



Structural, quantum chemical, vibrational and thermal studies of a hydrogen bonded zwitterionic co-crystal (nicotinic acid: pyrogallol)



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ABSTRACT

In the present work, a new co-crystal of nicotinic acid with pyrogallol (NICPY) has been grown in the zwitterionic form and the corresponding structural, vibrational, thermal, solubility and anti-cancer characteristics have been reported. The single crystal X-ray diffraction analysis confirms that the structural molecular packing of the crystal stabilized through N–H···O and O–H···O hydrogen bond. The stabilization energy of the hydrogen bond motifs were calculated in the solid state. Vibrational spectral studies such as Fourier transform-infrared (FT-IR) and FT-Raman were adopted to understand the zwitterionic co-crystalline nature of the compound, which has been compared with theoretically calculated vibrational frequencies. The thermal stability of the grown co-crystal was analyzed by TG/DTA study. The solubility of the NICPY co-crystal was investigated in water at different temperature and compared with that of the nicotinic acid, which is the parent compound of NICPY co-crystal. The grown crystals were treated with human cervical cancer cell line (HeLa) to analyze the cytotoxicity of NICPY crystals and compared with the parent compound, which shows that NICPY has moderate activity against human cervical cancer cell line.

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1. Introduction

In Pharmaceutical industry, there are several approaches such as formation of salts, polymorphs, solvates, hydrates and cocrystal to improve the physicochemical properties of a drug [1–4]. Salt formation is the most common and effective approach to modulate the physicochemical properties of the active pharmaceutical ingredients (API) [5]. The limitation behind the method is that it requires at least one site for ionisation [6]. In the absence of ionization center, cocrystallization of pharmaceutical compounds may be employed to enhance the efficiency of a drug [7,8]. There has been a great urge in the design of cocrystals attributing to their potential intellectual property and increase in the scope of cocrystallization over salt formation. The design of cocrystals generally involves supramolecular heterosynthons such as pyridine-carboxylic acid [9–15], amide-carboxylic acid [16–22], carboxylic acid-chloride [23–26], etc. The crystal engineering is quite interesting with the presence of any ionized (e.g. carboxylate) moiety in cocrystal [27]. The presence of ions in the cocrystal favours hydrogen bonding

with water as well as tighter crystal lattice of ionized molecules, thus improving solubility and stability of the drug when compared to the parent neutral forms [28]. Also, the existence of charged species in physiological pH range facilitates the drug to bind to the plasma targets in body [29,30].

Vitamins are organic compounds that are required by the human body for metabolism and to sustain life. They are found to be least explored as cofomers in cocrystallization. Cocrystallization of vitamins with APIs shows enhanced physicochemical properties of the cocrystals and also improves the potential of dual drugs. Nicotinic acid (NA) also known as niacin or vitamin B3 is a water soluble vitamin. NIC acts as active pharmacological drug for various diseases like pellagra, hyperlipidemia, cardiovascular heart disease, Alzheimer's disease, cancer, type II diabetes, etc. Considering its vitaminic and nutritional role, NIC has been cocrystallized with a polyphenolic compound, pyrogallol as human diets often comprise rich-phenolic foods and beverages such as fruits, vegetables, wines and teas, whose consumption is expected to lead to high concentration of phenolic compounds in the stomach fluid. The present study focuses on the enhancement of cytotoxic effect of the drug.

Nicotinic acid is not zwitterion in its pure form but surprisingly the crystal has crystallized in zwitterionic form in the present case.

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From the review of CSD, the number of entries for nicotinium zwitterion with NH^+ and COO^- groups are 17. But there are only 5 nicotinium zwitterionic co-crystals (CSD ref code: PEKROO, RUWFAR, RUWFAR01, RUWHAT, RUWHEX) [31]. The formation of salt or co-crystal can be predicted from ΔpK_a rule [$\Delta\text{pK}_a = (\text{pK}_a(\text{base}) - \text{pK}_a(\text{acid}))$]. When ΔpK_a is greater than 4, the ionized acid - base crystalline complex (salt) are observed exclusively and non-ionised acid–base complexes (cocrystal) are observed exclusively for $\Delta\text{pK}_a < -1$. For acid–base complexes whose ΔpK_a values lie between -1 and 4 , the behaviour of salt-co-crystal continuum (zwitterionic cocrystal) is observed [32]. The pK_a value of NIC has been calculated using ChemAxon (Marvin 15.11.30, Chemaxon software, www.chemaxon.com). For NIC, pK_a of acid has been calculated as 2.79 and that of for conjugate acid of the base has been calculated as 4.19. Therefore ΔpK_a of NIC has been calculated as 1.40, which means the formation of salt-co-crystal continuum is consistent in this zone. As expected, here we present a newly formed co-crystal, Nicotinic acid: pyrogallol (NICPY) containing carboxylate moiety, in zwitterionic form.

2. Materials and methods

2.1. Experimental

Nicotinic acid and pyrogallol were sourced from commercial suppliers and used as such without any further purification. Nicotinic acid (0.123 g) and pyrogallol (0.126 g) were dissolved in 15 ml of distilled water and left for crystallization at ambient temperature. Block morphology crystals were obtained after a week. The density of the crystals were measured by sink and swim method (flotation technique) using a liquid mixture of xylene and carbon tetrachloride. The observed density of the crystal was found to be $1.53 (1) \text{ mgm}^{-3}$. The preliminary crystallographic calculations, i.e., the unit cell parameters of NICPY and full data collection were done by Bruker SMART APEX CCD area detector diffractometer (graphite-monochromated, $\text{MoK}\alpha = 0.71073 \text{ \AA}$) [33]. Crystallographic data, details of data collection and refinement statistics are given in Table 1. The structure was solved by direct methods using SHELXL 2014 [34]. All the non-H atoms were refined anisotropically. All the H atoms were located in difference Fourier map and refined

Table 1
Crystallographic data and Structure refinement parameters for NICPY.

Empirical formula	$\text{C}_6 \text{H}_5 \text{NO}_2 \cdot \text{C}_6 \text{H}_6 \text{O}_3$
Formula weight	249.22
Temperature	294 (2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, $\text{Pca}2_1$
Unit cell dimensions	$a = 13.923 (1) \text{ \AA}$ $\alpha = 90^\circ$ $b = 11.978 (9) \text{ \AA}$ $\beta = 90^\circ$ $c = 12.967 (1) \text{ \AA}$ $\gamma = 90^\circ$
Volume	$2162.8 (3) \text{ \AA}^3$
Z, Calculated density	8, 1.531 Mg/m^3
Absorption coefficient	0.121 mm^{-1}
F(000)	1040
Crystal size	$0.15 \times 0.22 \times 0.25 \text{ mm}^3$
Theta range for data collection	$1.70\text{--}28.27^\circ$
Limiting indices	$-16 \leq h \leq 16, -14 \leq k \leq 14, -15 \leq l \leq 15$
Reflections collected/unique	19148/3813 [R(int) = 0.0279]
Completeness to theta = 25.00	97.4%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3813/2/351
Goodness-of-fit on F^2	1.097
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.039, wR2 = 0.1108$
R indices (all data)	$R1 = 0.0447, wR2 = 0.1193$
Largest diff. peak and hole	0.407 and $-0.288 \text{ e. \AA}^{-3}$
CCDC No	1501610

isotropically. A Perkin Elmer FT-IR spectrometer of model spectrum RXI with a resolution of $1\text{--}2 \text{ cm}^{-1}$ was used for IR spectral measurements. The samples were prepared using pellet technique with KBr and the spectra were recorded over the range $4000\text{--}400 \text{ cm}^{-1}$. The FT-Raman spectrum was recorded in the frequency range of $4000\text{--}400 \text{ cm}^{-1}$ using a BRUKER RFS 27 FT-Raman Microscope module. The Nd:YAG Laser source was operated at 1064 nm for the excitation with the resolution of 2 cm^{-1} . Thermogravimetric analysis (TGA) and Differential Thermal Analysis (DTA) were carried out for the crystals using a SDT Q600 thermal analyzer. The crystals were powdered and used for the analysis in the temperature range of $28\text{--}600 \text{ }^\circ\text{C}$ with a heating rate of $25 \text{ }^\circ\text{C/min}$ in air atmosphere.

2.2. Computational details

The theoretical computations were done on a Intel Core i5/3.20 GHz computer using Gaussian 09W [35]. Geometrical optimisations and computation of harmonic vibrational wave numbers were done for the minimum energy conformer of the molecular structure at HF and DFT/B3LYP levels invoking 6-311++G(d,p) basis set without any constraint on the geometry optimization [36]. It is accepted as a cost-effective approach for the computation of molecular structure, vibrational frequencies and energies of optimized structures. Initial geometry for the computation was taken from the Crystallographic Information File (CIF) obtained from single crystal XRD. The optimized structural parameters were used in the vibrational frequency calculations at the same level to characterize all stationary points as minima. Then vibrationally averaged nuclear positions of the structure were used for harmonic vibrational frequency calculations resulting in IR and Raman frequencies. By combining the results of the GAUSSVIEW program [37] with symmetry considerations, vibrational frequency assignments were made with high precision. The calculated frequencies were scaled to compensate for the approximation treatment of electron correlation, for the basis set deficiencies and for the anharmonicity. The calculated frequencies are scaled by 0.96 for B3LYP and 0.89 for HF [38]. There is always some ambiguity in defining internal coordination. However, the defined coordinate from complete set matches quite well with the motions observed using the GAUSSVIEW program. The frontier molecular orbital energies, energy gap between occupied and unoccupied molecular orbitals of NICPY is also calculated at HF and B3LYP level with 6-311++G(d,p) basis set.

2.3. Calculation of stabilization energy of hydrogen bonded motifs

The prediction of hydrogen bond strength from single point energy of the molecular structure are helpful in understanding which interactions are dominant in the crystal and therefore which interactions are more important during crystal formation [39]. The single point energy calculations of different graph-sets were calculated for the real crystal structure in their respective coordinates from X-ray structures at B3LYP/6-311++G(d,P) level of theory at room temperature [6,40,41]. The standard energy difference method [42,43] was used to calculate the energy of the hydrogen-bonding interaction between a donor and acceptor.

$$\Delta E_{\text{HB}}(R) = E_{\text{AD}}(R) - E_{\text{A}} - E_{\text{D}}$$

where ΔE_{HB} is the energy of hydrogen bonding interaction, R is the set coordinates that define the structure of the hydrogen bonding complex, $E_{\text{AD}}(R)$ is the total energy of the complex, and E_{A} and E_{D} are the individual energies of the acceptor and donor moieties respectively. This approach is more realistic and provides information on the effects of molecular packing and stabilization energy of the system. But for this purpose, much more computationally

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