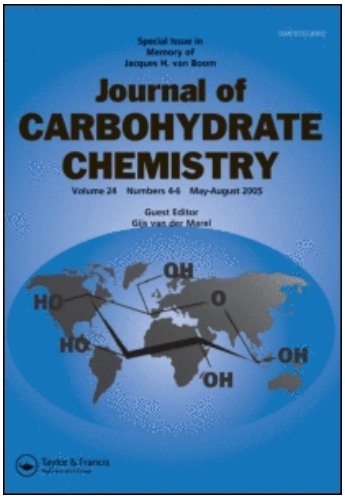

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Chiral Discrimination of Tolterodine Tartrate by Modified Cyclodextrins

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The chiral discrimination ability of two β-cyclodextrin derivatives (hosts) having a flexible pyrrolidinylidenesulfamido-appended moiety has been studied for the enantiomers of tolterodine tartrate (guest). Quenching of the fluorescence intensities of guests was observed in the presence of hosts. The S-enantiomer of the tolterodine tartrate was better recognized by these hosts. Enantioselectivity factors (α) and association constants (K_s) of the host–guest complexes were calculated.

Keywords Tolterodine tartrate, β-Cyclodextrin, Fluorescence intensity, Association constant

INTRODUCTION

(R)-Tolterodine tartrate, (*R*)-*N*,*N*-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenyl-propanamine L-hydrogen tartrate, is a new, potent, and competitive muscarinic receptor antagonist for the treatment of urge incontinence and other symptoms of unstable bladder. Tolterodine tartrate acts by relaxing the smooth muscle tissue in the wall of the bladder by blocking cholinergic receptors. After oral administration, tolterodine is metabolized in the liver resulting in the formation of the 5-hydroxymethyl derivative, a major pharmacologically active metabolite.[1] The number of chiral entities used in the pharmaceutical

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market as starting materials, intermediates, and prescribed drugs continues to increase each year. As a result of the difference in biological activity of individual enantiomers, rapid chiral analysis of these chemicals is extremely important in pharmaceutical,[2] medical, and biological fields.[3]

In continuation of our interest in developing modified cyclodextrins as chiral discriminating hosts,[4] we report herein the chiral discrimination of the enantiomers of tolterodine tartrate by pyrrolidinylidenesulfamido-modified β-cyclodextrins by using fluorescence as a signaling option.

The inclusion complexes of pharmaceutical compounds with cyclodextrins (CDs) results in altered biological and physicochemical properties[5] with numerous practical applications in pharmaceutical sciences and analytical to synthetic chemistry.[6] CDs are chiral in nature and this property renders them the capability of enantiomeric discrimination due to the formation of diastereomeric complexes.[7] The chiral recognition by CDs has since been widely investigated and CDs are now used as chiral selectors in many of the chromatographic techniques.[8]

CDs are cyclic oligosaccharides, involving six or more D-glucopyranose units, which form truncated cone-shaped molecules with a hydrophobic cavity. They form inclusion complexes with a variety of organic compounds in aqueous solution and are largely studied for their host–guest interaction properties and as building blocks for supramolecular structures.[9] Though CDs can be used for chiral discrimination, modification of one of the OH groups of CDs leads to increased chiral discrimination due to more specific interaction between the host and the guest.[10] For example, it is shown that modified CDs bearing appended moieties such as sulfonylpyrrolidinylidene moiety discriminate chiral drug molecules in aqueous solution with fluorescence spectroscopy.[4] It is observed from the literature that the sulfonyl group containing cyclodextrins acts as chemosensors through molecular recognition by discriminating the enantiomers of various guest molecules.[4,11] Since chiral discrimination by these cyclodextrin derivatives appeared to be the general property, these sulfonyl modified β-CD derivatives were attempted in the present investigation for the chiral discrimination of enantiomers of tolterodine tartrate. The mechanism of molecule detection by these modified cyclodextrins is shown in Figure 1 as explained by Ikeda et al.[12] The "self-inclusion

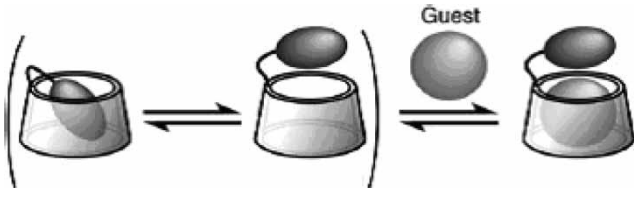

Figure 1: Inclusion of phenomenon of a guest into the appended moiety attached cyclodextrin.

state," in which the appended moiety is located in the interior of the CD cavity, is usually the major conformation, if a spacer is long enough for self-inclusion. An "induced-fit" conformational change of the appended moiety-modified CD occurs in association with accommodation of the guest, which displaces the appended moiety from inside to the outside of the CD cavity, generating the "non–self-inclusion state."

RESULTS AND DISCUSSION

A systematic study of the native β-cyclodextrin **1** and modified cyclodextrins **2** and **3** was undertaken for enantio recognition of the enantiomers of tolterodine tartrate (Fig. 2).

The fluorescence spectral data of the guests in the presence of different compositions of the hosts in 0.1 M tetraborate buffer were evaluated. Both the enantiomers experienced quenching of fluorescence intensity upon addition of various concentrations of the hosts **1**, **2**, and **3**. The hosts **2** and **3** showed enantioselectivity in fluorescence quenching of the enantiomers, whereas host **1** had not discriminated the enantiomers of the tolterodine tartrate.

The quenching in the fluorescence intensity of the S-enantiomer of the tolterodine tartrate was higher than the R-enantiomer in the presence of **2** and **3**. The fluorescence spectra of the enantiomers in 0.1 M tetraborate buffer (pH 7.2) in the absence and presence of **2** and **3** are shown in Figure 3. The fluorescence intensity of the guest decreases with increasing host concentration. The changes of fluorescence intensity induced by the hosts indicated that the

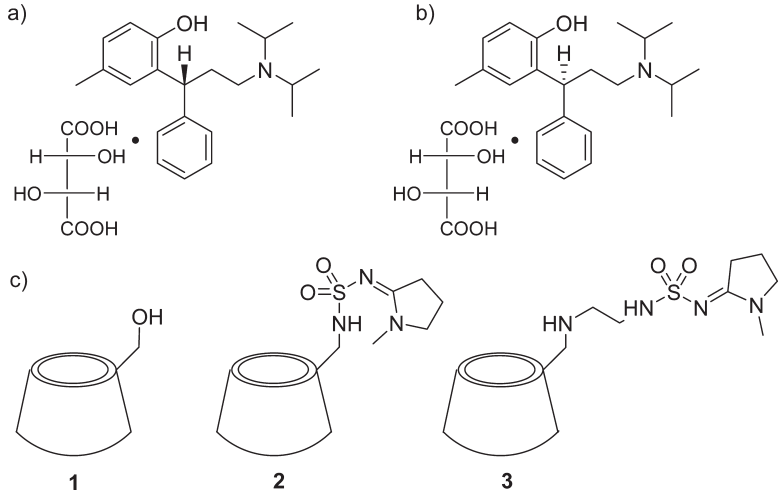

Figure 2: a) R-Tolterodine tartrate; b) S-Tolterodine tartrate; c) Native and modified β-cyclodextrins **1**, **2**, and **3**.

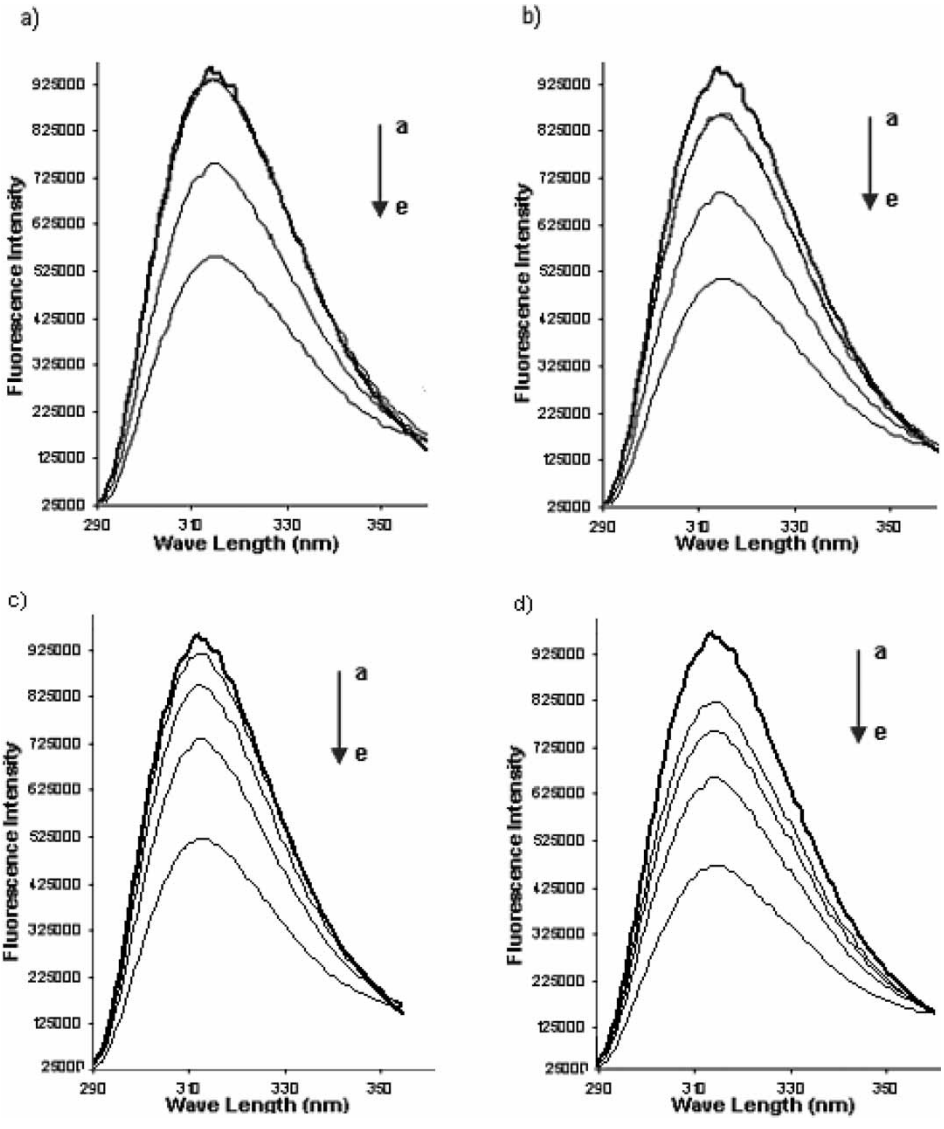

Figure 3: Fluorescence spectra of a) R-enantiomer b) S-enantiomer of Tolterodine tartrate with various concentrations of the host **2** and c) R-enantiomer d) S-enantiomer of Tolterodine tartrate with various concentrations of the host **3**. The concentration of **2** and **3** was from 0 to 0.1, 0.2, 0.5, and 1.0 mM (from a to e) and the concentrations of guests were 1×10^{-5} M.

hosts and guests have formed host–guest inclusion complexes and the decrease in fluorescence intensity with these hosts was higher in the case of S-enantiomer than R.

Enantiomer recognition of these hosts is evaluated in terms of enantioselectivity factors ($\alpha = \Delta F_S/\Delta F_R$)[13] of the guests with **2** and **3**. Here ΔF_S is

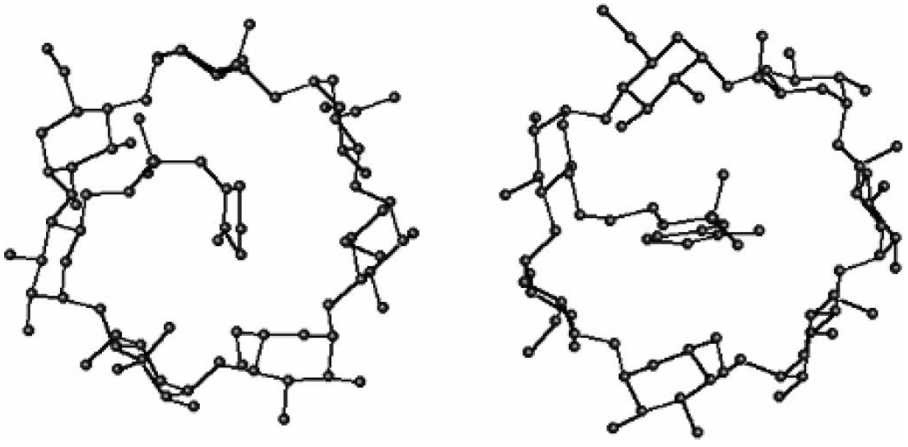

Figure 4: Energy-minimized structures of **2** and **3**. Energy minimization was carried out by MM2 force field.

$F_o - F_S$ and ΔF_R is $F_o - F_R$ where F_o is the fluorescence intensity of the guest alone, F_S the fluorescence intensity of the host–S-enantiomer complex, and F_R the fluorescence intensity of the host–R-enantiomer complex. The α values are 1.38 with **2** and 1.43 with **3**.

Crystal structure will be more applicable to explain the exact structure, self-inclusion state, and binding properties of the cyclodextrin derivatives. Efforts made to prepare single crystals of **2** and **3** were not successful. Therefore, molecular modeling studies were performed to get energy-optimized structures with the Hyperchem program and energy minimization by MM2 force field. The inclusion of the spacer into the cyclodextrin cavity is shown in Figure 4. From these structures it is clear that the spacer in both **2** and **3** is included in the cyclodextrin cavity.

To explain the stability of the complexes, association constants were calculated (Table 1) from the variation of the fluorescence intensities by using the *Benesi-Hildebrand* equation.[14]

For a 1:1 [Guest]–[Host] complex, the association constant K_s can be defined as follows:

$$[\text{Host}] + [\text{Guest}] \rightleftharpoons \text{Host:Guest}$$

$$K = \frac{[\text{H:G}]}{[\text{H}][\text{G}]}$$

The numerical value of K_s can be obtained from the observed fluorescence decrease F_o/F as a function of CD concentration.

$$1/(F_o - F) = 1/(F_o - F_{inf})[\text{H}]K_s + 1/(F_o - F_{inf})$$

Table 1: Association constants K_s (M^{-1}) of the Guest–Host complexes

Guest	1	2	3
R	$1.2 \times 10^2 \pm 10$	$1.1 \times 10^3 \pm 2 \cdot 10^2$	$4.0 \times 10^2 \pm 20$
S	$1.2 \times 10^2 \pm 10$	$1.5 \times 10^3 \pm 1 \cdot 10^2$	$2.5 \times 10^3 \pm 20$

where F_{inf} is the fluorescence intensity when all of the guest molecules have been complexed with the host molecules. This equation assumes that only a 1:1 complex is formed. This assumption can be readily tested using a reciprocal plot (Benesi-Hildebrand plot) of $\Delta F/F_o$ vs. $1/[CD]$. This plot will be linear if

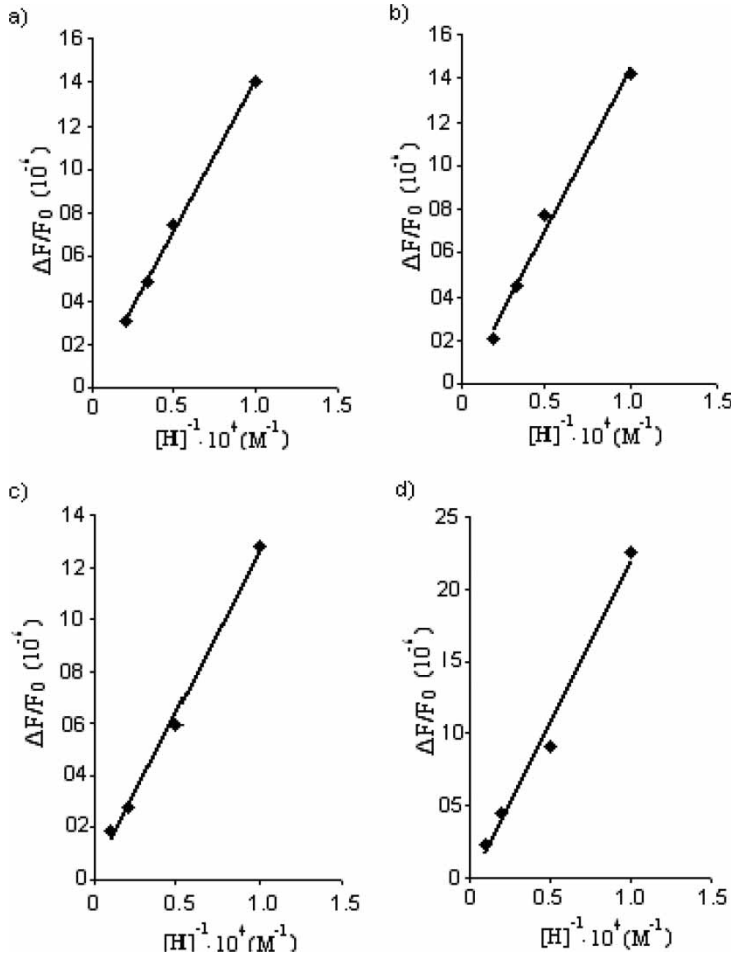

Figure 5: Estimation of association constants for a) R-enantiomer and b) S-enantiomer with **2** and c) R-enantiomer and d) S-enantiomer with **3**. The plot is based on the fluorescence-intensity changes at 314 nm with a 1:1 model: $\Delta F/F_o$ *vs.* $(H)^{-1}$.

only a 1:1 complex is formed, but will show curvature if complexes of other stoichiometry are being formed.[15] In Figure 5, *Benesi-Hildebrand plots* of the R- and S-enantiomers with **2** and **3** are shown. For all the host–guest complexes, the R values are in the range of 0.995 to 0.987, indicating that a 1:1 complex is formed.

Thus, a spectrofluorimetric method for the determination of tolterodine tartrate in bulk aqueous solution in the presence of modified cyclodextrins was developed based on the decrease in the fluorescence intensity of tolterodine tartrate. The results indicated that the hosts formed a 1:1 complex with the R- and S-enantiomers of tolterodine tartrate and have shown chiral discrimination by difference in the fluorescence quenching of these enantiomers.

EXPERIMENTAL

β-Cyclodextrin (Sigma Aldrich) was recrystallized from water and dried under vacuo at 60°C. Hosts **2** and **3** were synthesized by us as reported previously.[4] All solutions were prepared using high-purity water (milli-Q). Stock solutions of tolterodine tartrate (1×10^{-4} mol L^{-1}) and cyclodextrin derivatives (1×10^{-4} mol L^{-1}) were prepared by dissolving the appropriate amounts of the compounds in water. UV spectra were recorded on a Jasco spectrophotometer. Fluorescence spectra were recorded on a Fluorolog instrument in a 1×0.2 cm quartz cell.

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