

# Ferrocene- $\beta$ -Cyclodextrin Conjugates: Synthesis, Supramolecular Behavior, and Use as Electrochemical Sensors

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**Abstract:** Ferrocene with a  $\beta$ -cyclodextrin unit bound to one or both cyclopentadienyl rings through the secondary face were conveniently synthesized by regiospecific copper(I)-catalyzed cycloaddition of 2-*O*-propargyl- $\beta$ -cyclodextrin to azidomethyl or bis(azidomethyl)ferrocene. The supramolecular behavior of the synthesized conjugates in both the absence and presence of bile salts (sodium cholate, deoxycholate, and chenodeoxycholate) was studied by using electrochemical methods (cyclic and differential pulse voltammetry), isothermal titration calorimetry,

and NMR spectroscopy (PGSE, CPMG, and 2D-ROESY). These techniques allowed the determination of stability constants, mode of inclusion, and diffusion coefficients for complexes formed with the neutral and, in some cases, the oxidized states of the ferrocenyl conjugates. It was found that the ferrocenyl conjugate with one  $\beta$ -cyclodextrin unit forms a redox-controllable head-to-head homodimer in aque-

ous solution. The ferrocene-bis( $\beta$ -cyclodextrin) conjugate is present in two distinguishable forms in aqueous solution, each one having a different half-wave oxidation potential for the oxidation of the ferrocene. By contrast, only one distinguishable form for the oxidized state of the ferrocene- $\beta$ -cyclodextrin conjugate is detectable. The redox-sensing abilities of the synthesized conjugates towards the bile salts were evaluated based on the observed guest-induced changes in both the half-wave potential and the current peak intensity of the electroactive moiety.

**Keywords:** bile salts • cyclodextrins • ferrocene • sensors • voltammetry

## Introduction

Ferrocene (Fc)-containing compounds with molecular recognition binding sites have received much attention in recent years due to the possibility of building redox-switching or -sensing systems of a molecular or supramolecular nature

that can be controlled through the application of external stimuli.<sup>[1-3]</sup> In addition to its favorable electrochemical properties, Fc (unlike other metallocenes) is stable in aerobic aqueous and organic media, as well as under most of the chemical conditions normally used for synthesis.<sup>[1]</sup> These features make Fc a good building block for the construction and design of redox molecular switches and sensors by conjugation with molecules involved in molecular recognition processes. In this respect, most of the research has been concerned with the development of redox receptors for anions<sup>[2]</sup> and cations.<sup>[3]</sup> Electrochemical sensing for neutral organic molecules has been studied less extensively and, in particular, electrochemical recognition in aqueous solution has been studied the least.<sup>[1]</sup>

Cyclodextrins (CDs) are known to form inclusion complexes in aqueous solution with a large variety of organic molecules of hydrophobic nature.<sup>[4]</sup> Fc and Fc derivatives are good guests for  $\beta$ -cyclodextrin ( $\beta$ -CD), forming stable 1:1 complexes in water by penetrating the internal hydrophobic cavity of the host  $\beta$ -CD. A simple electron transfer reaction, such as the loss of an electron from the Fc guest, modifies its charge and electronic distribution and thus leads to very significant changes in the nature of the inter-

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