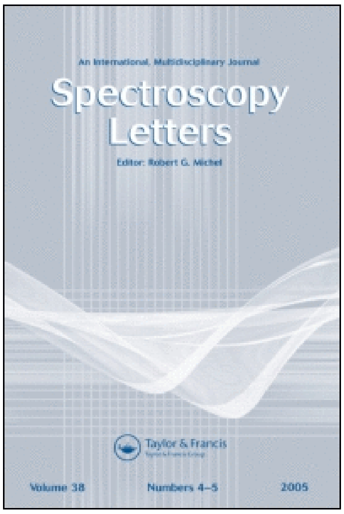

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Conformational Analysis of the Inclusion Complex of 3-Hydroxy-2-Naphthalenecarboxylate Anion with Heptakis-(2,3,6-Tri-Omethyl)-β-Cyclodextrin by 2D ^{1}Hnmr

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CONFORMATIONAL ANALYSIS OF THE INCLUSION COMPLEX OF 3-HYDROXY-2-NAPHTHALENECARBOXYLATE ANION WITH HEPTAKIS-(2,3,6-TRI-O-METHYL)-β-CYCLODEXTRIN BY 2D ^{1}HNMR

Keywords: inclusion; heptakis-(2,3,6-tri-o-methyl)-β-cyclodextrin; 3-hydroxy-2-naphthalenecarboxylate; 2D ^{1}HNMR

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ABSTRACT

Conformational analysis of the inclusion complex of heptakis-(2,3,6-tri-o-methyl)-β-cyclodextrin(TMβ-CD) with the 3-hydroxy-2-naphthalenecarboxylate anion in D_2O was undertaken by 1D and 2D ^{1}HNMR measurements. The results show that the naphthyl group of 3-hydroxy-2-naphthalenecarboxylate anion inserts lengthwise into the TMβ-CD cavity from the 6-OCH_3 side with an angle of the molecular axis.

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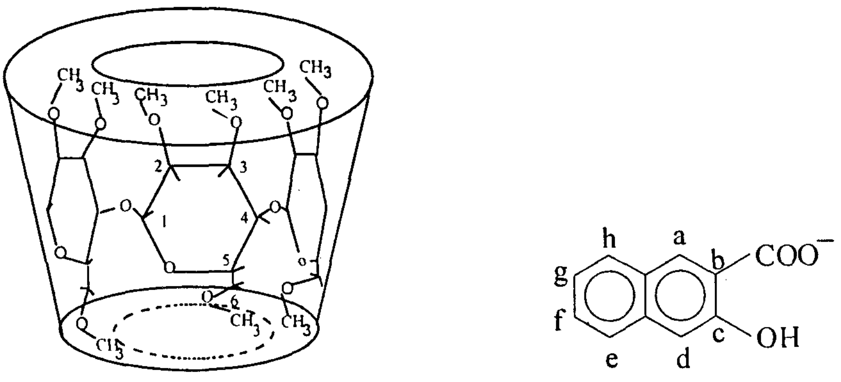
INTRODUCTION

It is well known that cyclodextrins(CDs) can include various guests into their hydrophobic cavities, leading to changes of the physical and chemical properties of the guests.[1] Permethylation of β-CD to form heptakis-(2,3,6-tri-o-methyl)-β-cyclodextrin (TMβ-CD) greatly improves its aqueous solubility, which may have pharmaceutical advantages to increase the often poor aqueous solubility of the apolar drug molecules.[2a] Compared to β-CD, TMβ-CD and its inclusion complexes have been studied less comprehensively. The current NMR technique is a powerful tool for structural and conformational analysis of the inclusion complex of CDs. The conformation of the inclusion complex of β-CD with benzene derivatives has been examined closely in aqueous solution, however, only a little work has been done for substituted naphthalene.[3] Furthermore, CDs can be used as catalysts themselves because they can provide a confinement environment caused by inclusion of the guest into the β-CD cavity, and the orientation direction of the guest in the β-CD cavity is thought to play an important role.[3-7] H. Hirai, et al. have found that the carboxylation of benzoic acid and 4-biphenylcarboxylic acid with carbon tetrachloride and copper powder in aqueous alkali can proceed with 100% selectivity in the presence of β-CD.[3] However, without β-CD the reaction cannot take place.

This paper reports the first investigation of the orientation of 3-hydroxy-2-naphthalenecarboxylate anion (3H2N), in the cavity of TMβ-CD, in aqueous solution, by measurements of the 1D ^{1}HNMR and 2D NOESY spectra. Such investigations may contribute to the selective substitution reactions of 3-hydroxy-2-naphthalenecarboxylic acid (3H2NA, $pKa_1=2.6$[8]) and its analogues, which are useful chemical raw materials and fluorescent compounds.[8]

EXPERIMENTAL

1D and 2D ^{1}HNMR spectra were recorded on a BRUKER AM-500 spectrometer at 300K (external standard: DSS at $\delta=0.00$ ppm). A 2D NOESY



TMβ-CD

3H2N

FIG. 1 Position numbers of protons of TMβ-CD and 3H2N.

spectrum was acquired in a sweep width of 3000Hz, 150ms mixing time, 512 × 2048 data points.

RESULTS AND DISCUSSION

FIGURE 1 shows the position, and numbers of protons of TMβ-CD and 3H2N. From the correlation in 2D COSY and NOESY spectra, as well as the ^{1}HNMR spectrum of TMβ-CD in $CDCl_3$,[2] we assigned all the resonances of protons of TMβ-CD in D_2O (external standard: DSS at δ=0.00 ppm). The chemical shifts of H1-H6 and 2, 3, 6-OCH_3 protons are 5.28, 3.34, 3.67, 3.74, 3.85, 3.64 (H6a), 3.85 (H6b), 3.51, 3.60 and 3.38 ppm, correspondingly.

FIGURE 2 exhibits the 1D 500 MHz ^{1}HNMR and portion of 2D NOESY spectra of the inclusion complex of TMβ-CD with 3H2N in D_2O at 300K. The resonance of 3H2N can be easily assigned from the correlation in the 2D NOESY spectrum. The assignments of the proton signals of TMβ-CD were undertaken on the basis of another portion of the 2D NOESY spectrum (see FIGURE 3) and comparison with

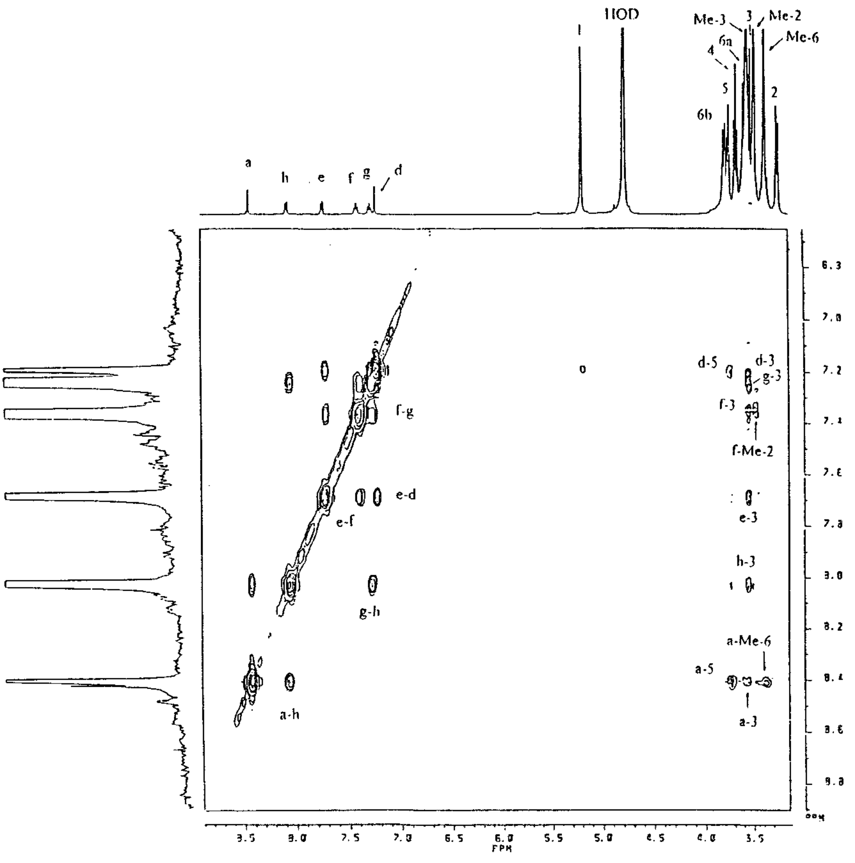


FIG. 2 The 1D 500 MHz ^{1}HNMR and portion of 2D NOESY spectra of the inclusion complex of TMβ-CD with 3H2N in D_2O at 300K.

^{1}HNMR spectra of related compounds.[9] In the presence of 3H2N, due to the magnetic anisotropy effect of the naphthalene ring of 3H2N, all the resonances of TMβ-CD shift upfield. The upfield shifts of H1-H6 and OCH_3 protons at 2, 3, and 6 positions are 0.10, 0.10, 0.18, 0.08, 0.13, 0.09 (H6a and H6b), 0.06, 0.07 and 0.03

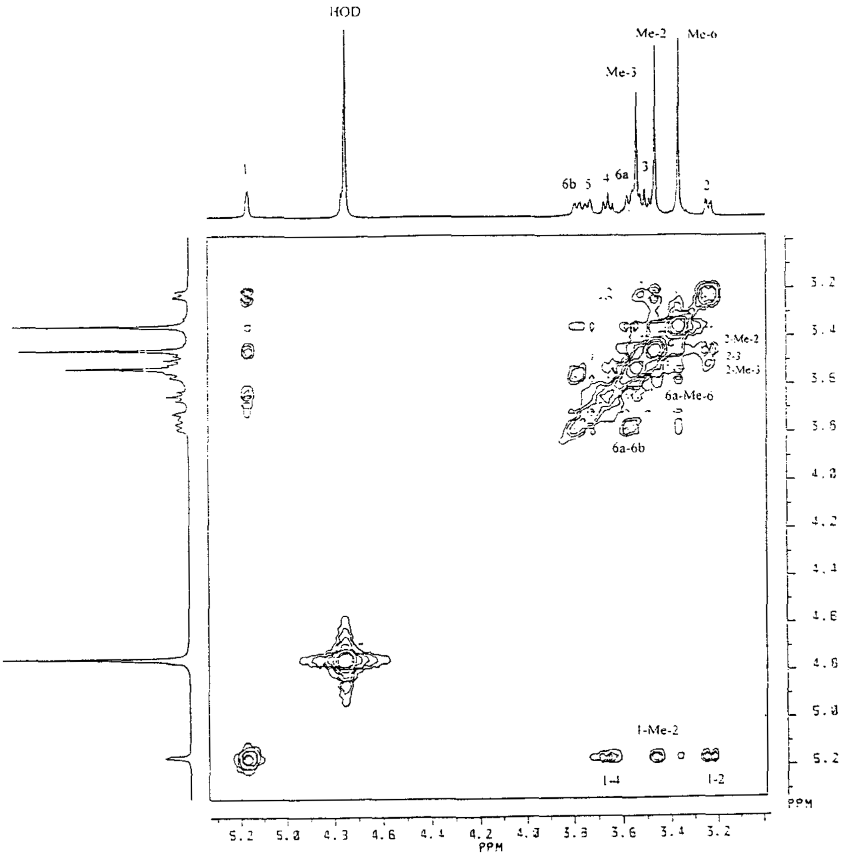


FIG. 3 The TMβ-CD portion of 2D NOESY spectrum of the inclusion complex of TMβ-CD with 3H2N in D_2O at 300K.

ppm, respectively. The most remarkable shifts are found for H3 and H5 protons in the interior of the cavity of TMβ-CD. In the 2D NOESY spectrum, the cross-peaks connecting the Ha resonance of 3H2N to the H5, H3 and OCH_3 protons at 6 position of TMβ-CD are clearly observed. This indicates that the Ha proton is situated close

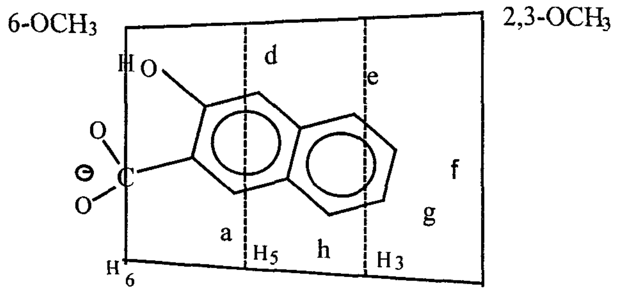


FIG. 4 Proposed conformation of the 3H2N-TMβ-CD inclusion complex in D_2O. ------H3 and ------H5 show planes comprised of the corresponding atoms of TMβ-CD.

to these protons of TMβ-CD. The cross-peaks connecting the Hd proton to the H5 and H3 protons can also be seen clearly, but that connecting to 6-OCH_3 protons cannot be found. This indicates that the Hd proton is situated near the H5 and H3 protons, but far from 6-OCH_3 protons. The cross-peaks connecting the He, Hf, Hg and Hh atoms of 3H2N to H3 atom of TMβ-CD can be obviously appreciated. This shows that He, Hf, Hg and Hh atoms of 3H2N are near the H3 atom of TMβ-CD. The correlation between the Hf proton and 2-OCH_3 protons is also clear, while that between Hg and 2-OCH_3 protons is obscure. This suggests that the Hf atom of 3H2N is near 2-OCH_3 protons of TMβ-CD as compared to the Hg atom. It seems that the 2-OCH_3 group may point to the molecular axis of TMβ-CD, while the 3-OCH_3 group points outside the cavity. Thus the cross-peak connecting the Hf atom to the 3-OCH_3 group does not appear. From what has been discussed above, the conformation of the TMβ-CD-3H2N inclusion complex in D_2O is proposed as shown in FIG. 4, in which TMβ-CD is illustrated simply by its inner cavity and 3H2N is depicted according to the crystal structure of 3H2NA.[10] The naphthyl group of 3H2N inserts lengthwise into the cavity of TMβ-CD from the 6-OCH_3 side and gives a tilt with the molecular axis of it. Therefore, we may predict that the substitution of the Hf and Hg protons of 3H2N occurs more easily than that of the Hd, He and Hh atoms, which are deeper enclosed within the cavity of TMβ-CD.

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