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Spectroscopic (FT-IR, FT-Raman, ^{13}C SS-NMR) and quantum chemical investigations to explore the structural insights of nitrofurantoin-4-hydroxybenzoic acid cocrystal

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Anuradha Shukla,^a Eram Khan,^a MHD. Bashir Alsirawan,^b Rajorshi Mandal,^c Poonam Tandon,^{a*}
Venu R. Vangala^{b*}

Cocrystallization is an attractive approach to improve the physicochemical properties of active pharmaceutical ingredients (API), which has great potential in the drug development. Accordingly, there is growing need to understand the physicochemical changes that occur upon co-crystallisation. This work focuses on the combined use of spectroscopy and density functional theory (DFT) calculations to understand the molecular structure, hydrogen bond interactions and physicochemical properties of a pharmaceutical cocrystal. Solid-state NMR (ssNMR) can provide detailed molecular structure information about pharmaceutical cocrystals and complexes. It is non-destructive and usually provides depth of structural insights that can complement well with vibrational spectroscopy. In this work, cocrystal of an antibiotic drug, nitrofurantoin (NF), with 4-hydroxybenzoic acid (4HBA) is examined to understand the capabilities of multiple spectroscopic techniques such as infrared (IR), Raman and solid-state NMR techniques, and to confirm the molecular structure and hydrogen bonding of cocrystal systems. The results of IR and Raman spectroscopy showed that for the cocrystal formation, NF and 4HBA molecules interact through N-H...O-H interaction between imide N-H of nitrofurantoin and phenolic -OH of 4-hydroxybenzoic acid, these interactions are also confirmed by natural bond orbital (NBO) and Quantum theory of atoms in molecules (QTAIM) analyses. It is critical to understand whether a given cocrystal, upon conceiving a modified crystalline structure to that of its API, show enhanced physical and chemical properties or not. Computationally, it is found that NF-4HBA cocrystal shows softer (more reactive) behaviour in comparison to NF as its cocrystal, NF-4HBA, has low band gap in comparison to API, NF. These results demonstrate that quantum chemical approach could be able to predict accurately as to how a cocrystal does in relation to its physical and chemical properties.

I. Introduction

Cocrystals are the solids that are crystalline single phase materials composed of two or more different molecular/ionic compounds present in a stoichiometric ratio which are neither solvates nor salts.^{1,2} A pharmaceutical cocrystal is a multiple component crystal in a definite stoichiometric ratio, one being the drug (API), while the other is a benign, non-toxic 'co-former' molecule where the interactions between them are hydrogen bonding, π - π or van der Waals interactions.^{1,3-6} Pharmaceutical cocrystals represent better alternatives to enhance drug physicochemical properties such as solubility, stability and bioavailability in pharmaceutical development without changing the chemical composition of the

API.^{2,7-14} Pharmaceutical cocrystals for the physical property optimisation have been described for several drugs through hydrogen bonding.^{15,16}

Nitrofurantoin (1-[[[5-nitro-2-furanyl]methylene]amino]-2,4-imidazolidinedione; NF) is an antibacterial drug that is used to treat bacterial infections of the urinary tract (bladder and kidneys).¹⁷ It has been reported that NF has poor water solubility (thus bioavailability) and its dissolution in water is therefore the rate-limiting step in its absorption from the gastrointestinal tract.¹⁸ It is also reported that physicochemical stability of NF could be one of the significant consideration for controlling the bioavailability of commercial preparations.¹⁹ Cocrystals of NF with the various co-formers have been reported, which offers improved physicochemical properties to the NF.^{9,20,21} Solid state nuclear magnetic resonance spectroscopy (SS-NMR) has been widely used for cocrystal analysis.²²⁻²⁴ The technique is non-destructive and is sensitive to hydrogen bonding.²⁵ Vibrational spectroscopic techniques, such as Raman and IR spectroscopy, represent attractive techniques for probing differences at the molecular level.²⁶ These techniques are also used for the complete characterization of the chemical composition of pharmaceutical cocrystals.²⁷⁻³⁰

In this study, we have expanded our work on cocrystal^{31,32} by considering the cocrystal of nitrofurantoin with 4-hydroxybenzoic acid. 1:1 co-crystal involving nitrofurantoin and 4-

^a Department of Physics, University of Lucknow, Lucknow 226007, Uttar Pradesh, India

^b Centre for Pharmaceutical Engineering Science, School of Pharmacy and Medical Sciences, University of Bradford, Bradford BD7 1DP, United Kingdom

^c Department of Chemistry, Indian Institute of Technology, Kharagpur 721302, India

* Corresponding authors. Tel.: +91 522 2782653; fax: +91 522 2740840

E-mail: poonam_tandon@hotmail.com, poonam_tandon@yahoo.co.uk (P. Tandon)

Tel.: +44 127423 6116, E-mail: V.G.R.Vangala@bradford.ac.uk (V. R. Vangala)

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hydroxybenzoic acid (NF-4HBA) has been taken for structural characterization (FT-IR, FT-Raman, solid state NMR) and structural activity. To consider all the possible nearest neighbor interactions, theoretical calculations were carried out on dimer model of NF-4HBA to obtain improved agreement with the solid phase experimental results. In the present work, the changes in the physicochemical properties during the co-crystallisation of NF with 4HBA has been discussed and the optimized geometries, intra/inter molecular hydrogen bonding (H-bonding) interaction, structure–activity relationship have also been analysed for monomer and dimer models of NF-4HBA cocrystal. To describe quantitatively the pattern of the intermolecular interactions in the NF-4HBA cocrystal, quantum theory of atoms in molecules (QTAIM) and natural bond orbital (NBO) analyses have been done. In this work, we seek to understand the details of the hydrogen bond in the monomer model of NF-4HBA cocrystal and to consider the similar interaction in dimer model of cocrystal and identify differences between the monomer and dimer model of NF-4HBA. Thus, the studies are performed on the structural properties of NF-4HBA.

II. Experimental Details

Fourier transform-infrared spectroscopy- Bio-Rad, FTS 3000MX FT IR spectrometer was used for transmission infrared spectra of the NF-4HBA and 4HBA. The spectra were collected for 64 scans at 4 cm⁻¹ resolution. Typically, ~25 mg of the sample was ground with KBr in an agate mortar and pressed with a steel die into a pellet.

Fourier transform-Raman spectroscopy- FT-Raman spectrum of the NF-4HBA was recorded on a Bruker IFS 55 EQUINOX with Raman attachment. This instrument uses a 1064 nm Nd-YAG laser line of power 500 mW as the excitation line for recording the Raman spectra in the region 20–3400 cm⁻¹. The spectra were collected for 512 scans at 4 cm⁻¹ resolution.

Dispersive Raman spectroscopy- A JYHoriba LabRAM HR Raman spectrometer was used for dispersive Raman. This instrument equipped with a confocal microscope, liquid-nitrogen-cooled charge coupled device (CCD) and a multichannel detector (256 pixels × 1024 pixels). The NIR 784.8 nm argon ion laser was selected to excite the Raman scattering. The Raman shift range collected was in the range of 100–1700 cm⁻¹ with spectral resolution 1.7–2 cm⁻¹.

CP-MAS solid state NMR spectroscopy- Cross-polarization Magic Angle Spinning (CP-MAS) solid state NMR spectra were acquired using a Bruker Avance III HD 400 MHz spectrometer fitted with a 4 mm HX-MAS BB/1H probe head. Samples were packed without further manipulation into 4 mm ceramic spinners. 116 scans were acquired using cross polarization with TOSS spinning sideband suppression. A 1 ms contact time, 120 s recycle delay and a spin rate of 10 kHz was used. Spectral referencing was with respect to an external sample of neat tetramethylsilane (carried out by setting the high-frequency signal from adamantane to 38.5 ppm). All solid-state NMR spectra were obtained at the EPSRC UK National Solid-State NMR Service at Durham.

III. Computational Details

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Density Functional Theory (DFT) has been used for the structural and electronic properties of NF-4HBA cocrystal. In the present study, DFT calculations were carried out using Gaussian 9.0 Program package.³³ The optimization of monomer and dimer model of NF-4HBA were performed by employing cc-pvTZ, correlation consistent polarized valence triple- ζ , basis set³⁴ and B3LYP functional.^{35,36} The pictorial visualisation of input and output files of studied molecules were done with the help of Gauss View5.0.³⁷ Gar2Ped software package³⁸ is used for the assignment of vibrational frequencies on the basis of the potential energy distribution (PED). For PED analysis, a complete set of internal coordinates were defined using Pulay's recommendations.³⁹ The natural bond orbital (NBO) analysis is done to show the possible molecular interactions between the molecular orbitals by NBO 5.0⁴⁰ program of Gaussian 09W. The pictorial verification for these molecular interactions is collected from the framework of the quantum theory of atoms in molecule (QTAIM) analysis with the help of AIM 2000 software.⁴¹

IV. Results and discussion

1. Geometry optimization and energies

NF-4HBA cocrystal crystallizes in the monoclinic system in $P2_1/c$ space group. Initial geometrical optimization of NF-4HBA cocrystal was performed using the crystallographic data of cocrystal reported by one of the authors of this work.⁹ Initial geometry for NF, 4HBA and NF-4HBA were minimized at the DFT level employing B3LYP/cc-pvTZ level of theory. To consider all nearest neighbour hydrogen bonding interactions present in the NF-4HBA cocrystal⁹, calculation is performed on dimer model of NF-4HBA. The ground state optimized structure of NF-4HBA (monomer), NF-4HBA (dimer), NF (monomer) and 4HBA (monomer) are shown in Fig. 1, Fig. 2, Fig. S1 and Fig. S2 respectively.

Fig. 1 Optimized structure of NF-4HBA (monomer model) with atom numbering scheme adopted in this study.

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Fig. 2 Optimized structure of NF-4HBA (dimer model) with atom numbering scheme.

The optimized structural parameters of the monomer and dimer model of NF-4HBA were compared with the experimental results⁹. For comparison see Electronic supplementary information (Table S1). The hydroxyl group (OH) of phenolic ring forms a hydrogen bond with the imide and C=O group of hydantoin ring of nitrofurantoin resulting in the formation of NF-4HBA cocrystal. As shown in Electronic supplementary information (Table S1) the calculated values of the bond lengths do not differ more than 0.02 Å from the experimental values for both monomer and dimer model of NF-4HBA, except for the bonds having one of the atoms as hydrogen. However, some discrepancy is observed in the case of bond length, C19-O28, O28-C39 and O26-C39 as these bonds (COOH group) are also involved in the hydrogen bonding which is not considered in any of the model. A comparison of the bond angles shows that calculations can replicate the experimental data within 1.5° in bond angles and 2.0° in dihedral angles for both monomer and dimer model of NF-4HBA, except for the angles having one of the atoms as hydrogen. Some discrepancy is also observed in the case of bond angles and dihedral angles for N7-N8-C17 and C30-C29-C39-O28, C37-C29-C39-O26 and C37-C29-C39-O28 respectively, as these atoms are also involved in the hydrogen bonding. The ground state energy of the monomer and dimer model of NF-4HBA cocrystal is -1400.03169380 a.u. and -2800.08332191 a.u. respectively. The binding energy of the analyzed monomer and dimer model of NF-4HBA was computed as the difference between the calculated total energy of the monomer and dimer and the energies of the isolated molecules i.e. NF and 4HBA. The ground state energy of NF and 4HBA are calculated as -903.78559393 a.u. and -496.23769995 a.u. respectively using same level of theory. Therefore, the binding energy of the monomer and

dimer model of NF-4HBA cocrystal was calculated as -5.61 kcal/mol and -24.08 kcal/mol respectively.

The calculated binding energy of monomer and dimer model of NF-4HBA has been corrected for the basis set superposition error (BSSE)⁴² and found to be -4.37 kcal/mol and -19.67 kcal/mol respectively.

2. Feasibility of formation of cocrystal

The feasibility of the reaction was checked theoretically with the aid of calculated electronic descriptors derived from DFT. All computed global descriptors are given in Table 1. The electrophilicity value of NF is higher than 4HBA. Therefore, the NF behaves as electrophile and 4HBA as nucleophile. Electrophilic charge transfer (ECT)⁴³ between the $\Delta N_{\max}$ values of interacting molecules A (NF) and B (4HBA) have been calculated using equation:

$$ECT = (\Delta N_{\max})_A - (\Delta N_{\max})_B$$

where

$$(\Delta N_{\max})_A = \frac{\mu_A}{\eta_A} \text{ and } (\Delta N_{\max})_B = \frac{\mu_B}{\eta_B}$$

$\Delta N_{\max}$ = maximum electronic charge transfer between reactants A and B, μ_A/μ_B and η_A/η_B is the chemical potential and hardness of reactant A/B respectively. If (i) $ECT > 0$, charge flow from reactant B to A, and (ii) $ECT < 0$, charge flow from A to B. ECT is calculated as 1.12 for reactant molecules NF and 4HBA, which indicates that charge flows from 4HBA to NF. Therefore, NF acts as electron acceptor and 4HBA as electron donor. The low value of chemical potential and high value of electrophilicity index for NF favour its electrophilic behaviour. In the same way, the high value of chemical potential and low value of electrophilicity index for 4HBA favour its nucleophilic behaviour. The specific site selectivity of the NF, 4HBA and NF-4HBA has been calculated with the aid of local (condensed)

fukui functions (FF).⁴⁴ The calculated local electronic descriptors values for NF, 4HBA, monomer and dimer model of NF-4HBA are listed in Electronic supplementary information (Table S2 and Table S3) and Table 2 respectively. In NF, the maximum value of electrophilic reactivity descriptor ratio ($f_k^+/f_k^- = 4.1814$) at N9 on imide group indicate that this site is comparatively more prone to nucleophilic attack and in the case of 4HBA, the maximum value of $f_k^-/f_k^+ = 3.7803$ at C1 of carboxylic group indicate that this site is comparatively more prone to the electrophilic attack. Therefore, there is probability of bond formation between imide and carboxylic acid. The bond formed between the H-atom of imide and oxygen atom of carboxylic acid is H-bond in nature as oxygen atom is highly electronegative in comparison to hydrogen atom which favours the formation of cocrystal. In case of monomer and dimer model of NF-4HBA, maximum values of all the three descriptors (f_k^+ , s_k^+ , ω_k^+) at C12 and O63, respectively. This indicates that these sites are more prone to nucleophilic attack. Maximum values of descriptors (f_k^- , s_k^- , ω_k^-) at O5 indicates that this atomic centre is

more prone to electrophilic attack in both monomer and dimer model of NF-4HBA cocrystal.

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Lipinski's rule of five describes the drug likeness and gives the rules for determining the biological or pharmacological activity of the compound.⁴⁵ According to the Lipinski's rules the compound must have (i) Molar refractivity from 40 to 130, (ii) Molecular weight from 180 to 500, and (iii) Number of atoms from 20 to 70. It is the molar refractivity (MR) value, which is responsible for the binding property and lipophilicity of the molecule, can be calculated by the Lorenz-Lorentz formula.^{46,47} The value of MR for NF and NF-4HBA cocrystal is 38.27 esu and 55.83 esu respectively and it reflects the binding property of both API and cocrystal. The molecular weight of NF and NF-4HBA (monomer model) is 238.16 and 376.29 g/mol. Also, the number of atoms in NF and NF-4HBA are 23 and 39. Thus, the NF-4HBA cocrystal also satisfies the criteria which determine the drug likeness of a molecule. As a result, NF-4HBA cocrystal may be used as an oral active drug.

Table 1 Calculated E_{HOMO} , E_{LUMO} , energy band gap ($E_L - E_H$), chemical potential (μ), electronegativity (χ), global hardness (η), global softness (S) and global electrophilicity index (ω) at 298.15 K for NF, 4HBA and NF-4HBA.

Molecule	E_H (eV)	E_L (eV)	$E_L - E_H$ (eV)	χ (eV)	μ (eV)	η (eV)	S (eV ⁻¹)	ω (eV)	ΔN_{max}
NF	-6.8548	-3.0700	3.78480	4.9624	-4.9624	1.8924	0.2642	6.5063	2.6223
4HBA	-6.7348	-1.3519	5.38296	4.0433	-4.0433	2.6915	0.1858	3.0371	1.5023
Monomer	-6.6137	-2.9508	3.66290	4.7823	-4.7823	1.8315	0.2730	6.2437	2.6112
Dimer	-6.4875	-3.3065	3.18100	4.8970	-4.8970	1.5905	0.3144	7.5386	3.0789

Table 2 Selected reactivity descriptors as Fukui functions (f_k^+ , f_k^-), local softnesses (s_k^+ , s_k^-), local electrophilicity indices (ω_k^+ , ω_k^-) for dimeric model of NF-4HBA.

Sites	f_k^+	ω_k^+	s_k^+	f_k^-	ω_k^-	s_k^-
From Hirshfeld atomic charges						
O1	0.00337	0.02543	0.00106	0.02174	0.16387	0.00683
O2	0.00606	0.04570	0.00191	0.07539	0.56830	0.02370
3O	0.00120	0.00904	0.00038	0.02327	0.17545	0.00732
O4	0.01715	0.12927	0.00539	0.02423	0.18265	0.00762
O5	0.00823	0.06207	0.00259	0.07786	0.58699	0.02448
N6	0.00188	0.01415	0.00059	0.04800	0.36182	0.01509
N7	0.01120	0.08445	0.00352	0.04638	0.34963	0.01458
N8	0.01177	0.08874	0.00370	0.01363	0.10277	0.00429
N9	0.01365	0.10293	0.00429	0.01883	0.14193	0.00592
C11	0.00860	0.06482	0.00270	0.03907	0.29450	0.01228
C12	0.02199	0.16578	0.00691	0.04958	0.37373	0.01559
C14	0.01736	0.13090	0.00546	0.06462	0.48715	0.02032
C16	0.01163	0.08770	0.00366	0.01790	0.13496	0.00563
C17	0.01284	0.09680	0.00404	0.04437	0.33446	0.01395
C19	0.00624	0.04703	0.00196	0.01703	0.12835	0.00535
C20	0.00271	0.02044	0.00085	0.00824	0.06215	0.00259
C21	0.00332	0.02499	0.00104	0.01829	0.13788	0.00575
O24	0.00176	0.01324	0.00055	0.00280	0.02108	0.00088
O26	0.00689	0.05192	0.00217	0.01258	0.09481	0.00395
O28	-0.00670	-0.05060	-0.00210	-0.00750	-0.05640	-0.00240
C29	0.00144	0.01082	0.00045	0.00179	0.01346	0.00056
C30	-0.00540	-0.04050	-0.00170	-0.01410	-0.10600	-0.00440
C32	-0.00590	-0.04470	-0.00190	-0.01280	-0.09620	-0.00400
C34	0.00090	0.00675	0.00028	0.00098	0.00736	0.00031
C35	0.01029	0.07759	0.00324	0.01365	0.10293	0.00429
C37	0.01006	0.07587	0.00316	0.01436	0.10825	0.00451
C39	0.00156	0.01176	0.00049	0.00248	0.01870	0.00078
O40	0.0115	0.08671	0.00362	0.01414	0.10658	0.00444
O41	0.02863	0.21579	0.00900	0.05472	0.41250	0.01720
O42	0.01512	0.11401	0.00475	-0.00500	-0.03740	-0.00160
O43	0.03245	0.24460	0.01020	0.02384	0.17968	0.00749
O44	0.03457	0.26064	0.01087	0.05839	0.44020	0.01836

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N46	0.02759	0.20796	0.00867	0.02480	0.18699	0.00789	
N47	0.03543	0.26712	0.01114	0.00627	0.04729	0.00197	
N48	0.01798	0.13557	0.00565	0.01478	0.11139	0.00465	
C50	0.02065	0.15565	0.00649	0.01959	0.14764	0.00616	
C51	0.05396	0.40681	0.01697	0.02882	0.21726	0.00906	
C53	0.0384	0.28949	0.01207	0.04417	0.33297	0.01389	
C55	0.03927	0.29603	0.01235	0.01628	0.12273	0.00512	
C56	0.04039	0.30445	0.01270	0.01937	0.14602	0.00609	
C58	0.01220	0.09198	0.00384	0.00986	0.07432	0.00310	
C59	0.00501	0.03775	0.00157	0.00256	0.01929	0.00080	
C60	0.02392	0.18034	0.00752	0.00239	0.01800	0.00075	
O63	0.05991	0.45163	0.01884	-0.00800	-0.06060	-0.00250	
O65	0.02706	0.20402	0.00851	0.00595	0.04485	0.00187	
O67	0.03470	0.26155	0.01091	0.00611	0.04604	0.00192	
C68	0.04717	0.35557	0.01483	0.00429	0.03234	0.00135	
C69	0.03534	0.26641	0.01111	0.00512	0.03859	0.00161	
C71	0.04722	0.35597	0.01485	-0.00240	-0.01709	-0.00070	
C73	0.03180	0.23970	0.01000	-0.00440	-0.03340	-0.00140	
C74	0.04757	0.35859	0.01496	-0.00330	-0.02480	-0.00100	
C76	0.03716	0.28014	0.01168	0.00525	0.03959	0.00165	
C78	0.01236	0.09314	0.00388	0.00220	0.01658	0.00069	

f_k^+ , f_k^- (in e); s_k^+ , s_k^- (in eV^{-1}) and ω_k^+ , ω_k^- (in eV).

3. Vibrational spectra and assignments

The calculated vibrational wavenumbers of monomer and dimer model of NF-4HBA and potential energy distribution (PED) along with the experimental FT-IR and FT-Raman wavenumbers are given in the Electronic supplementary information (Table S4). Changes in calculated and observed bond lengths and stretching wavenumbers of bonds, which are responsible for cocrystal formation, are given in the Table 3. The comparison of theoretical and experimental vibrational wavenumbers of NF was given in our previous work elsewhere.³¹ The theoretical and experimental vibrational wavenumbers of 4HBA calculated at same level of theory and their assignments using PED is given in the Electronic supplementary information (Table S5). The calculated and experimental infrared and Raman spectrum of NF-4HBA cocrystal is shown in Figs. 3 and 4 respectively. Comparison of experimental IR and Raman with the calculated vibrational wavenumber (scaled) of 4-HBA is shown in Electronic supplementary information (Figs. S3 and S4),

respectively. The assignments of vibrational wavenumbers are based on the comparison of experimental and theoretically obtained vibrational wavenumbers and PED values. Comparison of the theoretically calculated wavenumbers with experimental values reveals the overestimation of the calculated vibrational modes. Therefore the calculated vibrational wavenumbers are scaled down using scaling factor 0.965⁴⁸ to construct calculated vibrational frequencies nearer to the experimental one. The calculation on dimer model of NF-4HBA is performed to incorporate all possible hydrogen bond interactions present in the asymmetric unit of the cocrystal. The vibrational wavenumbers calculated using the dimer model of NF-4HBA show better agreement with the observed wavenumbers in comparison to monomer model of NF-4HBA as shown in the Electronic supplementary information (Table S4). Therefore, experimental wavenumbers are assigned using the calculated vibrational wavenumbers of dimer model of NF-4HBA.

Table 3 The Experimental and Theoretical bond length (in Å) and stretching frequency (in cm^{-1}) of the bonds involved in hydrogen bonding.								
Molecules	Groups present in NF				Groups present in 4HBA			
	N-H group		C=O group		O-H (phenolic) group		C=O group	
	Bond Length	Stretching frequency	Bond Length	Stretching frequency	Bond Length	Stretching frequency	Bond length	Stretching frequency
Experimental								
NF	0.920	3287 (IR)	1.206, 1.195	1782 (IR), 1744 (IR)	-	-	-	-
4HBA	-	-	-	-	0.874	3387 (IR)	1.266	1675 (IR)
Cocrystal	0.855	3220 (IR)	1.206, 1.224	1771 (IR), 1720 (IR), 1770 (Raman)	0.904	3197 (IR)	1.258	1664 (IR)
Theoretical								
NF (Monomer)	1.008	3503	1.195, 1.202	1809, 1771	-	-	-	-
4HBA (Monomer)	-	-	-	-	0.96276	3679	1.20853	1724
NF-4HBA (Monomer)	1.00756	3503	1.19716, 1.20320	1803, 1767	0.96299	3676	1.21552	1693
NF-4HBA (Dimer)	1.01455, 1.00752	3504, 3376	1.19756, 1.20967, 1.19482, 1.21489	1807, 1798, 1743, 1729	0.96343, 0.97837	3674, 3376	1.21485, 1.20946	1720, 1696

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Fig. 3 Experimental and calculated FT-IR absorbance spectra for NF-4HBA in the region 200-3800 cm^{-1} .

Fig. 4 Experimental and calculated FT-Raman spectra for NF-4HBA in the region 200-3800 cm^{-1} .

In case NF-4HBA, an imide N-H stretching vibration ($R2[v(\text{NH})]$) is observed at 3220 cm^{-1} whereas in pure NF (API), it is observed at 3287 cm^{-1} .³¹ Imide of both NF and NF-4HBA is hydrogen bonded but the type and strength of hydrogen bonding are different in both the cases. In the case of NF, imide N-H interact with the C=O of hydantoin ring of another NF molecule to form $\text{N-H}\cdots\text{O}=\text{C}$ hydrogen bonding.¹⁸ Whereas in the case of NF-4HBA, imide N-H interact with the phenolic O-H of 4HBA and this phenolic O-H further interact with the C=O of hydantoin ring of another NF molecule to stabilise the cocrystal structure and form $\text{N-H}\cdots\text{O}-\text{H}\cdots\text{O}$ type of hydrogen bonding. This $R2[u(\text{N-H})]$ is calculated at 3503 cm^{-1} and 3376 cm^{-1} in the case of monomer and dimer NF-4HBA model, respectively, and observed at 3220 cm^{-1} with IR spectroscopy. The observed IR peak at 3220 cm^{-1} exhibits better correlation with calculated mode of dimer model compared to monomer NF-4HBA. The difference between the calculated wavenumber of monomer and dimer NF-4HBA is due to inclusion of

$\text{N-H}\cdots\text{O}$ bond in the case of dimer model which was not considered in the case of monomer model.

The phenolic OH stretching frequency is observed within the region of $3420\text{--}3250 \text{ cm}^{-1}$.⁴⁹ The IR stretching frequency of phenolic O-H group ($R3[v(\text{OH})]$) is observed at 3387 cm^{-1} and 3197 cm^{-1} in the case of 4HBA and NF-4HBA, respectively. The corresponding OH group is calculated at 3679 , 3676 , and 3376 cm^{-1} in the case of 4HBA, monomer, and dimer NF-4HBA, respectively. The OH stretching mode shows a red shift in NF-4HBA in comparison to 4HBA. This downshift in wavenumber corresponds to an increase in observed/calculated O-H bond length from $0.874/0.904 \text{ \AA}$ in 4HBA to $0.96/0.98 \text{ \AA}$ in NF-4HBA and is related to the change in the type and strength of hydrogen bonding after cocrystallization. NF-4HBA shows $\text{O-H}\cdots\text{O}=\text{C}$ type hydrogen bonding⁹ whereas 4HBA, shows $\text{O-H}\cdots\text{O}-\text{H}$ type of hydrogen bonding.⁵⁰

In the case of NF, C=O group of hydantoin ring is forming hydrogen bond with imide NH of neighbouring molecule.⁵¹

However, in case of NF-4HBA, C=O group is forming hydrogen bond with OH group of 4HBA, Fig. 2. The corresponding hydrogen bonding is stronger in NF-4HBA compared to NF, as the calculated bond length of C=O is larger in NF-4HBA, 1.224 Å compared to NF, 1.195 Å Table 3. The C=O stretching of NF in the IR spectrum is observed at 1744 cm⁻¹,³¹ while it is observed at 1720 cm⁻¹ in NF-4HBA Table 3. The downshift of C=O stretching mode (R2[v(C=O)]) in NF-4HBA is attributed to the formation of hydrogen bonding with OH group of 4HBA.

4. ¹³C solid state NMR spectroscopy

The cocrystal was characterized by ¹³C CP MAS solid-state NMR. The NF and 4HBA show slight changes in ¹³C chemical shifts with respect to the NF-4HBA spectrum (Fig. 5), which are attributed to the changed chemical environments after the formation of the cocrystal. Chemical shifts of all carbon atoms present in the cocrystal can be assigned directly by consulting to the spectra of NF and 4HBA. Each chemically distinct carbon in the NF-4HBA cocrystal is represented by single peak, and no peaks of phase impurities can be found in the ¹³C spectrum. A single peak is observed for the chemically similar carbon atoms. Thus, it is easy to understand that the resulting NF-4HBA cocrystal is neither a physical mixture of NF and 4HBA, nor does it contain impurities at measurable concentrations. The ¹³C NMR chemical shifts of monomer and dimer model of NF-4HBA, NF and 4HBA were calculated with gauge-including-atomic-orbital (GIAO) method at B3LYP/cc-pvTZ level of theory. Experimental and calculated ¹³C chemical shift data of the NF-4HBA, NF and 4HBA are summarized in Table 4. For NF-4HBA, the maximum chemical shift difference between the experimental and calculated values is ≈5 ppm and ≈8 ppm in the case of dimer and monomer model, respectively, except for the C34 carbon atom due to neglect of N—H···O—H···O type of interactions in both monomer and dimer model. Chemical shift difference between the experimental and calculated values is within the level of calculation

error and confirms accessibility of computational accuracy. After the cocrystal formation, the experimental chemical shift changes of ¹³C spins are all less than 2.98 ppm, while for some carbon atoms (C34 and C29), significant experimental chemical shift changes are observed. The highest ¹³C chemical shifts of C39, C20, C34 and C16 at 174.60 ppm, 171.76 ppm 155.22 and 152.68 ppm, respectively, which shows the bonding with the electron attracting species (O and N) Fig. 1. The rest of the carbon atoms peaks of NF-4HBA are observed in the range of 46.82-133.69 ppm. According to experimental NMR spectra, a shift in C34 peak of 4HBA is observed from 159.69 ppm to 155.22 ppm in NF-4HBA, which is due to the change in the chemical environment of the COOH group after cocrystallization. Moreover, C29 peak is shifted from 123.38 ppm in 4HBA to 118.86 ppm in NF-4HBA and is attributed to COOH group attachment to this carbon atom which is involved in the hydrogen bonding. For the dimer model of NF-4HBA, the calculated ¹³C chemical shifts agree well with the experimental values, indicating that the dimer model is present in the crystal structure of NF-4HBA cocrystal.

Fig. 5 Experimental ¹³C CP-MAS solid state NMR spectrum of NF-4HBA, NF and 4HBA.

Table 4 Calculated and observed ¹³C NMR chemical shifts (δ/ppm) of NF-4HBA, NF and 4HBA.

Atom (monomer)	δ _{cal} Monomer	Atom (dimer)	δ _{cal} Dimer	δ _{exp}	Atom	δ _{cal}	δ _{exp}
					NF		
C39	173.633	C20, C59	174.9424, 171.8563	174.60	C11	168.49	168.9
C20	170.172	C39, C78	171.7006, 169.3109	171.76	C15	161.802	151.9
C34	170.05	C73, C34	168.3171, 166.4374	155.22	C14	158.587	151.9
C16	161.374	C16, C55	160.8337, 159.5331	152.68	C10	153.998	151.9
C11	160.03	C11, C50	157.9661, 157.2843	152.68	C13	127.858	133.1
C19	155.326	C58, C19	153.1795, 152.0918	152.68	C17	118.91	118.2
C30	142.269	C30, C69	139.5652, 138.1230	133.69	C16	117.3	118.2
C37	138.231	C37, C76	136.3329, 136.0551	133.69	C12	50.1449	49.8
C17	128.377	C17, C56	127.1572, 126.7055	132.61	4HBA		
C29	123.785	C29, C68	123.5877, 123.0555	118.86	C1	170.9341	171.72
C32	121.312	C32, C71	119.5812, 117.7590	115.24	C5	168.8916	159.69
C12	117.989	C51, C12	117.6414, 116.9278	115.24	C3	140.7431	134.44
C14	117.829	C14, C53	117.6929, 114.9780	115.24	C7	138.2101	134.44
C35	116.071	C74, C35	115.0416, 114.4458	114.01	C2	126.2127	123.38
C21	51.3006	C21, C60	50.1519, 48.1823	46.82	C4	119.2443	117.51
					C6	115.9072	115.26

5. Population of electrons and stabilization energy of natural bond

Many of the molecular and atomic properties are ruled by the electron density distribution¹. Thus, the analysis of the electron density distribution should have an interest and help to see the electronic structure of molecules and thus interactions. The natural bond orbital (NBO) analysis is one of the methods used for studying the intermolecular charge transfer in the molecule.⁵² The analyses of natural bond orbitals (NBOs) such as; lone pair (n), bonding (σ)

and anti-bonding (σ*) orbitals of monomer and dimer model of NF-4HBA performed in this work give the information about the population of electrons in an atom, bond order between the atoms, the strength of non-covalent interactions and types of orbital overlapping etc. NBO analysis has been performed on the title compound at the B3LYP/cc-pvTZ level to explain the inter-molecular rehybridization and delocalization of electron density between the molecules. The selected second-order perturbation theory analyses of the Fock Matrix, in the NBO basis for monomer and dimer model of NF-4HBA are presented in Electronic supplementary information

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(Table S6) and Table 5 respectively. Here only those hyperconjugative interactions are discussed which are involved in the hydrogen bonding.

The primary hyperconjugative interaction from unit 1 to unit 2 due to $n_1(N7) \rightarrow \sigma^*(C30-H31)$, secondary hyperconjugative interaction from $\sigma(C21-H23) \rightarrow \sigma^*(O28-C39)$ and primary hyperconjugative interaction from unit 2 to unit 1 due to $n_1(O28) \rightarrow \sigma^*(C30-H31)$ are responsible for the stabilization of the monomer model of NF-4HBA and stabilized the molecule with maximum energy ~ 1.13 kcal/mol. In the dimer model of NF-4HBA, total 4 units are present. The primary hyperconjugative interaction from unit (1) to unit (4) due to $n_1(O3)/n_2(O3) \rightarrow \sigma^*(O63-H64)$ stabilized the molecule up to ~ 10.67 kcal/mol and confirms the presence of

classical interaction $O63-H64 \cdots O3$. In the same way, intermolecular interaction from unit (2) to unit (3) due to $n_1(O24)/n_2(O24) \rightarrow \sigma^*(N48-H49)$ stabilized the molecule up to ~ 5.03 kcal/mol and confirms the presence of interaction $N48-H49 \cdots O24$. Another hyperconjugative interaction from unit (3) to unit (2) due to $n_1(O42)/n_2(O42) \rightarrow \sigma^*(C32-H33)$ stabilized the molecule up to ~ 1.04 kcal/mol and confirms the presence of hydrogen bonding $C-H \cdots O$. Due to formation of intermolecular hydrogen bonding between atoms, the electron density of antibonding orbitals of $N48-H49$ and $O63-H64$ bonds increase. Thus, the corresponding bonds become weaker and their stretching frequencies decrease (as shown in the Table 3).

Table 5 Second order perturbation theory analysis of Fock matrix in NBO Basis for dimeric model of NF-4HBA cocrystal.

Donor NBO (i)	ED(i)/e	Acceptor NBO (j)	ED(j)/e	E(2) ^a K cal/mol	E(j)-E(i) ^b a.u.	F(i,j) ^c a.u.
within unit 1						
$\sigma O1-C11$	1.98396	$\sigma^* N6-C16$	0.11191	5.04	1.21	0.072
$\pi O2-N6$	1.98242	$n(3) O5$	1.48375	10.97	0.18	0.076
$\pi O2-N6$	1.98242	$\pi^* O2-N6$	0.65646	7.62	0.32	0.053
$\pi O2-N6$	1.98242	$\pi^* C14-C16$	0.31667	5.35	0.45	0.047
$\pi N7-C17$	1.91114	$\pi^* C11-C12$	0.32783	11.83	0.35	0.061
$\pi C11-C12$	1.74199	$\pi^* N7-C17$	0.24558	18.14	0.28	0.063
$\pi C11-C12$	1.74199	$\pi^* C14-C16$	0.31667	19.07	0.29	0.067
$\sigma C11-C17$	1.97646	$\sigma^* N7-N8$	0.02694	5.25	1.10	0.068
$\sigma C12-C14$	1.96999	$\sigma^* N6-C16$	0.11191	8.17	0.99	0.082
$\sigma C12-C14$	1.96999	$\sigma^* C11-C17$	0.02925	6.19	1.13	0.075
$\pi C14-C16$	1.76047	$\pi^* O2-N6$	0.65646	26.29	0.17	0.066
$\pi C14-C16$	1.76047	$\pi^* C11-C12$	0.32783	14.94	0.30	0.061
$\sigma C17-H18$	1.97903	$\sigma^* O1-C11$	0.02780	5.84	0.90	0.065
$\sigma C20-C21$	1.97374	$\sigma^* N7-N8$	0.02694	5.47	1.04	0.067
$n(2) O1$	1.69716	$\pi^* C11-C12$	0.32783	30.45	0.35	0.093
$n(2) O1$	1.69716	$\pi^* C14-C16$	0.31667	29.30	0.35	0.091
$n(2) O2$	1.89004	$\sigma^* O5-N6$	0.05939	19.01	0.69	0.104
$n(2) O2$	1.89004	$\sigma^* N6-C16$	0.11191	16.31	0.58	0.087
$n(2) O3$	1.84843	$\sigma^* N9-C20$	0.07308	26.82	0.72	0.126
$n(2) O3$	1.84843	$\sigma^* C20-C21$	0.07112	19.36	0.62	0.100
$n(2) O4$	1.81904	$\sigma^* N8-C19$	0.10893	31.20	0.63	0.127
$n(2) O4$	1.81904	$\sigma^* N9-C19$	0.09695	30.58	0.62	0.125
$n(2) O5$	1.89330	$\sigma^* O2-N6$	0.05786	18.74	0.71	0.104
$n(2) O5$	1.89330	$\sigma^* N6-C16$	0.11191	14.19	0.58	0.081
$n(3) O5$	1.48375	$\pi^* O2-N6$	0.65646	153.77	0.14	0.137
$n(1) N7$	1.90578	$\sigma^* N8-C21$	0.04747	14.21	0.68	0.089
$n(1) N7$	1.90578	$\sigma^* C17-H18$	0.03396	10.28	0.76	0.080
$n(1) N8$	1.63535	$\pi^* O4-C19$	0.30301	52.46	0.29	0.111
$n(1) N8$	1.63535	$\pi^* N7-C17$	0.24558	38.06	0.27	0.094
$n(1) N8$	1.63535	$\sigma^* C21-H22$	0.02029	5.47	0.63	0.058
$n(1) N8$	1.63535	$\sigma^* C21-H23$	0.01984	5.28	0.64	0.057
$n(1) N9$	1.64071	$\pi^* O3-C20$	0.27345	65.78	0.27	0.122
$n(1) N9$	1.64071	$\pi^* O4-C19$	0.30301	46.50	0.29	0.105
$\pi^* O2-N6$	0.65646	$\pi^* C14-C16$	0.31667	21.26	0.13	0.067
$\pi^* N7-C17$	0.24558	$\pi^* C11-C12$	0.32783	143.47	0.01	0.071
$\sigma^* N8-C19$	0.10893	$\sigma^* N9-H10$	0.01330	6.28	0.02	0.040
$\sigma^* N8-C19$	0.10893	$\sigma^* N9-C20$	0.07308	7.09	0.05	0.055
From unit 1 to unit 2						
$\pi N7-C17$	1.91114	$\sigma^* C30-H31$	0.01485	0.08	0.79	0.007
$\sigma C21-H23$	1.96404	$\sigma^* O28-C39$	0.01951	0.06	1.13	0.007
$\pi^* O3-C20$	0.27345	$\pi^* O28-C39$	0.27550	0.07	0.02	0.002
From unit 1 to unit 3						
$\pi O2-N6$	1.98242	$\sigma^* N47-C60$	0.04753	0.05	0.76	0.006
$\pi O2-N6$	1.98242	$\sigma^* C60-H61$	0.02173	0.09	0.82	0.008

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n(1)O2	1.98086	$\sigma^*C60-H61$	0.02173	0.09	1.16	0.009
n(2)O2	1.89004	$\sigma^*C60-H61$	0.02173	0.36	0.66	0.014
n(2)O5	1.89330	$\sigma^*N47-C60$	0.04753	0.06	0.59	0.005
n(3)O5	1.48375	$\sigma^*N47-C60$	0.04753	0.11	0.58	0.008
π^*O2-N6	0.65646	$\sigma^*C60-H61$	0.02173	0.07	0.50	0.009
From unit 1 to unit 4						
$\sigma N9-C20$	1.99044	$\sigma^*O63-H64$	0.03969	0.19	1.30	0.014
n(1)O3	1.96670	$\sigma^*O63-H64$	0.03969	4.06	1.16	0.061
n(2)O3	1.84843	$\sigma^*O63-H64$	0.03969	10.67	0.73	0.081
n(2)O3	1.84843	$\sigma^*O63-C73$	0.02320	0.13	0.69	0.009
From unit 2 to unit 1						
$\pi O28-C39$	1.98594	$\sigma^*C21-H23$	0.01984	0.08	0.74	0.007
n(1)O28	1.97587	$\pi^*O3-C20$	0.27345	0.30	0.70	0.014
n(1)O28	1.97587	$\pi^*O4-C19$	0.30301	0.05	0.72	0.006
n(1)O28	1.97587	$\sigma^*C21-H22$	0.02029	0.29	1.06	0.016
n(1)O28	1.97587	$\sigma^*C21-H23$	0.01984	0.12	1.08	0.010
n(2)O28	1.85940	$\pi^*O3-C20$	0.27345	0.14	0.25	0.005
Within unit 2						
$\pi C29-C37$	1.64626	$\pi^*O28-C39$	0.27550	26.82	0.25	0.075
$\pi C29-C37$	1.64626	$\pi^*C30-C32$	0.28011	22.12	0.29	0.072
$\pi C29-C37$	1.64626	$\pi^*C34-C35$	0.38381	16.50	0.27	0.060
$\pi C30-C32$	1.67539	$\pi^*C29-C37$	0.39129	16.77	0.28	0.062
$\pi C30-C32$	1.67539	$\pi^*C34-C35$	0.38381	25.43	0.27	0.075
$\pi C34-C35$	1.63366	$\pi^*C29-C37$	0.39129	25.24	0.29	0.077
$\pi C34-C35$	1.63366	$\pi^*C30-C32$	0.28011	14.43	0.30	0.060
n(1)O24	1.96833	$\sigma^*C34-C35$	0.02810	6.70	1.16	0.079
n(2)O24	1.87631	$\pi^*C34-C35$	0.38381	27.07	0.36	0.094
n(1)O26	1.97739	$\sigma^*O28-C39$	0.01951	6.81	1.23	0.082
n(2)O26	1.82479	$\pi^*O28-C39$	0.27550	46.70	0.34	0.115
n(2)O28	1.85940	$\sigma^*O26-C39$	0.09135	30.66	0.63	0.126
n(2)O28	1.85940	$\sigma^*C29-C39$	0.06868	18.92	0.70	0.104
$\pi^*O28-C39$	0.27550	$\pi^*C29-C37$	0.39129	88.47	0.03	0.073
$\pi^*C34-C35$	0.38381	$\pi^*C29-C37$	0.39129	318.73	0.01	0.081
$\pi^*C34-C35$	0.38381	$\pi^*C30-C32$	0.28011	141.78	0.02	0.080
From unit 2 to unit 3						
$\sigma C34-C35$	1.98186	$\sigma^*N48-H49$	0.02595	0.09	1.14	0.009
n(1)O24	1.96833	$\sigma^*N48-H49$	0.02595	5.03	1.06	0.065
n(1)O24	1.96833	$\sigma^*N48-C58$	0.09203	0.05	1.01	0.007
n(2)O24	1.87631	$\sigma^*N48-H49$	0.02595	0.56	0.77	0.019
From unit 3 to unit 1						
n(1)O42	1.97532	$\pi^*C14-C16$	0.31667	0.08	0.71	0.007
n(2)O42	1.85525	π^*O2-N6	0.65646	0.18	0.14	0.005
n(2)O42	1.85525	$\pi^*C14-C16$	0.31667	0.06	0.27	0.004
From unit 3 to unit 2						
$\pi O42-C59$	1.99038	$\sigma^*C32-H33$	0.01745	0.09	0.83	0.008
$\sigma N48-H49$	1.98502	$\sigma^*O24-C34$	0.02557	0.14	1.02	0.011
$\sigma C59-C60$	1.97364	$\sigma^*C32-H33$	0.01745	0.07	1.08	0.008
n(1)O42	1.97532	$\sigma^*C32-H33$	0.01745	0.34	1.16	0.018
n(2)O42	1.85525	$\sigma^*C32-H33$	0.01745	1.04	0.71	0.025
Within unit 3						
$\pi O41-N45$	1.98250	n(3)O44	1.47286	11.25	0.18	0.077
$\pi O41-N45$	1.98250	$\pi^*O41-N45$	0.64678	7.61	0.32	0.054
$\pi O41-N45$	1.98250	$\pi^*C53-C55$	0.31542	5.48	0.44	0.048
$\pi N46-C56$	1.91209	$\pi^*C50-C51$	0.32673	11.87	0.35	0.061
$\pi C50-C51$	1.74975	$\pi^*N46-C56$	0.24502	18.12	0.28	0.063
$\pi C50-C51$	1.74975	$\pi^*C53-C55$	0.31542	18.97	0.28	0.067
$\sigma C50-C56$	1.97663	$\sigma^*N46-N47$	0.02723	5.15	1.10	0.067
$\sigma C51-C53$	1.97005	$\sigma^*N45-C55$	0.11760	8.12	0.98	0.081
$\sigma C51-C53$	1.97005	$\sigma^*C50-C56$	0.02922	6.17	1.14	0.075
$\pi C53-C55$	1.77603	$\pi^*O41-N45$	0.64678	23.42	0.17	0.064

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π C53-C55	1.77603	π^* C50-C51	0.32673	14.64	0.30	0.061
σ C56-H57	1.97872	σ^* O40-C50	0.02826	5.98	0.89	0.065
σ C59-C60	1.97364	σ^* N46-N47	0.02723	5.60	1.04	0.068
n(2)O40	1.69786	π^* C50-C51	0.32673	30.27	0.35	0.093
n(2)O40	1.69786	π^* C53-C55	0.31542	29.42	0.35	0.091
n(2)O41	1.88707	σ^* O44-N45	0.05994	19.53	0.70	0.105
n(2)O41	1.88707	σ^* N45-C55	0.11760	16.90	0.57	0.087
n(2)O42	1.85525	σ^* N48-C59	0.07889	26.16	0.69	0.122
n(2)O42	1.85525	σ^* C59-C60	0.07591	23.60	0.60	0.108
n(2)O43	1.82387	σ^* N47-C58	0.10971	31.30	0.63	0.127
n(2)O43	1.82387	σ^* N48-C58	0.09203	29.12	0.63	0.123
n(2)O44	1.89002	σ^* O41-N45	0.05797	18.98	0.71	0.105
n(2)O44	1.89002	σ^* N45-C55	0.11760	14.66	0.57	0.082
n(3)O44	1.47286	π^* O41-N45	0.64678	157.00	0.14	0.138
n(1)N46	1.90679	σ^* N47-C60	0.04753	14.16	0.68	0.089
n(1)N46	1.90679	σ^* C56-H57	0.03397	10.21	0.76	0.080
n(1)N47	1.63789	π^* O43-C58	0.31320	53.01	0.28	0.111
n(1)N47	1.63789	π^* N46-C56	0.24502	38.02	0.27	0.094
n(1)N47	1.63789	σ^* C60-H61	0.02173	5.36	0.64	0.058
n(1)N47	1.63789	σ^* C60-H62	0.02031	5.54	0.63	0.058
n(1)N48	1.63855	π^* O42-C59	0.26106	62.26	0.27	0.120
n(1)N48	1.63855	π^* O43-C58	0.31320	50.40	0.28	0.108
π^* O41-N45	0.64678	π^* C53-C55	0.31542	21.59	0.12	0.066
π^* N46-C56	0.24502	π^* C50-C51	0.32673	162.77	0.01	0.071
σ^* N47-C58	0.10971	σ^* N48-C59	0.07889	8.03	0.05	0.057
From unit 4 to unit 1						
σ O63-H64	1.98720	σ^* O3-C20	0.01275	0.29	1.31	0.017
σ O63-H64	1.98720	σ^* N8-C21	0.04747	0.08	1.02	0.008
σ O63-H64	1.98720	σ^* N9-C20	0.07308	0.05	1.15	0.007
n(1)O63	1.97543	σ^* N8-C21	0.04747	0.07	0.86	0.007
n(2)O63	1.85098	σ^* N8-C21	0.04747	0.15	0.59	0.009
Within unit 4						
σ O63-H64	1.98720	σ^* C71-C73	0.02638	5.08	1.28	0.072
π C68-C76	1.64946	π^* O67-C78	0.25997	25.14	0.26	0.074
π C68-C76	1.64946	π^* C69-C71	0.29265	22.97	0.28	0.073
π C68-C76	1.64946	π^* C73-C74	0.38624	16.11	0.27	0.059
σ C69-H70	1.97466	σ^* C68-C76	0.02167	5.11	1.05	0.065
π C69-C71	1.69828	π^* C68-C76	0.39728	15.71	0.28	0.061
π C69-C71	1.69828	π^* C73-C74	0.38624	24.17	0.27	0.074
π C73-C74	1.61727	π^* C68-C76	0.39728	26.49	0.29	0.078
π C73-C74	1.61727	π^* C69-C71	0.29265	14.36	0.29	0.059
n(1)O63	1.97543	σ^* C73-C74	0.03046	7.98	1.11	0.084
n(2)O63	1.85098	π^* C73-C74	0.38624	32.16	0.34	0.099
n(1)O65	1.97845	σ^* O67-C78	0.01819	6.47	1.25	0.080
n(2)O65	1.83638	π^* O67-C78	0.25997	43.55	0.34	0.112
n(2)O67	1.84872	σ^* O65-C78	0.09909	32.91	0.61	0.128
n(2)O67	1.84872	σ^* C68-C78	0.07114	19.89	0.69	0.106
π^* O67-C78	0.25997	π^* C68-C76	0.39728	138.64	0.02	0.073
π^* C73-C74	0.38624	π^* C69-C71	0.29265	203.91	0.01	0.079

^aE(2) means energy of hyperconjugative interaction (stabilization energy).

^bEnergy difference between donor (i) and acceptor (j) NBO orbitals.

^cF(i, j) is the Fock matrix element between i and j NBO orbitals.

6. Topological and energetic properties of the NF-4HBA

Population analysis can be used to study the important information about charge distribution and its changes due to intermolecular interactions. The popular is the natural bond orbital (NBO) method.⁵³ But the disadvantage of this method is basis set dependent. This disadvantage of NBO method of the electron density distribution is solved in the atoms in molecules (AIM) theory of Bader.^{54,55} The extensive use of AIM method is due to the fact that, it opposes the wave function quantum mechanics. This opportunity helps to study

a small part of a molecule, instead of dealing with the whole system.

AIM2000 program is used for detailed analysis of the electron distribution function. Properties of the electron density calculated at bond critical points (BCP) of H-bonds under consideration were characterized. The BCP is the point on the bond path at which the electron density has the lowest value. The electron density at BCP (ρ_{BCP}) and its Laplacian ($\nabla^2\rho_{\text{BCP}}$) are the most important AIM parameter for studying intra- and intermolecular

interactions. This is because these are correlated with the interaction energy. For the existence of hydrogen bond in the system, the value of electron density should lie within the range 0.0020–0.0400 a.u. and the corresponding Laplacian ($\nabla^2\rho_{\text{BCP}}$) should lie within the range 0.024–0.139 a.u.⁵⁶ Geometrical and topological parameters are useful tools to characterise the strength and nature of the H-bond. Rozas⁵⁷ proposed a set of criteria for the type of H-bonds based on AIM theory. The criteria provide a basis to distinguish between different types of hydrogen bond interactions.

Molecular graph of the monomer and dimer model of NF-4HBA is given in Figs. 6 and 7 respectively. For the bonds of interacting atoms in NF-4HBA, the electron density at BCP (ρ_{BCP}), its Laplacian ($\nabla^2\rho_{\text{BCP}}$), the density of the total electron energy (H_{BCP}), its two components (V_{BCP} and G_{BCP}) and hydrogen bond interaction energies are given in Table 6. The total energy density H_{BCP} (sum of the electron kinetic energy density (G_{BCP}) and the electron potential energy density (V_{BCP})) takes the negative sign but the values of H_{BCP} are close to zero. This may suggest that there is only a minor covalent factor contributing to the nature of the interaction between NF and 4HBA. Based on above mentioned criteria, O28...H23 (2.4233 Å), and H31...N7 (2.6344 Å) in the case of monomer model of NF-4HBA are medium hydrogen bonds as $\nabla^2\rho > 0$ and $H_{\text{BCP}} < 0$, whereas O2...H33 are in the range of van der Waals interaction. Thus, we conclude that there are hydrogen bond interactions between NF (API) and 4HBA (co-former), but not very strong. While in the case of dimer model of NF-4HBA, the bond distance reported for the non-bonded atoms viz. O3...H64 (1.8057 Å) and O24...H49 (2.0171 Å) are stronger than the other hydrogen bonds and their interaction energy is calculated as -10.09 kcal/mol and -4.6932 kcal/mol respectively. Also, the calculated values of $\nabla^2\rho_{\text{BCP}}$ are greater than zero and H_{BCP} are less than zero, which shows that they are medium hydrogen bonds. Based on these parameters all inter and intra molecular H-bonds present in the dimer model of the NF-4HBA are medium hydrogen bonds and their hydrogen bond interaction energies lie in the range -10.0955 to -1.1500 kcal/mol. AIM calculations speculate that the interaction between H31...N7 and C60...O5 can be attributed to the occurrence of a very weak interaction, although BCP has been detected between the H31...N7 and C60...O5 atoms, and the distance of 3.1265 Å and 3.3681 Å respectively between these atoms exceeds the sum of their van der Waals radii. According to AIM calculations,

the binding energy of monomer and dimer model of NF-4HBA is sum of the energies of all intermolecular interactions and this is calculated as -2.86 kcal/mol and -20.67 kcal/mol, respectively. Large difference in binding energies of monomer and dimer model of NF-4HBA is due to large number of intermolecular hydrogen bonding present in the dimer model of NF-4HBA. Due to which its binding energy is high in comparison to monomer model of NF-4HBA.

Fig. 6 The molecular graph of monomer model of NF-4HBA: bond critical points (small red spheres), ring critical points (small yellow sphere), and bond paths (pink lines).

Fig. 7 The molecular graph of dimer model of NF-4HBA: bond critical points (small red spheres), ring critical points (small yellow sphere), and bond paths (pink lines).

Table 6 Geometrical parameters (bond length) and topological parameters for bonds of interacting atoms of NF-4HBA cocrystal: electron density (ρ_{BCP}), Laplacian of electron density ($\nabla^2\rho_{\text{BCP}}$), electron kinetic energy density (G_{BCP}), electron potential energy density (V_{BCP}), total electron energy density (H_{BCP}) at bond critical point (BCP) and estimated interaction energy (E_{int}).

Interactions	Bond length (Å)	ρ_{BCP} (a.u.)	$\nabla^2\rho_{\text{BCP}}$ (a.u.)	G_{BCP} (a.u.)	V_{BCP} (a.u.)	H_{BCP} (a.u.)	E_{int} (kcal/mol)
Monomer							
O28...H23	2.4233	0.00906	0.03826	-0.002103	-0.005360	-0.007460	-1.6817
H31...N7	2.6344	0.00651	0.02200	-0.001175	-0.003149	-0.004320	-0.9880
O2...H33	3.3331	0.00135	0.00496	-0.000313	-0.000614	-0.000927	-0.1927
Dimer							
H31...N7	3.1265	0.00258	0.00823	-0.000486	-0.00108	-0.00157	-0.3403
O3...H64	1.8057	0.03610	0.09440	0.00429	-0.03220	-0.02790	-10.0955
O28...H23	2.4808	0.00900	0.03850	-0.00208	-0.00548	-0.00756	-1.7179
O42...N6	3.0658	0.00626	0.02700	-0.00154	-0.00367	-0.00520	-1.1500
C60...O5	3.3681	0.00423	0.01740	-0.000998	-0.00236	-0.00336	-0.7404
H33...O42	2.4039	0.01010	0.03520	-0.00162	-0.00557	-0.00718	-1.7462
O24...H49	2.0171	0.02060	0.07280	-0.00162	-0.01500	-0.01660	-4.6932
H61...O2	2.5335	0.00797	0.02830	-0.00140	-0.00428	-0.00567	-1.3413

7. Chemical reactivity
7.1 Frontier Molecular Orbitals (FMOs) analysis

There are several ways to calculate the chemical reactivity of the molecule. The simplest one involves the energy difference between the highest occupied molecular orbital (HOMO) and the lowest

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unoccupied molecular orbital (LUMO) of a molecule. These orbitals are also known as frontier molecular orbitals as they lie at the outermost boundaries of the electrons of the molecules. Frontier molecular orbitals (FMOs) play an important role in the electric and optical properties of the materials.⁵⁸ The electronic transitions of the NF, NF-4HBA (monomer) and NF-4HBA (dimer) were calculated in the gas phase using the time-dependent TD-DFT/cc-pvTZ method.

Fig. 8 HOMO-LUMO plot of the NF-4HBA cocrystal (a) for monomer model (b) for dimer model with orbitals involving in electronic transitions in the isolated (gaseous) phase.

The energy of the HOMO is directly related to the electron donating ability of molecules and LUMO energy is directly related to the electron accepting abilities of molecules. Energy difference between HOMO and LUMO orbital is the energy gap (ΔE) that determines the chemical reactivity of a molecule.⁶⁰ The pictorial representation of HOMO-LUMO energy level is shown in Fig. 8 for monomer and dimer model of NF-4HBA and in the Electronic supplementary information (Fig. S5) for NF. The energy band gap of NF, NF-4HBA (monomer) and NF-4HBA (dimer) are found to be 3.78 eV, 3.66 eV and 3.18 eV. The decrement in the value of the band gap from NF to NF-4HBA shows that cocrystal is chemically more reactive than API. The HOMO-LUMO energy gap ($\Delta E = 3.18$ eV) reflects the chemical activity of the NF-4HBA cocrystal, which confirms the charge transfer interaction within the cocrystal molecule.

7.2 Molecular electrostatic potential map of NF-4HBA

The molecular electrostatic potential (MEP) gives a pictorial method to recognize the relative polarity of the molecule. It can be used to analyse the electrophilic and the nucleophilic sites within the molecule where chemical reactions are likely to take place. The electrostatic potential is computed by creating an electrostatic potential grid. The different values of the electrostatic potential at the MEP surface are represented by different colours; red, electron rich; blue, electron deficient; light blue, slightly electron deficient region; yellow, slightly electron rich region; green, neutral; respectively.³¹

The total electron density and electrostatic potential surface (ESP) of the molecules under investigation are constructed by using B3LYP/cc-pvTZ method. The total electron density mapped with electrostatic potential surface of NF-4HBA is shown in Electronic supplementary information (Fig. S6). This orientation visibly show electrophilic region visible as red blob is localized over the C19=O and NO₂ group attached to the ring R1 and R2 of the

molecule respectively. In addition, a less negative area reflected as a yellowish blob is visible mainly over the C20=O of ring R1 and a more nucleophilic region localised on the OH and NH group and are reflected as a bluish blob. These electrophilic and the nucleophilic sites are responsible for the binding of the title molecules with the target proteins and therefore responsible for the chemical reactivity of the title molecule.

V. Conclusions

It was found that the non-covalent interactions contribute considerably to the stability of the cocrystal and have appreciable effects on the molecular geometry. In this work, numerous methods are used for investigating the variation in properties of the nitrofurantoin-4-hydroxybenzoic acid (NF-4HBA) cocrystal and investigated the hydrogen bond interactions between nitrofurantoin (NF) and 4-hydroxybenzoic acid (4HBA). The calculated interaction energy (E_{int}) of NF-4HBA using DFT methods is -4.37 and -19.67 kcal/mol for monomer and dimer model of NF-4HBA respectively after BSSE correction. The difference in the BSSE corrected (-4.37 kcal/mol and -19.67 kcal/mol) and uncorrected (-5.61 kcal/mol and -24.08 kcal/mol) interaction energy indicated that the magnitude of error was caused due to the basis set superposition error (BSSE). These results indicate that the BSSE is large and should be considered in calculations of the interaction energies. Electrophilic charge transfer ($\text{ECT} > 0$) indicates that charge transfer occurs from 4HBA to NF for NF-4HBA cocrystal formation. Local reactivity parameters show that C12 and O5 atomic centers are furthermore prone for nucleophilic and electrophilic attack in the case of NF-4HBA cocrystal. The NH, C=O and OH vibrational modes provide useful information on the intermolecular hydrogen bonding interaction for the NF-4HBA cocrystal. Downshifts (Red shift) in the stretching wavenumber and elongation in the corresponding bond lengths is observed in the case of NF-4HBA in comparison with NF due to hydrogen bonding functionalities such as NH, OH and C=O. The solid-state NMR spectra provided further evidence for the intermolecular interactions present in the NF-4HBA cocrystal. The NBO analysis of NF-4HBA cocrystal is made to confirm the hydrogen bond interactions observing at the intermolecular charge transfer, rehybridization, and delocalization of electron density in molecular systems. The formation of two hydrogen bonded interaction between N-H...O and O-H...O intermolecular hydrogen bonds in NF-4HBA cocrystal increases the electron density in the N-H and O-H antibonding orbitals associated with the red shift of N-H and OH stretching frequencies. The interaction energies of these bonds are also given by QTAIM analysis. QTAIM analysis (both monomer and dimer model) suggest that the hydrogen bonds present in NF-4HBA are moderate in nature as ($\nabla^2 \rho_{\text{BCP}} > 0$, $H_{\text{BCP}} < 0$) with the maximum hydrogen bond energy of $E_{\text{HB}} = 2.86$ kcal/mol and 20.67 kcal/mol respectively. The energy band gap explains the chemical reactivity of the molecule, concluding that NF-4HBA is more reactive and stronger electrophile than NF. These results suggest that cocrystals represent a viable alternative for an API, thereby offering new approach for expanding the properties in pharmaceutical formulation. Finally, theoretical computational calculations are very important in understanding the structural and various physicochemical properties of cocrystal as the experimental results alone may not be enough.

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The non-covalent interactions contribute considerably to the stability of the cocrystal and have appreciable effects on the molecular geometry as well