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Original article

Study on the inclusion behavior and solid inclusion complex of 5-amino-6-methyl-2-benzimidazolone with cyclodextrins

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ABSTRACT

The inclusion behaviors of three native or modified CDs including β-CD, 2-hydroxypropyl-β-CD (2-Hp-β-CD) and 2,6-dimethyl-β-CD (Me-β-CD) toward 5-amino-6-methyl-2-benzimidazolone (AMBI) were comparatively investigated by NMR and fluorescence titration in combination with IR spectra, X-ray diffractometry and scanning electron microphotographs. The experimental results jointly demonstrated that the phenyl ring of AMBI entered into the cavity of the CDs and located close to the narrow rims accompanied by the formation of the 1:1 inclusion complex with large stability constant in aqueous solution. The introduction of the hydroxypropyl unit to the host improved the solubility, ultimately effecting an obvious promoting in the fluorescence intensity and the stability constant

1. Introduction

In recent years, the construction of structurally well-defined host–guest systems for binding specific chemical and biological important functional heterocyclic compounds has evolved into the most attractive fields of supramolecular chemistry since the potential application in chemical sensing, materials science and chemical biology [1–3]. Relying on the non-bonding interactions like hydrogen bonds and van der Waals interactions, supramolecular host–guest investigation also has the potential to deepen our understanding of noncovalent association in complicated chemical and biological systems [4].

Among the most attractive hosts, cyclodextrins (CDs), which is a torus-shaped macrocycle oligosaccharides made up of 6–12 glucose units, has special ability in formation of inclusion water soluble complexes with a variety of water insoluble or poorly soluble functional organic compounds driven by the hydrophobic interaction between the CDs cavity and guest molecule, thus significantly improving the chemical and biological properties [5,6]. Especially the modification of native CDs can particularly enhance the solubility, chemical stability and bioavailability remarkably (Fig. 1). As a result, significant interest has been acquired in the use of CDs as molecular carrier systems in a variety of fields including organic catalysis, materials science, agricultural pharmacology and pharmaceutics [7].

On the other hand, benzimidazole derivatives, which represent a predominant structural motif among many natural compounds, organic dyes and pharmaceuticals, have drawn tremendous attention due to the well biological activities that they have shown in drug development toward a lot of challenging diseases [8]. Furthermore, as electron rich ligands, they play important roles in maintaining the dimensionality of the structure and providing supramolecular recognition sites for π–π aromatic stacking interactions, which gains special importance in organometallic chemistry [9]. Additionally, benzimidazole derivatives have been used as pigments with a broad range of hues in watercolor painting and electrophotographic developer toner for over 30 years due to their endurance and light resistance [10]. As a consequence, many organic reactions have been carried out in the presence of inclusion formation by CDs and benzimidazole derivatives making it highly significance in understanding the inclusion process between CDs and benzimidazole derivatives [11].

Recently, much work has been published on the studying of supramolecular recognition and inclusion between CDs and

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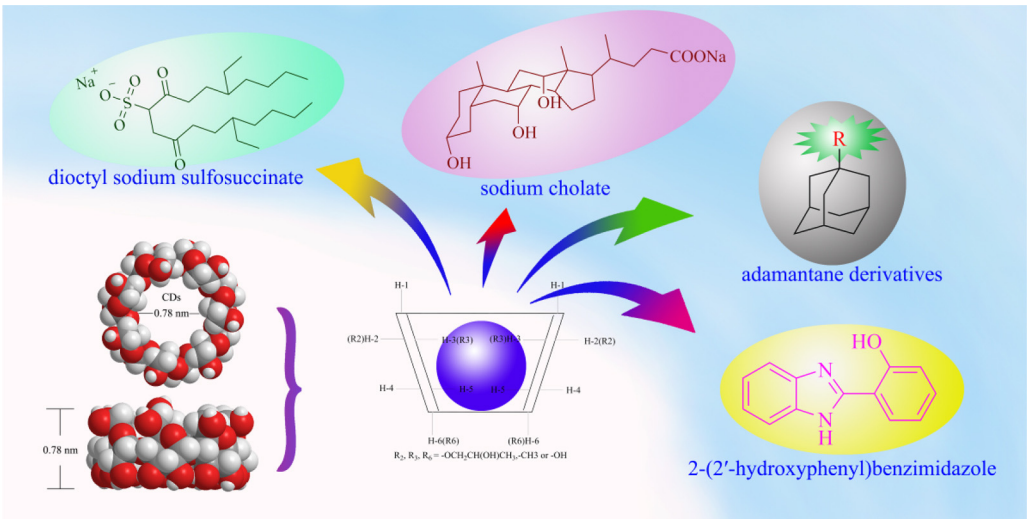

Fig. 1. Basic structures of β-CD and the inclusion of chemical and biological important guests.

important functional chemical and biological heterocyclic compounds [12]. For instance, Liu *et al.* [13,14] studied the molecular induced aggregation of hepta-imidazoliumyl-β-CD toward anionic surfactant and the selective binding of bile salts by β-CD derivatives with appended quinolyl arms. Fan *et al.* [15] reported the structural analysis of the inclusion complex of β-CD with m-nitrophenoxyacetic acid. However, few literatures focus on the investigation of inclusion properties of benzimidazole derivatives with CDs. At present, the research works related to this area are of great challenge and interest.

In this work, we focus on the study of the molecular association that takes place between 5-amino-6-methyl-2-benzimidazolone (AMBI) and three natural or modified CDs including β-CD, 2-hydroxypropyl-β-CD (2-Hp-β-CD) and 2,6-dimethyl-β-CD (Me-β-CD) by fluorescent titration and two dimensional protons nuclear magnetic resonance (2D ROESY) spectroscopy in combination with infrared spectroscopy (IR), scanning electron microphotographs (SEM) and X-ray diffractometry (XRD).

2. Experimental

2.1. General reagents

β-CD (molecular weight = 1135), 2-Hp-β-CD (averaged molecular weight = 1542, DS = 5.5), Me-β-CD (averaged molecular weight = 1310, DS = 12) were supplied by Aoboxing Bio-tech Co., Ltd., and was purified by recrystallization from double-distilled water. The benzimidazole derivative AMBI was purchased from Aldrich Chemical Inc. D_2O was purchased from CIL Chemical Company Inc. The Φ5 mm sample tubes were purchased from Norell Inc.

2.2. Preparation of solid complex of AMBI with the CDs

A solution of 1.0 mmol the CDs in 30 mL distilled water was prepared and added to a solution of 1.0 mmol AMBI in 10 mL methanol. This solution was continuously stirred for 12 h at 60 °C and for 12 h at room temperature. After cooling, a white precipitate was formed, then it was filtered off, washed with distilled water and dried at 60 °C for 4 h, white powdered products of inclusion complex were obtained.

2.3. Fluorescence measurement

Fluorescence measurements were performed by a Hitachi F-4500 spectrofluorometer using 1 cm quartz cell with 10 nm slit width, and fluorescence emission maximum of AMBI was obtained at 327 nm with 300 nm excitation. All experiments were carried out at 25 °C. 1 mL 1.25×10^{-4} mol/L AMBI solution was added into 25 mL cuvette, then 1.25×10^{-2} mol/L the CDs solution from 0 to 6.00 mL was added into the cuvette dropwise, respectively, and

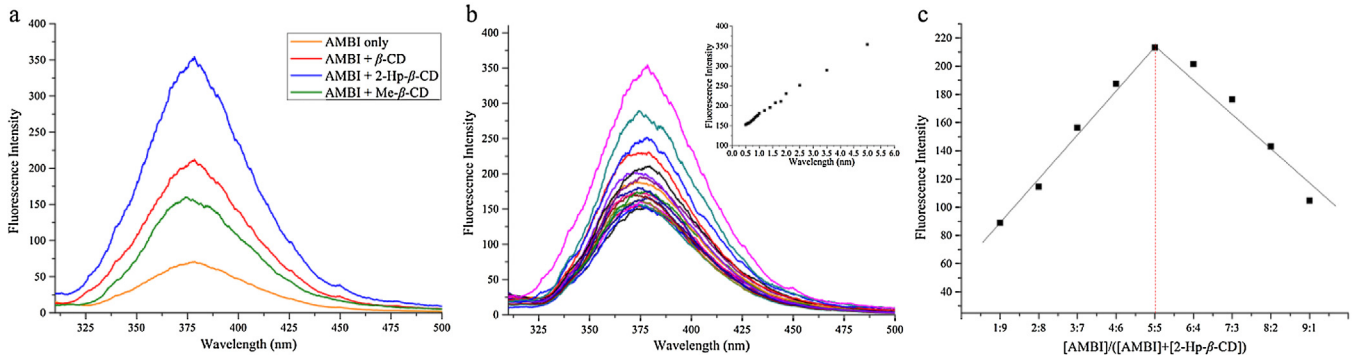

Fig. 2. (a) Fluorescence intensity of AMBI and the inclusion complex of AMBI with the CDs. (b) Fluorescent titration of AMBI (5 μmol/L) with different concentration of 2-Hp-β-CD (0–3 mmol/L). Inset: Fluorescence intensity of the inclusion complex of AMBI with 2-Hp-β-CD at 326 nm, λ_{ex} = 300 nm. (c) Job's plot of AMBI with 2-Hp-β-CD. The total concentration was 2 μmol/L.