Electrochemical evidence for inclusion complexes of thiotriazinone with cyclodextrins

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The formation of the inclusion complexes of thiotriazinone (TTZ) with α-cyclodextrin and β-cyclodextrin was studied by cyclic voltammetry and 1H-NMR. The oxidation and reduction reactions specific to thiotriazinone compounds are irreversible, diffusion controlled processes, and occur in a complex mechanism. The stable inclusion of thiotriazinone in β-cyclodextrin is proved by the significant changes of redox activity characteristic for TTZ and good electrochemical stability of the complex. Moreover, the present study demonstrates that β-cyclodextrin can serve as a carrier system, since the TTZ molecule can be gradually released from the inclusion complex with time.

1. Introduction

The chemistry of 1,2,4-triazinone ring derivatives has attracted an increasing amount of attention due to the intrinsic interest in their structures and their diverse applications in antibacterials,1,2 antidepressants, antiviral drugs,3 pesticides and herbicide dyes.4 Moreover, the chemistry of sulphur-containing 1,2,4-triazole ring systems with different biological activities has been well studied and comprehensively reviewed by Shaker.6 1,2,4-Triazin-2-methyl-6-hydroxy-3-thio-5-one (TTZ) is widely used in the production of cephalosporin pharmaceutical intermediates, such as ceftriaxone sodium. Only a few papers available in the literature have reported its effects as an antibacterial agent and human leukocyte elastase inhibitor.7

Since sulphur groups are rapidly oxidized by biological oxidants within physiological fluids, the oxidation of sulphur-containing compounds such as TTZ is a potential problem and thus, new strategies for the stabilization of pharmacological species must be developed. Cyclodextrin complex has been successfully used to improve the chemical stability, solubility and bioavailability of a numerous compounds. Moreover, through appropriate chemical architecture design, toxic compounds can be transformed into pharmacologically active species. α- and β-cyclodextrin are macrocycles (Scheme 1B) composed of six or seven glucopyranose units, respectively attached by α,1,4-linkages.8 Their ability to include various guest molecules into their hydrophobic cavities, generating stable inclusion complexes has been exploited by our group.9,10 The formation of inclusion complexes could affect or influence the properties of the guest molecules and, therefore, the variation of the delivery system can be a method to improve/change the chemical behavior of the guest.

Scheme 1. (A) Structures of the four isomers of thiotriazinone: TTZ1, TTZ2, TTZ3 and TTZ4. (B) Structure of α-cyclodextrin (when x = 6) and β-cyclodextrin (when x = 7).