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Solhe F. Alshahateet[a]
[a] Department of Chemistry, Mutah University, Mutah, Karak, Jordan

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Synthesis and Supramolecularity of Hydrogen-Bonded Cocrystals of Pharmaceutical Model *Rac*-Ibuprofen with Pyridine Derivatives

SOLHE F. ALSHAHATEET

Department of Chemistry, Mutah University, Mutah, Karak, Jordan

The cocrystals of a pharmaceutical model rac-ibuprofen with two pyridine-containing cocrystal formers were synthesized and their solid-state structures were carefully investigated in terms of crystal engineering and supramolecular chemistry. The target cocrystals were obtained by solvent-free grinding of rac-ibuprofen with the given cocrystal former and then suitable X-ray crystals were grown in acetonitrile solution and characterized by X-ray crystallography. Both structures adopted homo and hetero supramolecular synthons as well as other noncovalent interactions.

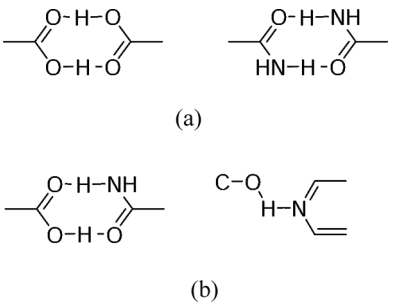
Keywords Crystal engineering; intermolecular forces; pharmaceutical model; solvent-free grinding; supramolecular synthons; X-ray crystal structures

Introduction

The self-assembly of two or more different types of molecules to form a multicomponent crystal is a phenomenon of great fascination to chemists [1]. The design of completely new multicomponent systems [2] provides a worthwhile challenge in both synthetic chemistry and crystal engineering [3]. Such substances generally fall into one of three categories: lattice inclusion compounds; inclusion complexes; and cocrystals, which were defined by Stahly [4] as crystalline structures with unique properties that are made up of two or more components. Recently, we were interested in designing new supramolecules with multicomponent systems and investigating their noncovalent intermolecular interactions [5–9]. Expert chemists at different research groups [10–13] investigated the design, synthesis, and applications of pharmaceutical cocrystals in terms of crystal engineering and supramolecular chemistry.

In this study, racemic ibuprofen was employed as active pharmaceutical ingredient (API) to be examined with a series of cocrystal formers possessing carboxylic acid (COOH), pyridine (N_{arom}), amino (NH_2), and amide ($CONH_2$) functionalities to form pharmaceutical cocrystals (PCC). Carboxylic acid functionality was chosen because it is overexpressed in APIs when compared to organic compounds in general. Alcohols and carboxylic acids represent 21 and 6% of the organic entries in the Cambridge Structural Database (CSD), respectively, but they are present in 33

Address correspondence to Dr. Solhe F. Alshahateet, Department of Chemistry, Science Building II, Mutah University, P.O. Box 7, Mutah 61710, Karak, Jordan. E-mail: s_alshahateet@mutah.edu.jo



Scheme 1. (a) Supramolecular homosynthons and (b) supramolecular heterosynthons.

and 25 of the top 100 prescribed drugs, respectively [11]. These substituted molecules do not pack efficiently by themselves in the solid state due to interruption of potential three-dimensional propagation of the offset aryl $\pi \ldots \pi$ (OFF) and edge-face aryl $C-H \ldots \pi$ (EF) intermolecular attractions [14]. Supramolecular synthons can be classified into two types: supramolecular homosynthons, which are composed of identical functional groups (self-association motifs, such as carboxylic acid or amide dimers), and supramolecular heterosynthons, which are composed of different functional groups (such as acid-aromatic nitrogen or acid-amide, Scheme 1).

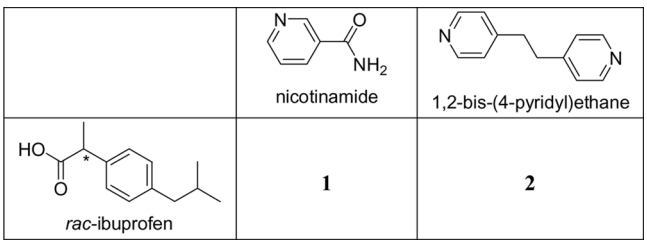
Our research program aims to design, synthesize and gain hydrogen-bonding networks involving active pharmaceutical ingredient with different cocrystal formers. In this article, we report on the synthesis and crystal structures of hydrogen-bonded cocrystals of *rac*-ibuprofen with two cocrystal formers; namely, nicotinamide (vitamin B_3) and 1,2-bis(4-pyridyl)ethane (BPE).

Results and Discussion

Preparation and Crystallization of the Hydrogen Bonded Rac-Ibuprofen Cocrystals

The two cocrystal formers, solvent, and racemic ibuprofen used in this study were obtained from commercial suppliers and were used without further purification (Scheme 2).

Cocrystallization via Grinding. Stoichiometric amounts of starting materials listed in Scheme 2 were ground with a mortar and pestle for 15 min, and the resulting powder was analyzed by infrared (IR) spectroscopy and X-ray powder diffraction.



Scheme 2. Molecular structures of cocrystal formers and *rac*-Ibuprofen used in crystallization experiments.

Cocrystallization via Solvent Evaporation. Synthesis of X-ray quality crystals of the two cocrystals was obtained by slow evaporation of acetonitrile solution of ibuprofen and each cocrystal former.

IR and X-Ray Powder Diffraction. It is well known that the infrared absorption band associated with the X-H bond stretching is considerably shifted to the longer wavelength by the hydrogen bond formation [15]. For cocrystals **1** and **2**, a broad peak for hydrogen bonding that was observed between 2,320 and 3,500 cm^{-1} completely disappeared. This might be due to the fact that molecules of the cocrystal former occupy the spaces between the molecules of ibuprofen and prevent the formation of hydrogen bonding. In addition, this could be due to the reduction in particle size of the drug. On the other hand, the X-ray powder diffraction studies showed that the crystallinity of the two cocrystals is reduced compared with the two individual components. In the case of solvent-free grinding, the resulting two cocrystals' crystallinity was improved. This is a good indication of the efficiency of grinding cocrystallization.

Single-Crystal X-Ray Data Collection and Structure Determination. Synthesis of X-ray quality crystals of the two cocrystals was obtained by slow evaporation of acetonitrile solution of ibuprofen and a given cocrystal former. Single crystals of **1** and **2** were examined under a microscope and suitable crystals were selected for single-crystal X-ray crystallography. Single-crystal X-ray diffraction data were collected on a Bruker Smart-1000 CCD diffractometer. The numerical details relating to the data collection, data processing, and refinement of the X-ray structures of the cocrystals **1** and **2** are listed in Table 1 (CCDC numbers: 773196 and 773198).

Crystal Structure of the Cocrystal 1. Cocrystal **1** crystallizes in the orthorhombic noncentrosymmetric space group $Pca2_1$ with four independent molecules (2A and 2B) in the asymmetric unit. In addition, a pseudoinversion center is present which is uncommon. However, this situation has been discussed in the literature [16]. The solid-state structure of **1** adopts different hydrogen-bonding motifs that contain both enantiomers (R/S). There are discrete sheets of either nicotinamide or ibuprofen. These nicotinamide and ibuprofen sheets are two molecules thick. The structure contains an infinite 1-D "tape" (two molecules thick) of the *S* enantiomer of ibuprofen. The next tape in the sheet is the *R* enantiomer. Both tapes are quite similar. These findings are in good agreement with that previously reported [17,18]. The molecular structure of **1** including thermal displacement ellipses with 50% probability is illustrated in Fig. 1. Hydrogen-bonding patterns in the cocrystal **1** are shown in Fig. 2. Acentrosymmetric supramolecular homosynthons exist via self-association (dimer) of amide molecules with N–H...O bond distances of 2.098(7) and 2.057(7) Å. In addition, the crystal structure adopted another two different types of supramolecular heterosynthons: the second hydrogen atom of the amino group is interacted with one oxygen atom of the ibuprofen molecule with a distance of 2.248(7) Å and one hydrogen atom of the hydroxy group with the aromatic nitrogen of the pyridine ring with a distance of 1.856(7) Å. A survey [19] on CSD was conducted and found that 77% of compounds that contain both 2-aminopyridine and carboxylic acid moieties generate 2-aminopyridine carboxylic acid supramolecular heterosynthons rather than carboxylic acid or 2-aminopyridine supramolecular homosynthons. In the absence of other competing functionalities, the occurrence of heterosynthons

Table 1. Numerical details of the solution and refinement of the crystal structures of **1** and **2**

Compound	**1**	**2**
Formula	$C_{19}H_{24}N_2O_3$	$C_{19}H_{24}NO_2$
Formula mass	328.40	298.39
Crystal system	*Orthorhombic*	*Triclinic*
Space group	*$Pca2_1$*	*P-1*
a (Å)	11.7129(16)	5.2837(4)
b (Å)	5.4915(8)	9.3142(7)
c (Å)	56.289(7)	17.9810(13)
α (°)	90	79.2780(10)
β (°)	90	82.4710(10)
γ (°)	90	80.651(2)
V ($Å^3$)	3,620.6(9)	853.26(11)
T (K)	223(2)	223(2)
Z	8	2
$D_{calc.}$ (g cm^{-3})	1.205	1.161
Radiation, λ (Å)	MoKα, 0.71073	MoKα, 0.71073
μ (mm^{-1})	0.082	0.075
Scan mode	$\theta/2\theta$	$\theta/2\theta$
No. of intensity measurements	17,259	9,167
No. of indep. obsd. reflections	5,574	2,999
F(000)	1,408	322
Goodness-of-fit on F^2	1.185	1.033
θ range for data collection	1.45 to 23.99°	2.25 to 24.99°
Completeness to θ max.	99.9%	99.9%
Final R indices [$I > 2\sigma$ (1)]	$R_1 = 0.0922$, $wR_2 = 0.2052$	$R_1 = 0.0699$, $wR_2 = 0.1735$
R indices (all data)	$R_1 = 0.1031$, $wR_2 = 0.2119$	$R_1 = 0.0843$, $wR_2 = 0.1837$
Largest peak in final diff. map e ($Å^{-3}$)	0.315	0.620
CCDC number	773196	773198

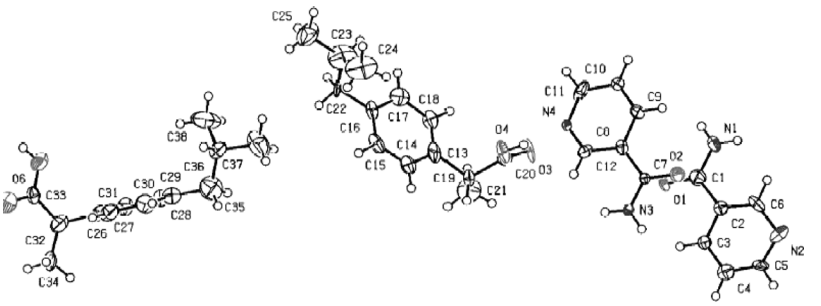


Figure 1. ORTEP plot of cocrystal **1**. The ellipsoids are presented in 50% probability.

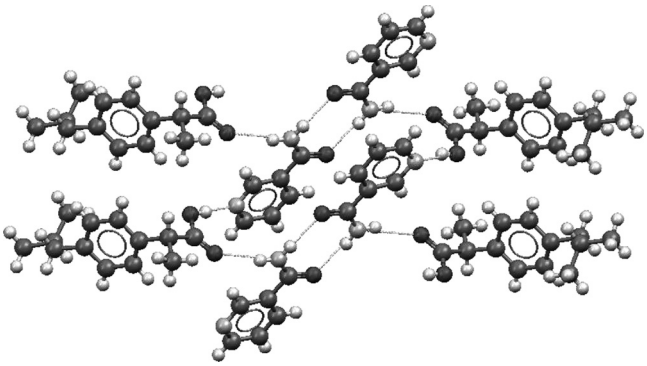


Figure 2. Crystal packing of cocrystal **1**. Both homo and hetero supramolecular synthons are shown. Network of different motifs of hydrogen bonds is presented.

increases to 97%; the CSD contains 607 crystal structures with both carboxylic acid and aromatic nitrogen moieties; 468 entries exhibit supramolecular heterosynthons. However, the CSD does not contain enough information to evaluate the predictability of even common supramolecular heterosynthons in the presence of competing hydrogen-bonding moieties. Carboxylic acid functionality was selected as a case study in this work because it represents one of the most ubiquitous functional groups in the area of crystal engineering and supramolecular chemistry [20–22]. Indeed, carboxylic acids are well known to self-associate via centrosymmetric dimers [23]. Furthermore, it is now recognized that carboxylic acids are ideally suited for cocrystals because they form persistent supramolecular heterosynthons with aromatic nitrogen moieties [24]. Bis *et al.* [25] cited various studies including CSD that investigated both homo and hetero supramolecular synthons. These studies suggest that some supramolecular heterosynthons are strongly favored over related supramolecular homosynthons. This is might be due to strength of the base used as a cocrystal former.

The C−N−C bond angle in pyridine is known to be sensitive to protonation [26,27], and its cationic form exhibits a higher value than that of the corresponding neutral molecules. The C−N−C bond angles in pyridine rings in **1** are 112.76(6)° and 119.77(6)°. These values are in good agreement with the C−N−C bond angle in the free aromatic nitrogen atom of pyridine ring encountered in 213 neutral 2-aminopyridines with an average value of 116(2)°. In addition, the two C−O bonds of the ibuprofen carboxylic acid group have different bond distances (1.18(9) and 1.32(9) Å). These values emphasize the fact that cocrystal **1** is formed only via a strong hydrogen bond between the proton-donor and proton-acceptor compounds; no proton transfer occurs. C−N−C bond angles in cocrystals containing a acid-pyridine hetero supramolecular synthon were investigated in some other studies and found to be in full agreement with what we report herein [28–34]. Three-dimensional molecular packing of **1** is shown in Fig. 3. Hydrogen bonds in the crystal structure of **1** are listed in Table 2.

Crystal Structure of the Cocrystal 2. Cocrystal **2** crystallizes in the triclinic space group *P-1* with two independent molecules (ibuprofen and 1,2-bis(4-pyridyl)-ethane) in the asymmetric unit. The molecular structure of **2** including thermal

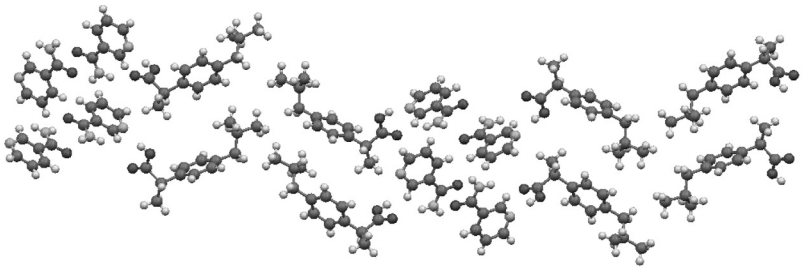


Figure 3. Three-dimensional molecular packing of cocrystal **1**.

Table 2. Hydrogen bonds for cocrystal **1** (Å and °)

D-H . . . A	d(D-H)	d(H . . . A)	d(D . . . A)	<(DHA)
N(1)-H(1A) . . . O(2)#1	0.87(6)	2.06(6)	2.905(7)	164.5
N(1)-H(1B) . . . O(5)#2	0.87(6)	2.25(7)	3.092(7)	164.1
N(3)-H(3A) . . . O(1)#3	0.87(7)	2.10(6)	2.939(7)	162.5
N(3)-H(3B) . . . O(3)#3	0.87(6)	2.25(7)	3.101(6)	166.7
O(4)-H(4A) . . . N(4)	0.83(7)	1.86(6)	2.682(7)	173.2
O(6)-H(6A) . . . N(2)#4	0.83(7)	1.82(7)	2.624(9)	164.4

Symmetry transformations used to generate equivalent atoms: #1: x, y − 1, z; #2: −x + 3/2, y, z + ½; #3: x, y + 1, z; #4: −x + 3/2, y − 1, z − 1/2.

displacement ellipses with 50% probability is illustrated in Fig. 4. The crystal structure of cocrystal **2** shows that one cocrystal former molecule (BPE) bridges two API molecules (ibuprofen) via a strong hydrogen bond (COO$\underline{H}$ . . . $\underline{N}_{arom}$) with a distance of 1.728(4) Å (Fig. 5). Cocrystal **2** contains two C−$\overline{O}$ bonds of carboxylic acid functionality of ibuprofen with different bond lengths: 1.185(3) and 1.303(3) Å. Once again, these findings together with the fact that both the C−N−C bond angle in the 1,2-bis(4-pyridyl)ethane molecule present in cocrystal **2** has the value of 116.7(3)° proved that no protonation occurred; that is, no proton

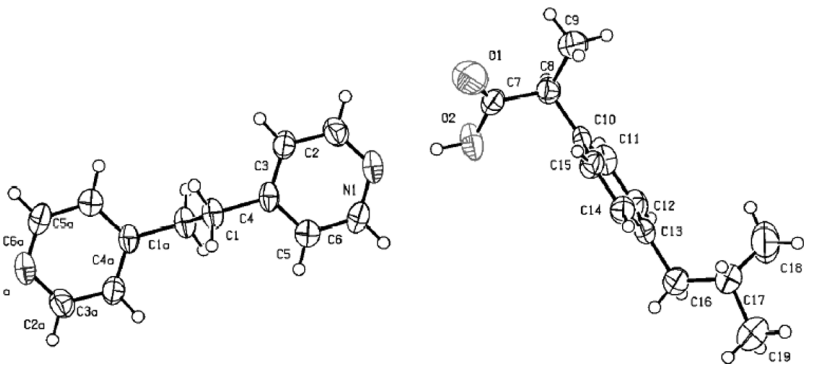


Figure 4. ORTEP plot of cocrystal **2** showing 50% probability ellipsoids.

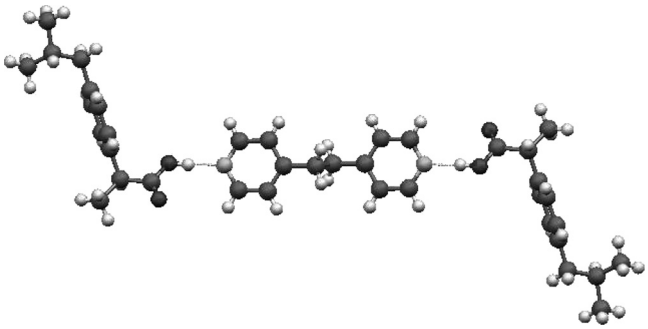


Figure 5. Hydrogen bonds in cocrystal **2**. 1,2-Bis(4-pyridyl)ethane inserts between two molecules of *rac*-ibuprofen through COOH$\underline{\ }\ldots\underline{\ }N_{arom}$.

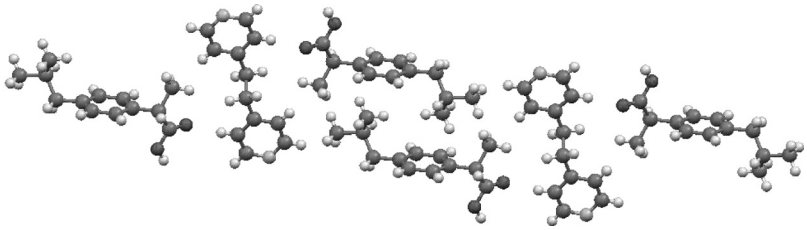


Figure 6. Three-dimensional molecular packing of cocrystal 2.

transfer. Three-dimensional molecular packing of **2** is shown in Fig. 6. Hydrogen bonds in the crystal structure of **2** are listed in Table 3.

The Relevance of pKa as a Predictor of Cocrystals vs Salts for Carboxylic Acids and Pyridines [12]. Δp*K*a of carboxylic acid vs. N$_{arom}$ moieties can be used to predict whether or not proton transfer will occur [Δp*K*a = p*K*a (base) − p*K*a (acid)]. In the pharmaceutical industry Δp*K*a > 3 is typically used as a criterion for selecting counterions for salt formation, although Johnson and Rumon [35] reported that Δp*K*a < 3.75 affords neutral COOH$\ldots$N$_{arom}$ interactions, whereas Δp*K*a > 3.75 results in proton transfer. The Δp*K*a values for cocrystals **1** and **2** are −0.81 and 1.68, respectively. However, more recently it has been reported that, even though Δp*K*a values tend to be reliable indicators of salt formation when Δp*K*a > 3, there is ambiguity in the Δp*K*a range of 0 to 3 [36].

Table 3. Hydrogen bonds for cocrystal **2** (Å and °)

D-H$\ldots$A	d(D-H)	d(H$\ldots$A)	d(D$\ldots$A)	<(DHA)
O(2)-H(2A)$\ldots$N(1)	0.94(4)	1.73(4)	2.661(3)	175(4)

Symmetry transformations used to generate equivalent atoms: #1: −x + 3, −y −1, −z + 1.

Conclusions

Our research program aims to design, synthesize, characterize and analyze new inclusion systems in terms of crystal engineering and supramolecular chemistry. Pharmaceutical cocrystallization is emerging as a possible alternative to polymorphs, salts, and solvates in the modification of an API during dosage form. *Rac*-ibuprofen was selected as a model pharmaceutical compound because it contains a carboxylic acid functionality. It formed hydrogen-bonded cocrystals when crystallized with two cocrystal formers; namely, nicotinamide (vitamin B_3) and 1,2-bis(4-pyridyl)ethane. The two crystal structures proved that the resulted compounds are cocrystals rather than salts (proton transfer compound). Different supramolecular synthons exist in each crystal structure, such as amide dimer, acid-aromatic nitrogen, NH_2 dimer, and some others. Our research in this area is still ongoing because the goal of pharmaceutical cocrystallization is to engineer pharmaceutical cocrystals with specific improved properties.

Experimental

Solution and Refinement of the Crystal Structures

Reflection data were measured at 223(2) K on a Bruker SMART Apex-1000 diffractometer equipped with a charge-coupled device (CCD) detector and Mo-Kα sealed tube. SMART [37] was used for collecting frame data, indexing reflection, determination of lattice parameters, integration of intensity of reflections, and scaling. SADABS [38] was used for absorption correction and SHELXTL [39] for space group, structure determination, and least-squares refinements on F^2. All hydrogen atoms were included in calculated positions with isotropic thermal motion linked to that of bonded atom. Crystallographic data (cif) have been deposited with the Cambridge Structural Data Centre (CCDC) with reference numbers 773196 and 773198. See http://www.ccdc.cam.ac.uk/conts/retrieving.html for crystallographic data in cif or other electronic format. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: 44(0)-1223–336033 or E-mail: deposit@ccdc.cam.ac.uk).

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