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^{1}H NMR titration and quantum calculation for the inclusion complexes of *cis*-cyclooctene, *cis*, *cis*-1, 3-cyclooctadiene and *cis*, *cis*-1, 5-cyclooctadiene with β-cyclodextrin

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ABSTRACT

The inclusion behavior of *cis*-cyclooctene, *cis*, *cis*-1, 3-cyclooctadiene and *cis*, *cis*-1, 5-cyclooctadiene with β-cyclodextrin (β-CD) was studied by using ^{1}H NMR method in D_2O/CD_3OD solution and PM3 quantum-chemical simulation in vacuum. The experimental results indicate that each guest molecule penetrates deeply into β-CD cavity and forms equimolecular inclusion complex with the host. The association constants of the complexes were determined by non-linear least-square method on the bases of the conversion-dependent chemical shift of two protons of the host molecule. The inclusion process and the most probable structure of the inclusion complexes were simulated using PM3 energy scanning and optimization. The trend of stability of the three inclusion complexes deduced from their calculated stabilization energies agrees well with the order of their association constants obtained from NMR experiments.

1. Introduction

Cyclodextrins (CDs) are cyclic oligomers of D-glucose and named α-, β- and γ-CD for hexamer, heptamer, and octamer, respectively (Fig. 1). They have a hydrophobic cavity that can accommodate guest molecules of appropriate size [1]. CDs have been widely used in pharmaceutical science [2], catalysis [3], separation technology [4] and in other fields.

Many methods including UV–vis [5], fluorescence spectroscopy [6], NMR spectroscopy [7], etc. were used to study the stability of CD complexes in solution, among them ^{1}H NMR titration was one of the most important method to qualitatively investigate the formation of CD complexes. The complexation of CD with guest molecules often causes changes in the chemical shifts of ^{1}H's and ^{13}C's involved in the CD and/or guest. The chemical shift of a given signal is a weighted mean of the shifts corresponding to the exchanging sites due to the fast exchange between the bound and free host (or guest). Fast exchange can be deduced from the fact that the signals shift under varying guest/host ratio without changing their number. The magnitude of chemical shift is a critical function of position of proton in the molecule, size of CD cavity as well as host/guest ratio. Moreover, the observed chemical shift changes in ^{1}H NMR titration can also provide the conformation of formed supramolecular complexes and independent signals for the evaluation of association constant (K_a), which was difficult to extract, e.g. from UV–vis titration, and impossible from calorimetric data [8,9].

Cyclooctene have been frequently used as probe for the study on enantiodifferentiating photoisomerization of sensitizer-appended CDs, such as 6-*O*-benzoyl-β-CD [10], 6-*O*-(methyl phthaloyl)-β-CD [11] and *O*-permethylated 6-*O*-benzoyl-β-CD [12]. More recently, we have reported the photoisomerization of (*Z*)-cyclooctene sensitized by 6-*O*-(*m*-methoxybenzoyl)-β-CD can give a chiral (*E*)-cyclooctene in up to 46% ee [13], which is the highest value for supramolecular photochirogeneses with analogous CD hosts till now. The most commonly used technique for examining the complexation behavior of (*Z*)-cyclooctene with CD hosts was circular dichroism, which was limited by calculating all of the possible conformations of CD complexes [14].

Intensive theoretical works were performed over the past few years on CDs [15]. Most computational studies of CDs involved host–guest complexation, their structures, energies, preferred bonding orientations, and so on. Early quantum calculations were performed with semi-empirical CNDO method [16], followed by molecular mechanics (MM) [17] and molecular dynamics (MD) [18] with various force field approaches. Recently, some higher level of quantum calculations, *ab initio* methods at the Hartree-Fork or the density functional theory levels with a minimal basis set, were carried out [19]. PM3 quantum-mechanical semi-empirical method

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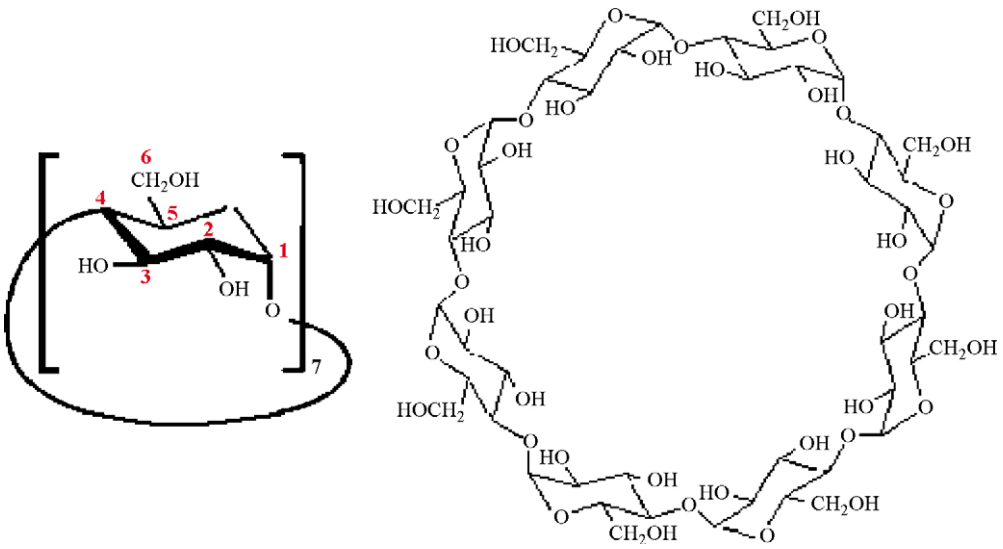

Fig. 1. The structure of β-CD.

(PM3) has a good computational efficiency that permits the modeling of large systems such as CDs. The precision is almost comparable to that of *ab initio* with medium-sized basis sets for large systems. It also performs better than AM1 in biochemical systems due to its improved description of the interaction between non-bonded atoms [20].

In the present work, *cis*-cyclooctene, *cis*, *cis*-1, 3-cyclooctadiene and *cis*, *cis*-1, 5-cyclooctadiene were selected as guests to investigate the effects of double bonds in guest molecules on the stability of their CD complexes. The association constants of complexes of β-CD were determined using ^{1}H NMR titration method in solution followed by non-linear least-square regression. PM3 method was applied to study the inclusion process of the three guest molecules with β-CD, the stabilization energy and their minimum energy structures of 1:1 inclusion complexes were calculated.

2. Experimental

2.1. Materials

β-CD (95%) was purchased from Suzhou Weijing Plant, China. It was recrystallized three times from distilled water, dried at 105 °C for 8 h and subsequently dried in vacuum at 100 °C for 24 h. All the other chemicals were of analytical grade and being used without further purification.

2.2. ^{1}H NMR method

The ^{1}H NMR was recorded on Varian INOVA-400 MHz at 293 K in D_2O:CD_3OD = 1:1 (v/v). Chemical shift was given on the δ scale (ppm) and referenced to an external sample of TMS (δ = 0.00) in a capillary to avoid the complexation of TMS with CD's [21]. Experiments were performed when the concentration of the host was kept constant and the concentration of the guest was varied. The association constants (K_a) for these host–guest systems were determined by ^{1}H NMR titration, in conjunction with the non-linear least-square fit of the data to 1:1 models [22]. The observed chemical shift(δ) of H3 or H5 of β-CD and the association constant (K_a) are described as follows:

$$G + H = C \tag{1}$$

$$\delta = \delta_H(1-\chi) + \delta_C\,\chi \quad \text{where } \chi = [C]/[H]_t \tag{2}$$

$$[H]_t(\delta - \delta_H) = [C](\delta_C - \delta_H) \tag{3}$$

$$K_a = \frac{[C]}{[H][G]} \tag{4}$$

$$[H]_t = [H] + [C] \tag{5}$$

$$[G]_t = [G] + [C] \tag{6}$$

where H, G, C represent the host, guest and the complex, respectively; $[H]_t$, $[G]_t$ means the concentration of host and guest molecule at initial state; [H], [G], [C], represent the concentration of host, guest, and complex at final stage, respectively; δ_H, δ_C are the chemical shift of the host, complex, and the observed chemical shift(δ) is a weighted mean of δ_H and δ_C (Eq. (3)); K_a, association constant, namely, at equilibrium Eq. (7) is derived from Eq. (4)–(6)

$$K_a = \frac{[C]}{([H]_t - [C])([G]_t - [C])} \tag{7}$$

$$[C] = \frac{([H]_t + [G]_t + 1/K_a) \pm \sqrt{([H]_t + [G]_t + 1/K_a)^2 - 4[H]_t + [G]_t}}{2} \tag{8}$$

Then,

$$\delta - \delta_H = \frac{\delta_C - \delta_H}{2} \times \left\{ \frac{[G]_t}{[H]_t} + 1 + \frac{1}{K_a[H]_t} \pm \sqrt{\left(\frac{[G]_t}{[H]_t} + 1 + \frac{1}{K_a[H]_t}\right)^2 - 4\frac{[G]_t}{[H]_t}} \right\} \tag{9}$$

For a given value of $[G]_t/[H]_t$, the value of δ–δ_H can be determined by experiment, K_a may be calculated from Eq. (9) for each δ_C–δ_H. The titration curves were shown in Fig. 4.

2.3. Calculation and methodology

The complexation process of β-CD with *cis*-cyclooctene, *cis*, *cis*-1, 3-cyclooctadiene and *cis*, *cis*-1, 5-cyclooctadiene was studied using PM3 method. All calculations were performed with *Gaussian 98* [23]. The initial structure of β-CD was constructed with the help of crystal structure [24] and optimized with PM3 method, no geometry constraint was imposed on the optimization. To help analysis of the final results, all the glycosidic oxygen atoms of β-CD were