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Spectroscopic investigation on cocrystal formation between adenine and fumaric acid based on infrared and Raman techniques

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ABSTRACT

As an important component of double-stranded DNA, adenine has powerful hydrogen-bond capability, due to rich hydrogen bond donors and acceptors existing within its molecular structure. Therefore, it is easy to form cocrystal between adenine and other small molecules with intermolecular hydrogen-bond effect. In this work, cocrystal of adenine and fumaric acid has been characterized as model system by FT-IR and FT-Raman spectral techniques. The experimental results show that the cocrystal formed between adenine and fumaric acid possesses unique spectroscopical characteristic compared with that of starting materials. Density functional theory (DFT) calculation has been performed to optimize the molecular structures and simulate vibrational modes of adenine, fumaric acid and the corresponding cocrystal. Combining the theoretical and experimental vibrational results, the characteristic bands corresponding to bending and stretching vibrations of amino and carbonyl groups within cocrystal are shifted into lower frequencies upon cocrystal formation, and the corresponding bond lengths show some increase due to the effect of intermolecular hydrogen bonding. Different vibrational modes shown in the experimental spectra have been assigned based on the simulation DFT results. The study could provide experimental and theoretical benchmarks to characterize cocrystal formed between active ingredients and cocrystal formers and also the intermolecular hydrogen-bond effect within cocrystal formation process by vibrational spectroscopic techniques.

1. Introduction

As a great potential receptor, DNA can easily combine with small molecules, which has been a major interest in chemotherapy [1,2]. The interaction between DNA and small molecules has led to the development of many novel anticancer [3] and antimicrobial agents [4]. There are a number of studies investigating the interaction between DNA and small molecules [5,6] or metal ions [7–9]. Such studies have helped us better understand the role of DNA association with small molecules. Adenine is one of the key components in the DNA double helix. The 9H and 7H tautomers of adenine (shown in Fig. 1) and protonic adenine have been reported [10–12]. Cocrystals between adenine and some selected small molecules such as salicylic acid [13,14], oxalic acid [15] could be formed via hydrogen-bond effects. Thompson et al. [16] examined cocrystal of adenine forming with succinic acid, fumaric acid and maleic acids by X-ray diffraction (XRD). Byres et al. [17] reported cocrystals formed between adenine with benzoic acid, adipic acid, salicylic acid, 2,6-dihydroxybenzoic and 3,5-dihydroxybenzoic acid. Perumalla et al. [18] detected cocrystal between adenine and benzoic acid. Observing the molecular structures of cocrystal formed between adenine and small acids has shown that there are many potential hydrogen-bond donors and acceptors within the structure of adenine (Fig. 1, "↑"donors, "↓"acceptors [15]). Meanwhile, water and methanol (as solvent molecules) can take part in the formation of hydrogen bonding network. Cocrystals of hydrated adeninium and 2, 6-dihydroxybenzoic acid [17], methanol adeninium, adipic acid [14] and hydrated adeninium, oxalic acid [15] have been reported. The hydrogen-bond network between adenine and cocrystal former (CCF) has been disrupted due to the presence of water or other solvents, which will affect the characters of cocrystal and studies of interaction between adenine and CCF.

Several theoretical and experimental studies have shown that the 9H amino form of adenine is the most stable tautomer in the gas phase and also in aqueous solution [19,20]. However, the energy difference between 9H-adenine and its 7H tautomer is 7–8 kcal mol^{-1} in the gas phase, and the energy gap becomes significantly smaller in the polar solvent [21,22]. Based on the above-mentioned issues, anhydrous ethanol was chosen as solvent during cocrystallization via slow evaporation method, in order to decrease the transformation possibility between adenine tautomers. Fumaric acid is one of the suitable model cocrystal formers due to the compound containing two typical carboxyl groups (shown in Fig. 2). Grinding synthesis is another chosen method to prepare cocrystal between adenine and fumaric acid.

At present, the techniques such as X-ray powder diffraction (XRD), infrared (IR) absorption, terahertz (THz) absorption and Raman

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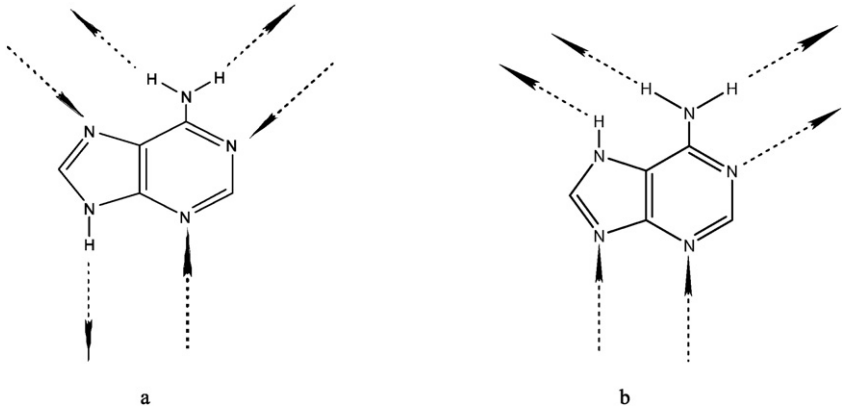

Fig. 1. Possible donor and acceptor positions of 9H (a) and 7H (b) adenine.

scattering spectroscopies [23–28] have been usually applied to characterize the cocrystal formation. As an effective and direct method, XRD has been used to directly detect cocrystal [23]. However, it may cause transformation of polymorphs because of its high energy. New emerging THz absorption spectroscopy provides vibrational spectral features in the low-frequency region below 100 cm^{-1} which are associated with intermolecular vibrational modes of molecules, and recently this technique has been applied to characterize the cocrystal formation in pharmaceutical field [25–27]. The vibrational Raman and IR spectroscopies are the most used ones since they are easy handling, in-situ and on-line monitoring capabilities, and also high reproducibility. These vibrational techniques offer lots of information about crystalline structures related modification from molecular level with high sensitivity and selectivity [28]. In this study, the cocrystal of adenine with fumaric acid was prepared by slow evaporation method from methanol and also grinding method. The cocrystal has been characterized by FT-IR, FT-Raman spectroscopic tehcniques. Meanwhile, DFT calculations have been used to simulate the optimized structures and frequencies of adenine, fumaric acid and their corresponding cocrystal. Comparing theoretical and experimental results, the difference between starting materials and the corresponding cocrystal formed due to the intermolecular hydrogen-bond effect between adenine and fumaric acid could be shown clearly.

2. Experimental and theoretical methods

2.1. Samples preparation

Adenine and fumaric acid were obtained from Sigma-Aldrich (purity 99%), and used without further purification. The API adenine and CCF fumaric acid were ground before mixing to achieve particles with several micrometer sizes. Physical mixture was obtained by gently mixing two compounds with a 1:1 molar ratio in a glass vial by using a vortex mixer during 10 mins. Solvent cocrystal was prepared by slow solvent evaporation method. Equimolar adenine and fumaric acid were dissolved in amount of ethyl alcohol. The solution was slowly evaporated at room temperature and the corresponding solvent cocrystal was produced during several days. Grinding cocrystal was performed by co-milling adenine with fumaric acid under 1:1 molar ratio in 25 mL stainless steel milling jars using a planetary ball mill (QM-3SP, gear type, Nanjing University Instrument Plant) with a frequency of 25 Hz at room temperature.

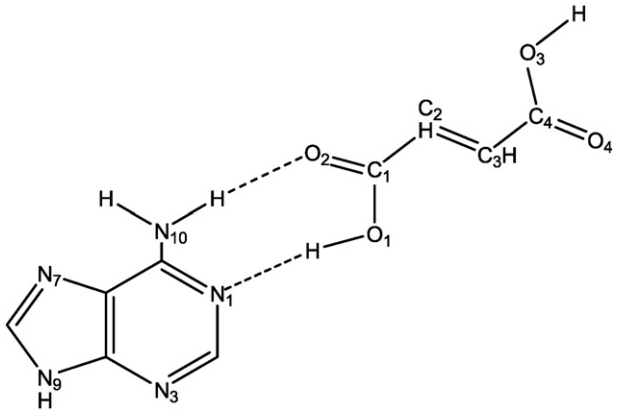

Fig. 2. The structures of cocrystal formed between 9H adenine and fumaric acid.

2.2. IR and Raman spectroscopy

FT-IR spectra in the frequency range 4000–400 cm^{-1} with 4 cm^{-1} spectral resolution were measured in the reflection mode using an FT-IR spectrometer Avatar 370. All the spectra were averaged over 128 scans.

FT-Raman spectra were recorded at room temperature in the range 3700–100 cm^{-1} with 2 cm^{-1} spectral resolution using an FT-Raman spectrometer Nicolet Raman 960. All the spectra were averaged over 128 scans.

2.3. DFT calculation

The equilibrium geometry and vibrational spectra of adenine, fumaric acid and cocrystal were performed using the Gaussian 03 program package [29]. According to the spectra of solvent cocrystal and grinding cocrystal and the study of Thompson et al. [10], 9H adenine was confirmed to form cocrystal with fumaric acid (structure shown in Fig. 2). Frequency analysis was used B3LYP/6–31G (d,p). The corresponding scaling factor was chosen to be 0.96 [30].

3. Results and discussion

3.1. Vibrational spectroscopic analysis of adenine, fumaric acid and cocrystal

3.1.1. FT-IR spectroscopy

FT-IR spectra in the region of 400–1800 cm^{-1} for adenine, fumaric acid and their solvent/grinding cocrystal are presented in Fig. 3. The spectra of solvent cocrystal and grinding cocrystal are almost identical, which means that alcohol did not involve in the formation of hydrogen bonding and just assisted the connection between adenine and fumaric acid during the cocrystal formation process. Comparing with adenine, fumaric acid and their physical mixture, the FT-IR spectrum of cocrystal has some differences in the frequencies of the vibrational bands and