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Interaction Study of Co-Crystallization or Salt Formation Between 5-Hydroxyisophthalic Acid and 4,4′-Bipyridine using NMR and Powder X-Ray Diffraction

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When an organic acid and an organic base are used for the study of potential co-crystallization then on the basis of differences in their pK_a salt, co-crystal or proton transfer is possible. A study of the Cambridge Structural Database (CSD) revealed that no cocrystal or salt formation has been observed between 5-hydroxyisophthalic acid (5-HIPA) and 4,4′-bipyridine (4,4-BIPY). This fact provided motivation for the study of interaction between these two leading to co-crystallizations or salt formation. On comparing differences in their pK_a values these two lays in transition range where three possibilities as mentioned above may be present. In this study, it is emphasized on exploring interaction between 5-HIPA and 4,4-BIPY, using solution state NMR and powder X-ray diffraction (PXRD) and find feasibility of cocrystal formation, salt formation or proton transfer. After studying this system, evidence were found in support of proton transfer between 5-HIPA and 4,4-BIPY and molar ratio for maximum interaction between acid and base was also mapped and found to be 1:1.

Keywords: Cocrystal, Proton Transfer, NMR, 5-Hydroxyisophthalic Acid, 4,4′-Bipyridine.

INTRODUCTION

Crystallization involves the separation of solid phase from supersaturated solution or mother liquor [1]. It is alluring from a scientific and technological standpoint since it is a form of self-assembly process, which has been acknowledged as one of the major technologies in the large scale production of nano-structures [1,2]. Solid-state chemistry addresses different issues like polymorphism, which is also an important phenomena and can be defined as occurrence of material(s) in more than one crystalline form (like diamond and graphite) with same chemical composition, directing crystalline morphology of organic, inorganic and hybrid materials to get designer materials [3]. The significance of crystalline characteristics in agrochemicals and pharmaceuticals is also stressed since they influence physico-chemical features such as ease of handling in production processes, durability and longevity, dissolution, absorption, potency and so on [4].

Crystallization is a supramolecular reaction and clearly differs from molecular synthesis [5,6]. It can be broken down into two steps: nucleation and growth, however they really happen at the same time. In some favorable situations, studies of aggregation processes in solution can yield chemical insights into the nucleation and growth of the crystallization process, as well as chemical insights into the final organization of the molecules in the solid state [2].

Cocrystals have been defined as solids that are crystalline single-phase materials composed of two or more different molecular or ionic compounds generally in a stoichiometric ratio, which are neither solvates nor simple salts [7]. The constituents of cocrystal intermingle through non-covalent interactions for example H-bond, electrovalent bond, van der Waals forces and π-π stacking. These forces gives rise to cocrystal lattice energy, which results in a structure with greater stability than their original structure [8,9]. Due to the intermolecular force of attraction cocrystal formed display physical and chemical characteristics that vary from the sub-components [10]. Melting temperature, dissolution, chemical inertness and mechanical behaviour are examples of these kind of properties. Certain cocrystals have been discovered as polymorphs, with varying physical characteristics depending on the shape of crystal [10]. The creation of energy materials, pharmaceuticals, and other composites relies heavily on cocrystal engineering [11]. Efforts have been successfully done to increase drug's bioavailability

by forming cocrystal of an active pharmaceutical ingredients (API) [12]. Proton transfer from acid to base has been reported in number of cases along with cocrystallization and it gives rise to salt formation [13-15].

Desiraju *et al*. [16] provided a concept based on supramolecular synthons to address the directional intermolecular forces (for example H-bonding, π-π stacking, C–H···π interactions, *etc*.) that dictate a periodic assembly. There are considerable efforts to investigate the early stages of crystal nucleation by various analytical tools. While X-ray diffraction methods address the ordered assembly of molecules, spectroscopic techniques provide valuable information about the intermolecular interactions between the solute-solvent and solute-solute molecules in under-saturated solution [17].

Solution state NMR can be used to study the intermolecular interactions responsible for the nucleation process. This information, usually derived from complexation-induced changes in chemical shift from proton NMR, can provide clues to the self-organization of the molecules eventually observed in the three-dimensional structure of multicomponent solids [1,18,19]. The concentration-dependent variations in chemical shift (^{1}H) of two different compounds were used to forecast how these compounds would pack in the crystal lattice. Solution state NMR has been used to explore the accumulation of dye molecules in aqueous solution, the interaction of pharmaceuticals, and the aggregation of steroid [1,20-22].

Desiraju *et al*. [23] studied the aggregation in solution state of compounds containing aniline-phenol functional groups with the help of NMR and proposed that hydrogen bonding and π-π stacking aided their aggregation to form cocrystals. They identified that the amine-phenol synthon C–H···O was responsible for supramolecular aggregation and transformation into the crystal from solution state. In a related study, Ramanan *et al*. [24] studied the co-crystallization of orotic acid and isoorotic acid with a series of amine and pyridine based coformers. They studied the role of the acid···pyridine synthon on the supramolecular behaviour of both these acids with organic bases.

5-Hydroxyisophthalic acid (5-HIPA) is a precursor material for a wide range of goods, including pharmaceuticals, agriculture products and polymeric substances [25]. 5-HIPA has recently received a lot of attention as a drug intermediate since it is utilized to make X-ray contrast materials (radiopaques) like iomeprol [26]. 4,4′-Bipyridine (4,4-BIPY) may bond between metal centers to generate coordination polymers due to its structure in uniform polymerization [27,28]. The electronic effects involving two paramagnetic metal atom or ions can also be facilitated by 4,4-BIPY [29,30].

As, in Cambridge Structural Database (CSD) no results were found for cocrystal or salt formation between 5-HIPA and 4,4-BIPY. Therefore, these two were selected for studying interactions and possibilities for cocrystal and/or salt formation with each other. In present study, the problem of proton transfer or salt formation between 5-hydroxyisopthalic acid and organic base 4,4′-bipyridine was tried to fix with the help of change in chemical shift observed in solution state NMR and diffractograms acquired through powder X- ray diffraction.

EXPERIMENTAL

First, the solubility of 5-hydroxyisopthalic acid (5-HIPA) and 4,4′-bipyridine (4,4-BIPY) in water was measured, following which 0.02 g of 5-HIPA (A) and 0.013 g of 4,4-BIPY (B) (Fig. 1) was dissolved in 10 mL and 5 mL of water, respectively to yield two samples with concentrations A = 1.09×10^{-2} M and B = 1.70×10^{-2} M. A series of solutions of different concentrations of A, B and mixture of A and B were prepared by adding the different volumes (5, 15, 35, 75, 155, 315, 635 µL) of prepared sample in 500 µL of solvent (400 µL H_2O and 100 µL D_2O). ^{1}H NMR spectra were recorded at various concentrations of the mixtures on a Bruker 400 MHz NMR spectrometer equipped with 5 mm BBO probe. These spectra were recorded using a pulse acquire experiment with and without presaturation at room temperature.

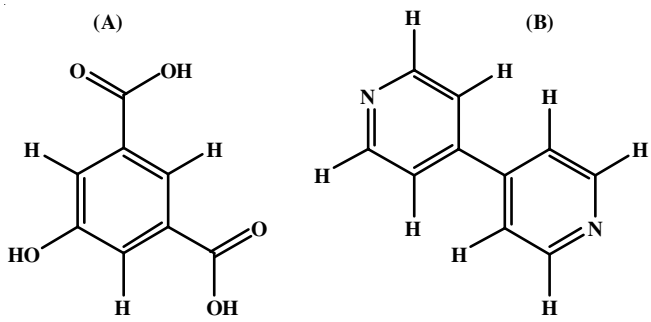

Fig. 1. Structure of 5-hydroxy isophthalic acid (A) and 4,4-bipyridine (B)

The reactants were weighed and mixed together in the molar ratio (1:1, 1:2, 1:3, 1:4, 1:5, 2:1, 3:1, 2:3 and 3:2) and ground using mortar and pestle. The mixture formed after grinding was dissolved in minimal amount of water and kept for a few days in order to evaporate the solvent and obtained a solid precipitate. The precipitate was filtered and dried in air. X-ray diffraction patterns of all the samples were recorded using a powder-X-ray diffractometer to ascertain the crystallinity of the products.

Data obtained from ^{1}H NMR spectra from samples of 5-HIPA (A) and 4,4-BIPY (B*)* base with different molar ratio is plotted (Fig. 2). Peaks 1 and 2 are from base and peaks 3 and 4 from acid. From above plots one could find that in solution with molar ratio 1:1 greater change in chemical shifts is observed, which indicate the presence of interaction between A and B. Mixture of A and B with same composition is used for the solution state, whereas NMR were used for obtaining solid samples by mixing and grinding. It appears from the PXRD patterns (Fig. 3) that new phase(s) appear to form, particularly with compo-sitions 1:1 and 1:2 molar ratio. During this study, we did not succeed to grow suitable single crystals to solve the structure of the molecular complex solid.

RESULTS AND DISCUSSION

The equilibrium constant, log K to be precise, for the proton transfer from acid to base is proportional to the difference in the pK_a of base and acid. The first and second pK_a values of bipyridine are 3.17 and 4.82, respectively, while the first and

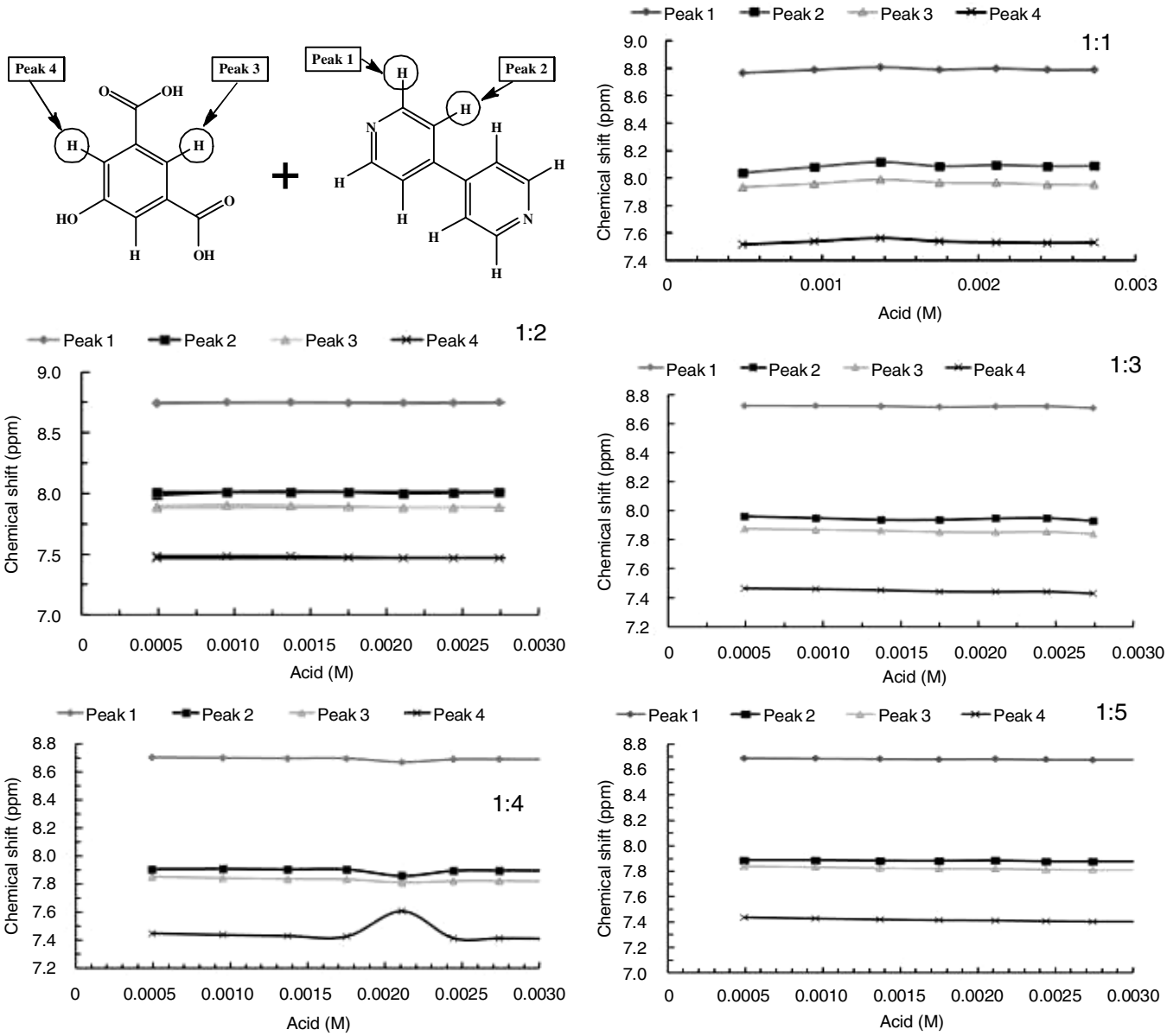

Fig. 2. Chemical shift *vs.* concentraton (acid) plots for different molar raio of acid and base solutions (1:1 to 1:5) in water D_2O solvent system

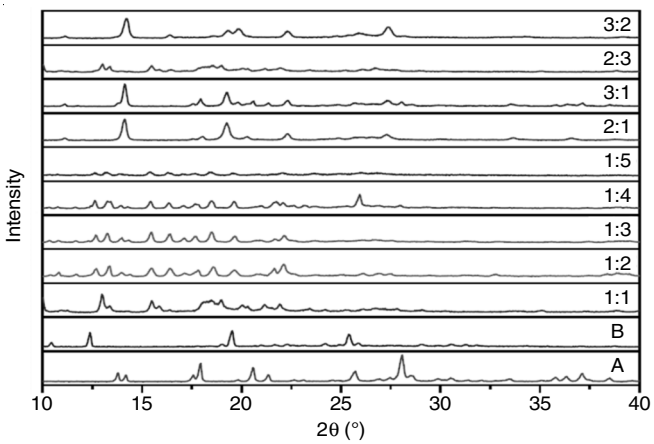

Fig. 3. Overlay of powder X-ray diffractions (PXRD) of samples of different molar ratio of 5-hydroxyisopthalic acid (A); 4,4,-bipyridine (B) and their mixture in different molar ratio (1:1; 1:2; 1:3; 1:4; 1:5; 2:1; 3:1; 2:3) made by grinding

second pK_a values of isophthalic acid are 3.46 and 4.46, respectively. On the basis of difference between pK_a values of 4,4-BIPY and 5-HIPA ΔpK_{a1} = -0.29 and ΔpK_{a2} = 0.36. It falls in transition range where all probabilities are possible that it may form salt or cocrystal or transfer of proton may occur.

On CSD data analysis, we could not find any cocrystal or salt of 4,4-BIPY with 5-HIPA. Attempts were made to form co-crystal between 5-HIPA and 4,4-BIPY in solvent mixture of methanol and acetone to record single crystal XRD, but no cocrystals were obtained. The limited efforts to assign the correct unit cell parameters and giving proper indices to different peaks observed in PXRD. In overlaid powder patterns of mixtures of 5-HIPA and 4,4-BIPY (Fig. 3), new peaks are observed as compared to their pure form. These peaks signify formation of new phases.

^{1}H NMR spectra recorded for the mixtures prepared for co-crystal formation are shown in Fig. 4. The chemical shift

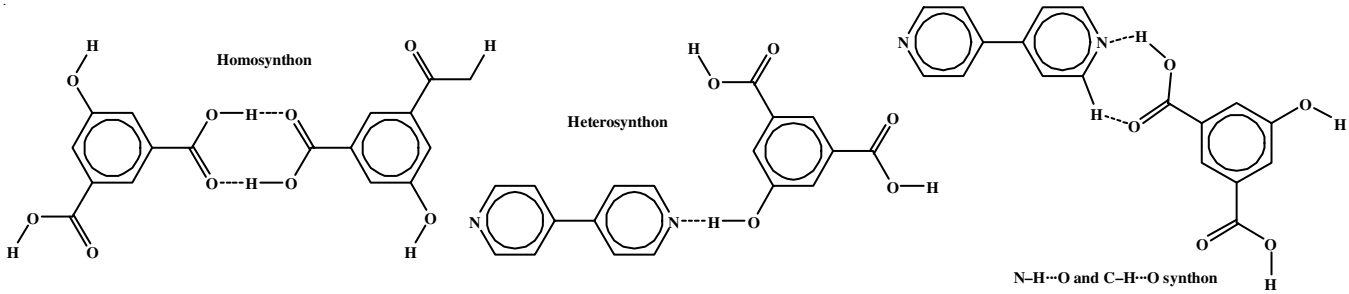

Fig. 5. Favorable interactions between 5-hydroxy isophthalic acid and 4,4-bipyridine. Upper parts show homosynthon and heterosynthon and lower part shows most important N–H···O and C–H···O interactions

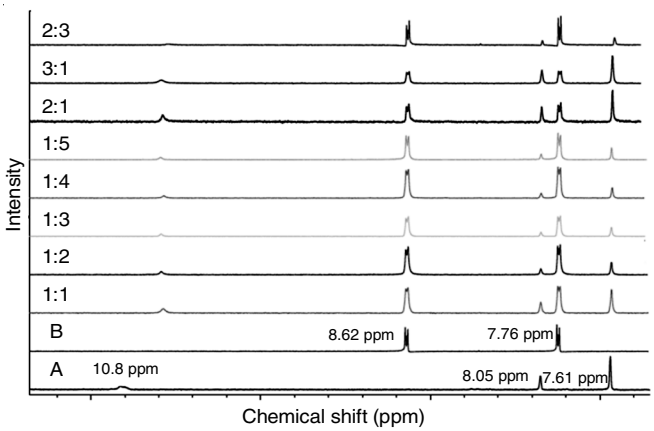

Fig. 4. NMR spectra of 5-hydroxyisopthalic acid (A); 4,4,-bipyridine (B) and their mixture (1:1; 1:2; 1:3; 1:4; 1:5; 2:1; 3:1; 2:3)

is around 10.8 ppm belongs to proton of carboxylic acid of 5-hydroxyisophthalic acid as proved by D_2O exchange. This peak is shifting towards shielded region when mixed with 4,4′-bipyridine in 1:1 molar ratio. But there is no such changes observed in the peaks of 4,4-BIPY.

The aromatic proton peaks of 5-HIPA are slightly shielded. There is no such change in chemical shift value of protons when molar ratio is changed from 1:1 to 1:2; 1:3 and so on. It confirmed that maximum interaction is occurring in 1:1 molar ratio of 5-HIPA and 4,4-BIPY and could be shown by N-H …O and C-H…O interactions (Fig. 5). Downfield shift for the base and up field shift in the chemical shift values for the acid (5-HIPA) were observed for 1:1 molar ratio mixture. It indicates that in the equimolar mixture the electron density in the base (4,4-BIPY) is less than in its pure form, while the opposite is true in the acid. The study shows the transfer of proton from the carboxylic acid to the base's N, favouring salt formation through transfer of proton. The possible interactions between 5-HIPA and 4,4-BIPY are epitomized in Fig. 5. These non-bonded interactions mainly arise through hydrogen bonds and are important for the observed structural diversity. These interactions should be responsible for the changes observed in chemical shifts of the different combinations of acid and base. With the help of data presented in Figs. 2 and 4, proton transfer from acid to base is confirmed.

Conclusion

In this study, probably first time, non-bonding interaction between 5-hydroxyisophthalic acid (5-HIPA) and 4,4′-bipyridine (4,4-BIPY) are studied, which is a new combination. After studying changes in chemical shift values and overlaid powder X-ray diffractions of samples in different molar combinations of 5-HIPA and 4,4-BIPY, formation of 1:1 complex is recommended. Chemical shift measurements corroborate transfer of proton from acid (5-HIPA) to base (4,4-BIPY) instead of expected cocrystallization. This result would be helpful for pharmaceutical industry in the designing of cocrystal or salt using 5-HIPA or 4,4-BIPY. In present case, due to lower solubility of 5-HIPA, 4,4-BIPY and their mixture in the aqueous phase, application of solution state NMR spectroscopy is restricted for exploring nucleation and/or aggregation leading to crystallization, which was the undelaying motive of the study. This investigation would help in future for understanding the process of nucleation and aggregation using solution state NMR spectroscopy supported by PXRD.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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