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STUDIES ON MOLECULAR INTERACTIONS OF β-CYCLODEXTRIN AND ANTIULCER AGENT

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The search for the lowest energy conformation of complex {β-cyclodextrin (β-CD)+chlorambucil} were carried out by molecular mechanics method. Theoretical calculations of molecular interactions of complex were carried out using the molecular orbital method. The correlation between energy changes and molecular structures are discussed. The large interaction energies calculated by the molecular orbital method bears out the inclusion phenomenon.

Keywords: *ab initio molecular orbital method, host-guest chemistry, molecular interaction, molecular mechanics*

Introduction

In liquid phase a vast crowd of molecules gather closely, oscillating and rotating violently. Colliding with each other, they distinguish a kind of molecules from another one. In particular, stereospecific interactions due to neighboring surfaces may play the leading role in, e.g., enzyme-substrate reactions, antigen-antibody reactions, some kinds of mechanisms of senses of smell and taste, and so on. Therefore, elucidating the role of asymmetric inter-molecular interactions owing to the stereospecific structures of molecules is really important for understanding the mechanisms of chemical and biochemical reactions. The accumulation of accurate and quantitative values of the changes in thermodynamic functions on molecular inclusion of alcohol into the cavities of α- and β-cyclodextrin (CD) in aqueous solutions have been carried out systematically by microcalorimetry [1, 2], in order to clarify the mechanisms of molecular recognition and discrimination in aqueous solutions. In the latest, some studies of complex with cyclodextrin have provided thermodynamic data [3, 4, 5]. In this paper we planned to clarify the interaction of CD that is host and chlorambucil that is antiulcer agent. Chlorambucil has the chloroethyl radical as shown in Fig. 1. There is fear of the sidereactions of the wound of the malignant tumor induction that originates in long-term use, the leucopoenia, and the gastric mucosa and depilations, etc. along with administering the chlorambucil that is the antiulcer drug.

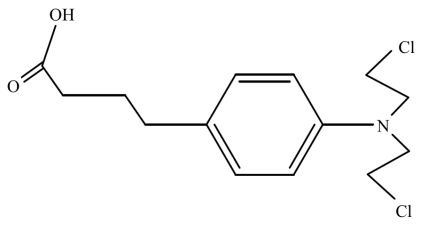

Fig. 1 Structural formula of chlorambucil

Chlorambucil is slightly soluble in water, and is soluble in DMSO [6]. The improvement of the stability of chlorambucil and the solubility can be expected for CD to form the chlorambucil and the inclusion complex. CD + chlorambucil complex formations have been studied by UV spectroscopy [7]. But there were few structural and energetic researches. The identification of the main forces involved in complexation phenomena are central issues in the field of CD+drug research. It is very difficult to estimate the interaction of β-CD+chlorambucil by the microcalorimetry in aqueous solutions, because this measurement system contains the following five components, CD, chlorambucil, DMSO, buffer and water. Therefore, it was attempted to decide the intermolecular interaction by the computational chemistry. As for molecular dynamics method, it is known that even most stable conformation is not often found, moreover as suitable interaction potentials in this system doesn't exist, the molecular dynamics simulation was not used. In this work we examine to clarify the intermolecular interaction of the system by molecular orbital method.

Computational method

The geometry of β-CD was obtained from the crystal structure reported in the literature [8]. The structure

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of the guest molecules was obtained from chemfinder [9]. Each molecule's geometry was minimized with the MMFF94s force field by using the COMFLEX5 program [10]. We set a molecule of β-CD which including a guest molecule in the central of the cavity. To decide the lowest energy structure, conformation search was performed by COMFLEX5 program with the MMFF94s force field. This program has the following feature; the lowest energy conformer doesn't depend on the initial structure that user input. The obtained lowest energy conformer was the initial structure of the ab initio molecular orbital calculations. Geometry optimization by ab initio molecular orbital calculations was performed by using Gaussian 03 program [11]. Semi-empirical molecular orbital calculations were performed by using mopac 2002 program [12].

Results and Discussion

Searching the conformational space

The search for the lowest energy conformation of complex (β-CD + chlorambucil) were carried out by molecular mechanics method, and are shown in Fig. 2. The benzene ring of the chlorambucil exists in the β-CD cavity. The chloroethyl radical of chlorambucil exists on out of the side of the secondary hydroxyl group for β-CD.

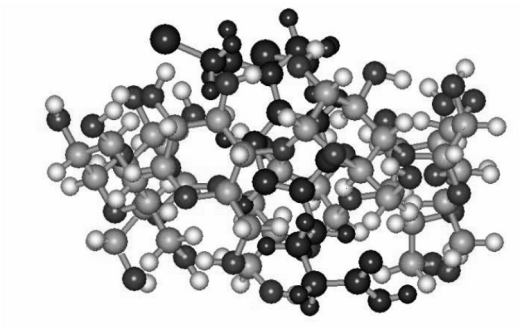

Fig. 2 Lowest energy conformer of complex (β-cyclodextrin+chlorambucil) which determined by molecular mechanics method

Ab initio molecular orbital method

The obtained lowest energy conformer by using molecular mechanics was the initial structure of the ab initio molecular orbital calculations. Geometry optimization by ab initio molecular orbital calculations were carried out, at the RHF/6-31G(d) level and the RHF/STO-3G level theory. All energy calculations by the ab initio molecular orbital method were done with the SCF=tight option in the gas phase. As shown in Fig. 3, chlorambucil may form intermolecular hydrogen bond (O—H- - -O) with the oxygen atoms of the side of the primary hydroxyl group for β-CD. There O—H distance is 0.09513 nm, and the H- - -O distant is 0.18774 nm. The O—H- - -O angle is 167.723°. The benzene ring of chlorambucil exists in β-CD cavity, and the majority of the chloroethyl radical of chlorambucil has been exposed outside β-CD cavity. There are four intramolecular hydrogen bonds of the side of the secondary hydroxyl group for β-CD.

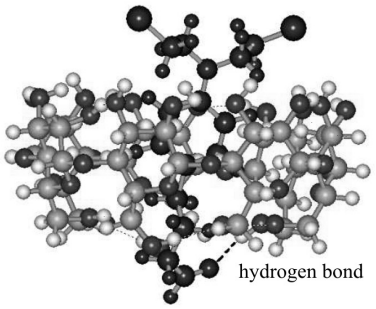

Fig. 3 Lowest energy conformer of complex (β-cyclodextrin+chlorambucil) which determined by ab initio molecular orbital method at the RHF/6-31G(d) level

Semi-empirical molecular orbital method

To handle the PM5 Hamiltonian who reproduced heat of formation well, it calculated by the semi-empirical molecular orbital method in the gas phase. The obtained lowest energy conformer by using molecular mechanics was the initial structure. Geometry optimization was carried out with mopac 2002 program.

In order to confirm whether the molecular orbital method of this work was able to be used to clarify the interaction of host-guest complex by comparing with experimental result, the semi-empirical molecular orbital calculations and ab initio molecular orbital calculations of complex (β-CD+cyclohexanol) were carried out. Because host-guest interactions of α- and β-CD+cyclohexanol were reported by precise calorimetric method [2]. To estimate the molecular interaction energies of β-CD+chlorambucil, heats of formation of β-CD, chlorambucil and complex of β-CD+chlorambucil were determined. The molecular interaction energies of β-CD+chlorambucil was calculated by using the following Eq. (1).

$$\Delta E(\text{int.}) = \Delta H_f(\text{complex}) - \Delta H_f(\text{host}) - \Delta H_f(\text{guest}) \quad (1)$$

The total interaction energies were corrected by Basis Set Superposition Error (BSSE). The values of ΔH_f (host) and ΔH_f (guest) were calculated with the fixed structure that optimized complex. The obtained βE(int.) are listed in Table 1 together with calorimetric data of Δ-CD+cyclohexanol. The ΔE (int.) of cyclohexanol system calculated by STO-3G basis set is agreed well with the calorimetric data of cyclohexanol

Table 1 Energy aspects {Δ*E*(int.)} of the cyclodextrin – guest molecules complexation by the molecular orbital (MO) method

system	β-CD + chlorambucil	β-CD + cyclohexanol
MM→ab initio MO{HF/6-31G(d)}	–51.90	–36.51
MM→ab initio MO (HF/STO-3G)	–16.61	–8.19
MM→semi-empirical MO (PM5)	–59.9	–4.1
Exp.(calorimetry)	Not available	–5.68*

All data were given in kJ mol^{-1} , *Ref. 2

system as shown in Table 1. The molecular orbital method can be used to discuss the interaction energy of the host-guest complex. The interaction energies calculated by some basis functions are all negative. The interaction energies calculated by 6-31G (d) basis set are larger than those calculated by STO-3G basis set. Chlorambucil molecules are stabilized largely on inclusion into a β-CD cavity. The large interaction energies calculated by the molecular orbital method bears out the inclusion phenomenon.

Enthalpy and entropy of inclusion

Enthalpies and entropies of each compound were determined by frequency calculation [13] at the RHF/STO-3G level of optimized structures by Eqs (2) and (3)

$$H=E_{elec}+ZPE+E_{vib}+E_{rot}+E_{trans}+RT \quad (2)$$

$$S=S_{elec}+S_{vib}+S_{rot}+S_{trans} \quad (3)$$

where subscript of elec, vib, rot and trans denote electronic, vibrational, rotational and translational respectively, and ZPE means zeropoint energy.

As the computer resource was insufficient, the frequency calculation are the higher level than the RHF/STO-3G level was not executed. The enthalpies and entropies of inclusion were calculated by Eqs (4) and (5), and listed in Table 2 together with the Gibbs energies of inclusion which calculated by Eq. (6). The thermodynamic functions of interactions were corrected by BSSE and the deformation energy.

$$\Delta H_{inc}=H(\text{complex})-H(\beta\text{-CD})-H(\text{chlorambucil}) \quad (4)$$

$$\Delta S_{inc}=S(\text{complex})-S(\beta\text{-CD})-S(\text{chlorambucil}) \quad (5)$$

$$\Delta G_{inc}=\Delta H_{inc}-T\,\Delta S_{inc} \quad (6)$$

Table 2 The changes of thermodynamic functions on 1:1 inclusion of chlorambucil into β-cyclodextrin cavity at 298.15 K

ΔH_{inc}/kJ mol^{-1}	ΔS_{inc}/J K^{-1} mol^{-1}	ΔG_{inc}/kJ mol^{-1}
–46.09	–71.31	–24.83

Thermodynamic functions of inclusion of chlorambucil into β-CD are large negative values. This inclusion process is advantageous energetically.

Conclusions

The large interaction energies for (β-CD+chlorambucil) were calculated by the molecular orbital method. Chlorambucil molecule is stabilized largely on inclusion into β-CD cavity, accompanying a large entropy decrease. The enthalpically stabilization is due to a hydrogen bond formation, and van der Waals interactions by favorable fit. The space of the extent that chlorambucil can rotate doesn't exist. This inclusion process is an enthalpy driven process.

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