New Crystal Forms for Biologically Active Compounds. Part 1: Noncovalent Interactions in Adducts of Nevirapine with XB Donors

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Abstract: Stabilization of specific crystal polymorphs of an active pharmaceutical ingredient is crucial for preventing uncontrollable interconversion of various crystalline forms, which affects physicochemical properties as well as physiological activity. Co-crystallization with various excipients is an emerging productive way of achieving such stabilization in the solid state. In this work, we identified an opportunity for co-crystallization of antiviral drug nevirapine (NVP) with a classical XB donor, 1,2,4,5-tetrafluoro-3,6-diiodobenzene (1,4-FIB), as well as 1,3-diiodobenzene (1,3-DIB), which has been seldom employed as an XB donor to date. In the X-ray structures of NVP·1,4-FIB and NVP·1,3-DIB co-crystals, different hydrogen and halogen bonding modes were detected and further investigated via DFT calculations as well as topological analysis of the electron density distribution within the framework of the QTAIM method at the M06/DZP-DKH level of theory. Estimated energies of these supramolecular contacts vary from 0.6 to 5.7 kcal/mol.

Keywords: nevirapine; crystal engineering; noncovalent interactions; halogen bonding; hydrogen bonding; DFT; QTAIM

1. Introduction

Important physicochemical properties of active pharmaceutical ingredients (APIs) such as melting point, rate of dissolution, hygroscopicity, as well as thermal, mechanical and even chemical properties can vary significantly depending on the particular solid form [1]. Existence of several polymorphic states can impede the solubility, stability, bioavailability and, as a result, the desired physiological activity of the drug. Therefore, controlling which form an API in question exists in, before it is made into an approved dosage form, is of critical importance [2]. Currently, 85% of known APIs exhibit (pseudo)polymorphism and 50% of APIs can exist in multiple forms [3]. Hence, the importance of developing reliable approaches to stabilizing a particular crystal form of an API cannot be overestimated. Ideally, a desired polymorph should be stabilized to such an extent that it becomes thermodynamically stable, is not affected by humidity levels (i.e., it does not form hydrates in humid environments) and, in general, acts as a nonomorphic compound [4]. Judicious engineering of co-crystals (i.e., crystalline forms that consist of two or more components that are solid at room temperature) has attracted growing attention as a productive means of stabilizing an API in a specific solid form [5]. The development of an optimal, stable co-crystal entails elements of discovery and rational design and, therefore, carries aspects of utility, novelty and non-obviousness which are critical criteria for intellectual property protection [6]. This makes the process of co-crystal design and engineering an advantageous process in itself, potentially leading to excipients (non-API components of...
the solid form) which can themselves be protected by a patent [7]. Moreover, engineering of completely novel crystal forms for an API with suboptimal physicochemical characteristics can lead to a novel solid form of a drug which is characterized by improved aqueous solubility and bioavailability [8].

The main principle of crystal engineering has been the ‘exploitation of noncovalent interactions between molecular or ionic components for the rational design of solid-state structures that might exhibit interesting electrical, magnetic, and optical properties’ [9]. Thus, co-crystallization has prominently emerged as a tool to generate multiple solid forms for a given API with an aim to select the most suitable ones [7,10–12]. Candidate co-crystals, in turn, can be obtained by crystallization from a solution [13–15] or by mechanochemical means [16–18].

To a prevailing degree, however, when noncovalent interactions are concerned, hydrogen bonding (HB) [19] is implied [20]. Considering that over the last decade, the halogen bond (XB) [21] has emerged as an effective tool for crystal engineering [22–29] and designing supramolecular constructs [30–32], it is surprising that literature reports on the utility of XB in engineering new API crystal forms has been relatively scarce [20,33–36]. Our recent engagement in crystal engineering based on XB in metal complexes [37–45] prompted us to consider exploring new opportunities for filling the above void and applying the XB approach towards identifying novel API crystal forms. We screened a number of important APIs for the formation of co-crystals with known potential as well as recently synthesized [46] donors of halogen bonds. One of the APIs employed in our program was the known antiviral drug nevirapine (NVP, IUPAC name 11-cyclopropyl-4-methyl-5,11-dihydro-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one), which acts as non-nucleoside reverse transcriptase inhibitor (NNRTI) and is used for treatment of HIV-1 infection and AIDS [47,48]. In addition to antiviral activity, it has been reported to bind to CYP3A4 and CYP2B6 cytochromes [49] and to display some anticancer activity [50–52]. Various crystal structures of NVP have been described [53–60]. In the majority of these structures, the NVP molecule acts as an HB donor (via the N–H motif) and an HB acceptor (via the carbonyl O and pyridine N atoms).

We performed a comprehensive analysis of ten XRD structures of NVP solvates, two structures of unassociated NVP, and six structures of NVP adducts with carboxylic acids, saccharine and polycaprolactone using the Olex2 program. This analysis revealed that (i) the O carbonyl atom is the nucleophilic center for 51 noncovalent interactions including HBs and lp(O)···π(C) interactions; and (ii) the amide H atom is the electrophilic center for 23 examples of HBs. Other peripheral atoms are also involved in both HBs and lp(O)···π(C) interactions (Figure 1). Many of these contacts, especially the C–H···X (X = N, O) HBs, were not discussed or were simply overlooked in the corresponding reports, although they are real HBs in accordance with the IUPAC definition for HBs [19].

![Figure 1](image_url)

**Figure 1.** Statistical analysis results for the crystal structures containing nevirapine. Blue arrows highlight atoms that act as nucleophilic components of noncovalent interactions, while those acting as electrophilic components are marked by red arrows. Only the interactions of nondisordered fragments were taken into account, while π-stacking interactions were not.
Previously, we have already attempted [61] to involve NVP in co-crystallization with molecular iodine as an XB donor. Contrary to our expectations at the time, instead of a co-crystal, we obtained an intriguing salt form, nevirapinium pentaiodide hydrate, which was investigated by crystallography to reveal the presence of numerous HBs and an unusual I₄–I···O=C interionic XB. In continuation of these efforts, NVP was co-crystallized with 1,2,4,5-tetrafluoro-3,6-diodobenzene (1,4-FIB), an XB donor that has already been employed in the co-crystal formation for such biologically active compounds as nicotine [62], pyrazinamide, lidocaine and pentoxifylline [20]. Additionally, we used 1,3-diododibenzene (1,3-DIB), a rarely employed [63] XB donor. To our delight, both attempts resulted in the formation of nevirapine co-crystals with these XB donors. Herein, we present the results of these studies.

2. Experimental Section

2.1. Materials

Nevirapine, 1,2,4,5-tetrafluoro-3,6-diodobenzene, 1,3-diododibenzene and MeOH were obtained from commercial source and used as received.

2.2. X-ray Structure Determination

A crystal of NVP·1,3-DIB was measured on a SuperNova, Dual, Cu at zero, Atlas diffractometer at 100 K using monochromated MoKα (λ = 0.7107) radiation. A crystal of NVP·1,4-FIB was measured on an Xcalibur, Eos diffractometer at 100 K using monochromated MoKα (λ = 0.7107) radiation. The structures have been solved by the direct methods by means of the SHELX program [64] incorporated into the Olex2 program package [65]. For crystallographic data and refinement parameters, see Supplementary Material (Table S2). The carbon-bound H atoms were placed in calculated positions and were included in the refinement in the ‘riding’ model approximation, with Uiso(H) set to 1.5Ueq(C) and C–H 0.98 Å for CH₃ groups, with Uiso(H) set to 1.2Ueq(C) and C–H 0.99 Å for CH₂ groups and with Uiso(H) set to 1.2Ueq(C), C–H 0.95 Å for CH groups. Empirical absorption correction was applied in the CrysAlisPro [66] program complex using spherical harmonics, and implemented in the SCALE3 ABSPACK scaling algorithm. Supplementary crystallographic data for this paper have been deposited at the Cambridge Crystallographic Data Centre (CCDC 1882105 and 1882106) and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

2.3. Computational Details

The single-point calculations based on the experimental X-ray geometries of NVP·1,4-FIB and NVP·1,3-DIB have been carried out at the DFT level of theory using the M06 functional [67] with the help of the Gaussian-09 [68] program package. The Douglas–Kroll–Hess 2nd-order scalar relativistic calculations requested relativistic core Hamiltonian were carried out using the DZP-DKH basis sets [69–72] for all atoms. The topological analysis of the electron density distribution with the help of the atoms in molecules (QTAIM) method developed by Bader [73] has been performed by using the Multiwfn program [74]. The Wiberg bond indices were computed by using the natural bond orbital (NBO) partitioning scheme [75]. The Cartesian atomic coordinates of model supramolecular clusters (NVP)₄(1,4-FIB)₃ and (NVP)₃(1,3-DIB)₃ are presented in Supporting Information, Table S3.

3. Results and Discussion

3.1. Halogen Bonding in NVP·1,4-FIB and NVP·1,3-DIB

Slow evaporation of MeOH solutions of NVP containing an equimolar amount of either 1,4-FIB or 1,3-DIB at room temperature gave co-crystals NVP·1,4-FIB and NVP·1,3-DIB, respectively. The results of the XRD study indicated that both adducts contained the C–I···N XB (Figure 2), numerous HBs as well as a number of other interactions. DFT calculations and topological analysis of the electron density distribution within the framework of the QTAIM method confirmed the noncovalent nature of
these contacts and allowed evaluation of their energies (0.6–5.7 kcal/mol) (for details see theoretical study section).

In both adducts, one or both of the pyridine nitrogen atoms of nevirapine molecule were found to be involved in XBs as nucleophiles. In NVP·1,4-FIB, both pyridine nitrogen atoms form the C–I···N XBs with comparable geometric parameters (Table 1). Analysis of the data in CCDC related to C–I···N XBs between 1,4-FIB and various pyridine rings revealed that the shortest p-I–C₆F₄–I···N(pyridine) XB had been documented for an adduct of 1,4-FIB with 4-(dimethylamino)pyridine (d(I···N) = 2.6672(18) Å) [76] whereas the longest p-I–C₆F₄–I···N(pyridine) XB had been observed in a 1,4-FIB adduct with pyridine-2-thioamide (d(I···N) = 3.215(4) Å) [77]. Thus, the C–I···N XB lengths found in NVP·1,4-FIB (2.988(4) and 2.973(4) Å) fall within this range and can be regarded as rather common for the XBs between 1,4-FIB and a pyridine ring.

In the NVP·1,3-DIB co-crystal, only one nitrogen atom (that of the unsubstituted pyridine ring) forms a C–I···N XB (Table 1). To the best of our knowledge, this structure represents the second example of a supramolecular assembly where 1,3-DIB acts as XB donor. Previously, Uekusa et al. [63] reported the adduct of 1,3-DIB with N-(4-bromosalicylidene)-3-aminopyridine, demonstrating the C–I···N XBs (3.081(3) Å). It should be noted that isomeric 1,4-diiodobenzene (1,4-DIB) is a well-known participant in the C–I···N XBs. In most cases involving 1,4-DIB, the lengths of such contacts are in the range 2.928(4)–3.076(11) Å [23,78–81]. Noticeably larger lengths (3.313(3)–3.462(2) Å and 3.239(3) Å, respectively) were encountered in the case of bifurcate C–I···(N,N) contacts [82] as well as for

![Figure 2](image_url). The important noncovalent interactions in NVP·1,4-FIB (a) and NVP·1,3-DIB (b) co-crystals obtained in this work.
C–I···N≡C–R XB involving much less nucleophilic Nsp atoms [79]. Thus, the relatively long XB in the NVP·1,3-DIB co-crystal (3.231(3) Å) can be rationalized by steric rather than electronic effects.

Table 1. Parameters of the C–I···N XBs in the co-crystals obtained in this work.

<table>
<thead>
<tr>
<th>Structure</th>
<th>C–I···N</th>
<th>d(I···N), Å</th>
<th>RIN</th>
<th>Z(C–I···N), °</th>
<th>Eint</th>
<th>Eint</th>
</tr>
</thead>
<tbody>
<tr>
<td>NVP·1,3-DIB</td>
<td>C1S–I1S·N1</td>
<td>3.231(3)</td>
<td>0.92</td>
<td>156.09(11)</td>
<td>2.5</td>
<td>2.4</td>
</tr>
<tr>
<td>NVP·1,4-FIB</td>
<td>C1S–I1S·N1</td>
<td>2.988(4)</td>
<td>0.85</td>
<td>174.33(10)</td>
<td>4.4</td>
<td>3.8</td>
</tr>
<tr>
<td>C2S–I2S·N4</td>
<td>2.973(4)</td>
<td>0.84</td>
<td>175.88(13)</td>
<td>4.4</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Comparison 1</td>
<td></td>
<td>3.53</td>
<td>1.00</td>
<td>180</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Comparison is the vdW radii sum [83] for distances and classic XB angle. 2 RIN = d(I···N)/(RvdW(I) + RvdW(N)). 3 Eint = −V(r)/2 [84]. 4 Eint = 0.429G(r) [85].

3.2. Hydrogen Bonding in the NVP·1,4-FIB and NVP·1,3-DIB Co-Crystals

Dimerization of nevirapine molecules upon the N–H···O=C HB formation was evident in both structures (Figure 2). Almost the same supramolecular features can be found in NVP (PABHIJ [53] and PABHIJ01 [58]) crystals as well as in numerous crystals of nevirapine solvates (GIRWUA [54], KACPAH [55], OKETII [57], TISJEL [59], TISJEL01, YIVQIE, YIVQOK, YIVVQK [86]) and adducts (LATQOO, LATQUU [56], ZEYSAA [80]). Only in co-crystals with relatively strong HB donors (H2O, TISJAH [59] and TISJAH01 [58]; cis-HO2C(CH=CH)CO2H, LATQII; HO2C(CH2)2CO2H, LATQEE; HO2C(CHOH)2CO2H, LATRAB [56]) is said dimerization absent because at least the C=O nevirapine functionality is involved in O–H···O=C HBs.

NVP·1,3-DIB also contains weaker C–H···O=C HBs supporting the N–H···O=C HBs (Figure 2), the C–H···N hydrogen bonding between NVP molecules, and the C–H···I interactions between 1,3-DIB molecules.

Notably, NVP·1,4-FIB demonstrated weak C–H···O and C–H···N interactions between NVP molecules, and the numerous C–H···F and C–H···I HBs between NVP and 1,4-FIB molecules. The latter interactions are interesting because the same C–H moiety in the cyclopropyl group is involved in both C–H···I interactions (Figure 2). Note that the simultaneous formation of HBs and XBs with the I atoms in 1,4-FIB was previously reported by us [42]. The geometrical parameters of HBs are represented in Table S1.

3.3. Theoretical Study of Different Noncovalent Interactions in NVP·1,4-FIB and NVP·1,3-DIB

Inspection of the crystallographic data suggests the presence of different noncovalent interactions responsible for the formation of a supramolecular structure of NVP·1,4-FIB and NVP·1,3-DIB. In light of this, in addition to structural analysis, a detailed computational study was undertaken. In order to confirm or disprove the hypothesis on the existence of these supramolecular contacts and quantify their energies from a theoretical standpoint, we carried out DFT calculations and performed topological analysis of the electron density distribution within the framework of Bader’s theory (QTAIM method) [73] for the (NVP)4·(1,4-FIB)3 and (NVP)3·(1,3-DIB)3 model supramolecular cluster (Supporting Information, Table S3). We have already used a similar approach to study noncovalent interactions (e.g., hydrogen, halogen and chalcogen bonding, metallophilic interactions, stacking) in various organic, organometallic and coordination compounds [42–44, 86–89]. The results of these calculations are summarized in Table 2. The contour line diagrams of the Laplacian distribution ∇2ρ(r), bond paths, and selected zero-flux surfaces for (NVP)4·(1,4-FIB)3 and (NVP)3·(1,3-DIB)3, are shown in Figure 3. To visualize the noncovalent interactions studied, we carried out reduced density gradient (RDG) analysis [90] and plotted RDG isosurfaces for (NVP)4·(1,4-FIB)3 and (NVP)3·(1,3-DIB)3 (Figure 3).
The QTAIM analysis of (NVP)\textsubscript{4}·(1,4-FIB)\textsubscript{3} and (NVP)\textsubscript{3}·(1,3-DIB)\textsubscript{3} demonstrated the presence of appropriate bond critical points (3, −1) (BCPs) for all noncovalent interactions listed in Table 2. The low magnitude of the electron density (0.005–0.024 a.u.), positive values of the Laplacian (0.018–0.097 a.u.), and close to zero positive energy density (0.001–0.003 a.u.) in these BCPs are typical for noncovalent interactions [91]. We have defined energies for these contacts according to the correlations proposed by Espinosa et al. [84] and Vener et al. [85], and one can state that the strengths of these supramolecular contacts vary from 0.6 to 5.7 kcal/mol. The balance between the Lagrangian kinetic energy $G(\mathbf{r})$ and potential energy density $V(\mathbf{r})$ at the BCPs reveals the nature of these interactions; if the ratio $-G(\mathbf{r})/V(\mathbf{r}) > 1$ is satisfied, then the nature of appropriate interaction is purely noncovalent; in case the $-G(\mathbf{r})/V(\mathbf{r}) < 1$, some covalent component takes place [92]. Based on this criterion, one can state that a covalent contribution is absent in all supramolecular contacts listed in Table 2. The negligible values of the Wiberg bond indices for these supramolecular contacts additionally confirm their electrostatic nature, and analysis of the basins of total electron density (also known as QTAIM basins) reveals that delocalization indices are also negligible for all noncovalent interactions listed in Table 1.
### Table 2. Values of the density of all electrons—$\rho(r)$, Laplacian of electron density—$\nabla^2 \rho(r)$, energy density—$H_b$, potential energy density—$V(r)$, Lagrangian kinetic energy—$G(r)$ (a.u.) at the bond critical points (3,−1), corresponding to different noncovalent interactions in (NVP)$_2$·(1,4-FIB)$_3$ and (NVP)$_2$·(1,3-DIB)$_3$, bond lengths—$l$ (Å), as well as energies for these contacts $E_{int}$ (kcal/mol), defined by two approaches, appropriate Wiberg bond indices (WI), and delocalization indices (DI).

<table>
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<tr>
<th>Contact</th>
<th>$\rho(r)$</th>
<th>$\nabla^2 \rho(r)$</th>
<th>$H_b$</th>
<th>$V(r)$</th>
<th>$G(r)$</th>
<th>$E_{int}$</th>
<th>$E_{int}$</th>
<th>$l$</th>
<th>WI</th>
<th>DI</th>
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<tr>
<td>(NVP)$_2$·(1,4-FIB)$_3$</td>
<td>I1S···N1</td>
<td>0.019</td>
<td>0.060</td>
<td>0.001</td>
<td>−0.014</td>
<td>0.014</td>
<td>4.4</td>
<td>3.8</td>
<td>2.988</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>I2S···N4</td>
<td>0.019</td>
<td>0.062</td>
<td>0.001</td>
<td>−0.014</td>
<td>0.015</td>
<td>4.4</td>
<td>4.0</td>
<td>2.973</td>
<td>0.04</td>
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<td></td>
<td>H3···O1</td>
<td>0.024</td>
<td>0.097</td>
<td>0.003</td>
<td>−0.017</td>
<td>0.021</td>
<td>5.3</td>
<td>5.7</td>
<td>1.980</td>
<td>0.02</td>
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<td>H9···O1</td>
<td>0.005</td>
<td>0.020</td>
<td>0.001</td>
<td>−0.003</td>
<td>0.004</td>
<td>0.9</td>
<td>1.1</td>
<td>2.702</td>
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<td>−0.004</td>
<td>0.006</td>
<td>1.3</td>
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<td>0.032</td>
<td>0.002</td>
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<td>1.6</td>
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<td>0.034</td>
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<td>0.026</td>
<td>0.002</td>
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<td></td>
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<td>−0.008</td>
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<td>4.7</td>
<td>4.8</td>
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<td>0.002</td>
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<td>0.031</td>
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<td>0.006</td>
<td>1.3</td>
<td>1.6</td>
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<tr>
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<td>H6···I2S</td>
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<td>0.020</td>
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<td>−0.003</td>
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<td>3.1</td>
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</tr>
</tbody>
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1 $E_{int} = -V(r)/2$ [84]. 2 $E_{int} = 0.429G(r)$ [85].

### 4. Conclusions

We have identified a new opportunity for co-crystallization of an active pharmaceutical ingredient, nevirapine, with 1,2,4,5-tetrafluoro-3,6-diiodobenzene, a classical XB donor, and 1,3-diodobenzene, which has been seldom employed as an XB donor to date. Our findings provide another solid, proof-of-principle example of successfully employing halogen bonds for the design and discovery of stable crystalline forms of important drug substances. These results also lay the ground for exploring similar opportunities for other bioactive compounds with a wider range of potential donors of halogen bonds. The distinctive features of the crystal structures obtained and characterized in detail in this work are the presence of XBs with the pyridine N atoms, an XB never observed for nevirapine before. Encouraged by these findings, we aim to continue screening for novel instances of XBs stabilizing the crystal structure of active pharmaceutical ingredients. The results of these studies will be reported in due course.

**Supplementary Materials:** The following are available online at http://www.mdpi.com/2073-4352/9/2/71/s1, Table S1: Parameters of the X-H···Y HBs in the co-crystals obtained in this work; Table S2: Crystal data and structure refinement for NVP-1,4-FIB and NVP-1,3-DIB; Table S3: Cartesian atomic coordinates of model supramolecular clusters.


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