. Lastly, diazonium salts are easily and rapidly prepared in one step from a wide range of anilines and its reduction takes place within seconds to minutes. However, until now, there have not been literatures about the studies on the electrochemical immobilization of β-CD on electrode surface by diazotizatin.

In this work, we demonstrate for the first time the synthesis of a novel β-cyclodextrin derivative containing one phenylamino by

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Mitsunobu reaction, at the same time, we prepared a MPA-β-CD-modified electrode by the electrochemical reduction of aryl diazonium salts on glassy carbon electrode. Furthermore, with the modified electrode we investigated qualitatively the binding behavior of MPA-β-CD for ferrocene, which was detected by differential pulse voltammetry in Fc solution.

2. Results and discussion

2.1. Synthesis

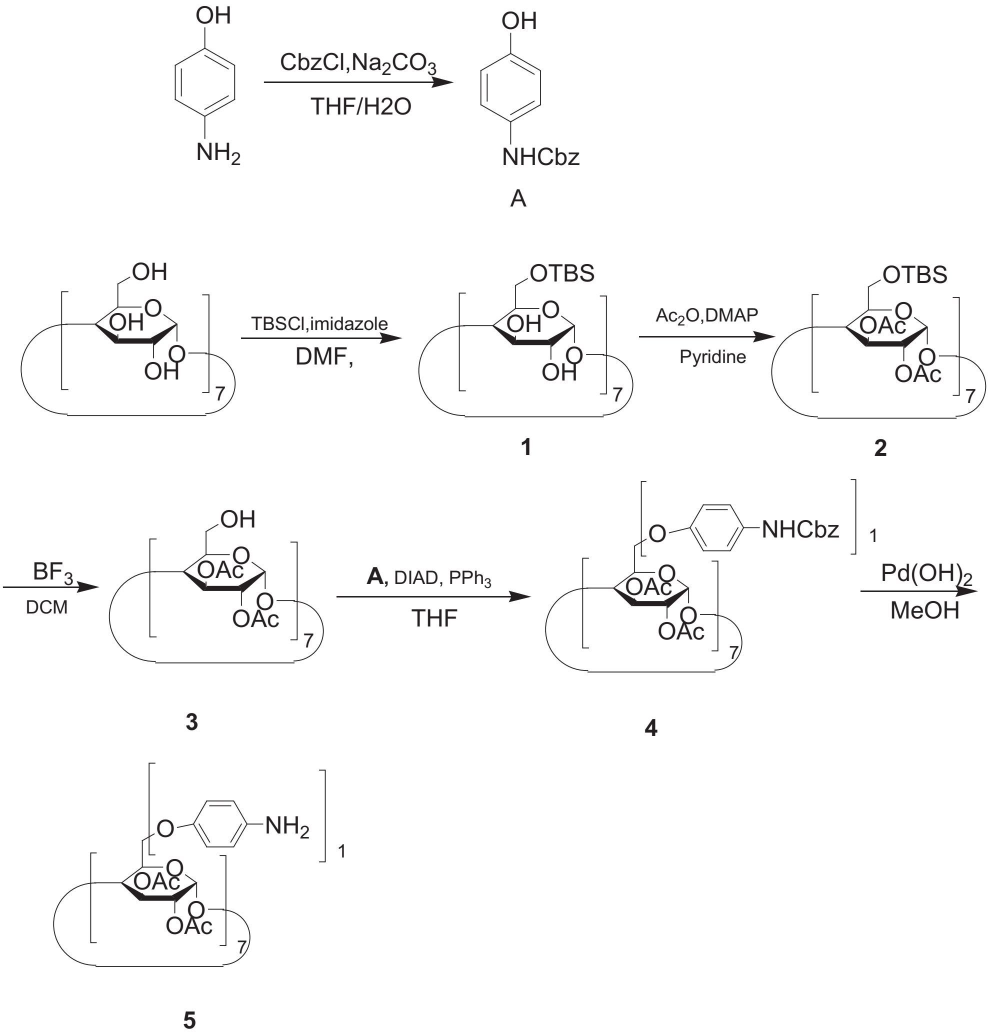
The synthesis of MPA-β-CD was shown schematically in Scheme 1. Hydroxyl groups present at the 2-, 3-, and 6-positions compete for the reagent and make selective modification extremely difficult, and thereby, the synthesis of monofunctionalization of native cyclodextrin involves in sequence (1) protection of the primary side with silyl groups, (2) protection of the secondary side with acetyl groups, (3) desilylation of the primary side, (4) Mitsunobu reaction, monosubstitution of the primary hydroxyl group of β-cyclodextrin was achieved. Although the process was slightly long, the purification of every step reaction was easily achieved by flash chromatography. In this strategy, each reaction is carefully chosen to give a high yield and the products were easily separable and purifiable by flash column chromatography.

During the course of the preparation of the target compound **5**. The Mitsunobu reaction is a key step. In recent years, the scope of the Mitsunobu reaction in natural products synthesis has been extensively discussed and reviewed.[25]The application of this classical reaction is the synthesis of some types of ethers.[26]In this nucleophilic substitution reaction, we tried a variety of reaction conditions, such as ratio of the reactants, reaction time, the adding sequence, and finally we got the optimal condition as described in the Experiment section. The Monosubstitution was in good yield under the optimal condition. More importantly the selectivity of this reaction was well controlled according to the final product.

The special structure of the target compound MPA-β-CD was confirmed by ^{1}H NMR, ^{13}C NMR, and ESI-Mass. Judging by the ration of the aromatic protons in the aminophenoxy group at 7.14–7.40 and the proton of β-cyclodextrin at the C-5, only one hydroxyl group of β-cyclodextrin at the 6-position was substituted by aminophenoxy group. In addition, ESI-Mass spectra also showed the presence of monosubstitution.

2.2. Immobilization of MPA-β-CD on GCE

The formation of MPA-β-CD diazonium was shown in Scheme 2, which occurred via diazotization of MPA-β-CD to form the aryl diazonium in aqueous acidic medium. The diazonium cations generated in situ from MPA-β-CD was investigated by cyclic



Scheme 1. Schematic representation of MPA-β-CD.