A "hidden" co-crystal of caffeine and adipic acid†

Dejan-Krešimir Bučar,[ab] Rodger F. Henry,[c] Xiaochun Lou,[a] Thomas B. Borchardt[d] and Geoff G. Z. Zhang*[a]

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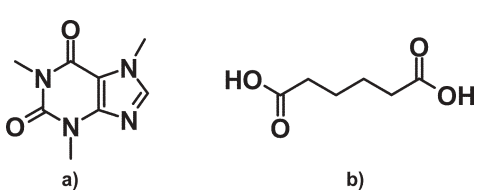
Co-crystal formation between caffeine and adipic acid has been explored over the years without success; utilizing the newly developed co-crystal screening method, we have finally discovered this "hidden" caffeine and adipic acid co-crystal.

The performance and shelf-life of solid pharmaceutical formulations are influenced by many properties of the pharmaceutical agent (PA) and excipients (*e.g.* solubility, dissolution rate, bioavailibility, stability and compatibility). In order to achieve optimum performance of drug formulations, manipulation of the active pharmaceutical ingredient (API) solid form is sometimes desirable. In doing so, the APIs have traditionally been subjected to salt, polymorph and solvate (*e.g.* hydrate) formation to tailor their physical and chemical properties.[1] The need for new pathways to tuned APIs and the importance of API solid forms in the context of performance have encouraged pharmaceutical scientists to take advantage of crystal engineering to design PA containing co-crystals. Co-crystals are a long known (but poorly investigated) class of crystalline compounds which contain two or more molecules[2] that are solids at ambient temperatures.[3] In co-crystals, PAs self-assemble *via* functional groups, such as amides and carboxylic acids, with complementary functional groups of a co-crystal formed into new robust structural motifs. These co-crystals may provide desirable physical and chemical properties for formulation development while the original pharmacologic activities are preserved. In the last several years, concepts of supramolecular chemistry[4] have been successfully applied to alleviate or eliminate various limiting properties of the APIs.[5–7]

One example of the application of crystal engineering in design of solid forms of APIs was recently published by Jones and co-workers.[7] In this paper, a crystal engineering study was presented using caffeine as a model compound. It was demonstrated that the physical stability (*i.e.* hydration potential upon exposure to high relative humidity) can be modified by co-crystal formation with various aliphatic dicarboxylic acids. The authors described the synthesis of caffeine co-crystals containing oxalic, malonic, maleic and glutaric acids in different ratios as well as conformational polymorphs thereof. The authors have also explored co-crystal formation with some other acids such as fumaric, L-tartaric and adipic acid. However under the conditions studied and with the screening method employed (*i.e.* solvent-drop grinding[8]) co-crystallization attempts with these acids were unsuccessful. In fact, co-crystals of caffeine with various aliphatic dicarboxylic acids were studied over twenty five years ago by Nishijo *et al.*[9] Co-crystals were successfully formed for oxalic, maleic, malonic and glutaric acids as characterized by powder X-ray diffractometry, IR spectroscopy and thermal analysis (these co-crystals were described as "solid complexes"). The authors also explored co-crystal formation with adipic acid. Interestingly, consistent with the more recent report,[7] they failed to obtain co-crystals comprising caffeine and adipic acid.

Recently, we have developed an efficient co-crystal screening method, utilizing the thermodynamically driven solution-mediated phase transformation.[10] In this method, a suspension/slurry containing both components of the co-crystal system is prepared in an appropriate solvent. This approach provides an optimal environment for the putative co-crystal formation because the activity values of both components are held at one. This method was applied to sixteen pharmaceutically related co-crystal systems and was found 100% successful.[10] Therefore, we challenged ourselves and the newly developed screening method with such systems where previous attempts to form co-crystals were unsuccessful.

With this contribution, we would like to expand the series of known co-crystals containing caffeine and aliphatic dicarboxylic acids with an 1 : 1 caffeine–adipic acid co-crystal (**1**). The chemical structures of caffeine and adipic acid are presented in Scheme 1. Adipic acid was chosen for this study for the reason mentioned above. In addition, adipic acid is recognized as a promising compound to explore the co-crystal formation with imidazole-ring containing molecules based on the following three considerations. First, adipic acid is a pharmaceutically acceptable salt former and an excipient which is considered safe. Second, co-crystal formation is expected since proton-transfer (therefore salt formation) is not supported by the pK_a values of caffeine (0.61) and adipic acid (4.41, 5.28).[11] Third, a Cambridge Structural Database (CSD)[12] survey of possible hydrogen-bond patterns within a caffeine–dicarboxylic acid complex disclosed two robust supramolecular



Scheme 1 The chemical structures of (a) caffeine and (b) adipic acid.

[a]*Solid State Sciences, Global Pharmaceutical R&D, Abbott Laboratories, North Chicago, IL, 60064, USA. E-mail: Geoff.GZ.Zhang@abbott.com; Fax: 1- 847-937-2417; Tel: 1-847-937-4702*
[b]*Department of Chemistry, University of Iowa, Iowa City, IA, 52242, USA*
[c]*Structural Chemistry, Global Pharmaceutical R&D, Abbott Laboratories, Abbott Park, IL, 60064, USA*
[d]*Solid State Chemistry, Global Pharmaceutical R&D, Abbott Laboratories, North Chicago, IL, 60064, USA*
† The HTML version of this article has been enhanced with colour images.

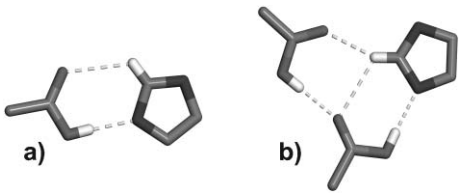


Fig. 1 The most common acid–imidazole heterosynthons present in caffeine–dicarboxylic acid co-crystals.

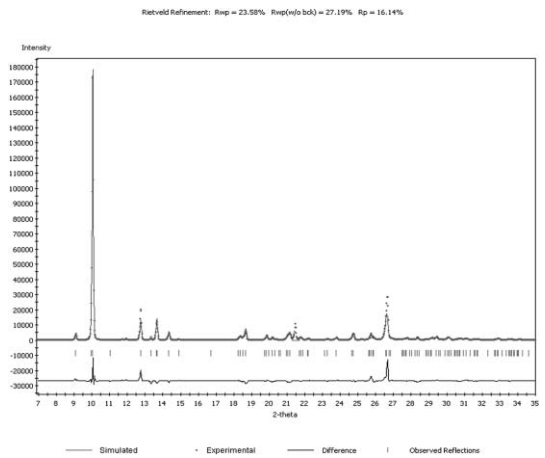


Fig. 2 Comparison of the experimental PXRD pattern of the bulk material of compound **1** with the calculated pattern using Rietveld methods.

synthons characteristic for caffeine–carboxylic acid assemblies.[7,13] The first one is a $R_2^2(7)$ heterosynthon (Fig. 1(a)) which tends to direct a 2 : 1 caffeine–dicarboxylic acid co-crystal formation. The second one, a $R_3^3(11)$ network based on $R_2^2(7)$ and $R_2^2(6)$ synthons, is usually present in 1 : 1 caffeine–dicarboxylic acid co-crystals (Fig. 1(b)).

To explore co-crystal formation of caffeine and adipic acid, the following screening procedure[10] was applied: a suspension of caffeine and adipic acid (1 : 1 molar ratio) in acetonitrile‡ was prepared and equilibrated overnight at ambient temperatures. The powder X-ray diffraction pattern of the residual solid after equilibration indicated a phase transition from the physical mixture of caffeine and adipic acid to a new solid phase – potentially a co-crystal of caffeine and adipic acid.

Single crystals were subsequently grown *via* solvent evaporation from acetonitrile solution§ and the molecular structure was determined by X-ray diffractometry.¶ The experimental XRPD pattern of the bulk material was compared with the single-crystal structure using Rietveld methods (Fig. 2). When the strong preferred orientation present in the experimental pattern is taken into account, the fit with the simulated pattern is good. The preferred orientation models available, however, were not adequate to completely account for the data in the sample. This can be most clearly seen in the intensity difference in the (2,1,−2) peak near $2\theta = 27^\circ$. Additionally a weak peak, not accounted for in the simulated pattern can be seen at $2\theta = 21.4^\circ$. This peak can be assigned as the (0,1,1) peak of adipic acid, indicating that a small amount of adipic acid remained in the powder sample. Crystallographic data confirmed co-crystal formation in a 1 : 1 molar ratio in the triclinic $P\bar{1}$ space group. The crystal structure also reveals the formation of the heterosynthon illustrated in Fig. 1(b) which is consistent with other known 1 : 1 caffeine–dicarboxylic acid co-crystal structures. The asymmetric unit of compound **1** contains one molecule of caffeine and two half adipic acid molecules, which lie about independent inversion centers. A Fourier difference map analysis reveals that no salt formation *via* proton transfer occurs during the crystallization process. Difference maps unequivocally located the acid H atoms adjacent to O3 and O5 and in the refinement these were allowed for as riding atoms with O–H = 0.82 Å. In addition, the difference in the two C–O bond lengths of both adipic acid molecules indicates a lack of delocalization typical for ionized species.

Caffeine and adipic acid build a three-component caffeine–acid–caffeine adduct linked with a strong O3–H···N4 hydrogen bond and a C5–H···O4 weak C–H···O hydrogen bond type interaction (Fig. 3). This trimeric adduct is assembled with another molecule of adipic acid, which links the caffeine–acid–caffeine trimer into a molecular tape *via* O5–H···O4 and C5–H···O6 hydrogen bonds (Fig. 3). The tapes are, in the solid state, assembled into "zipper"-like structures (Fig. 4), this formation is stabilized by weak C–H···O hydrogen bond type interactions. The "zipper"-layers of compound **1** are stacked in a ABAB manner and held

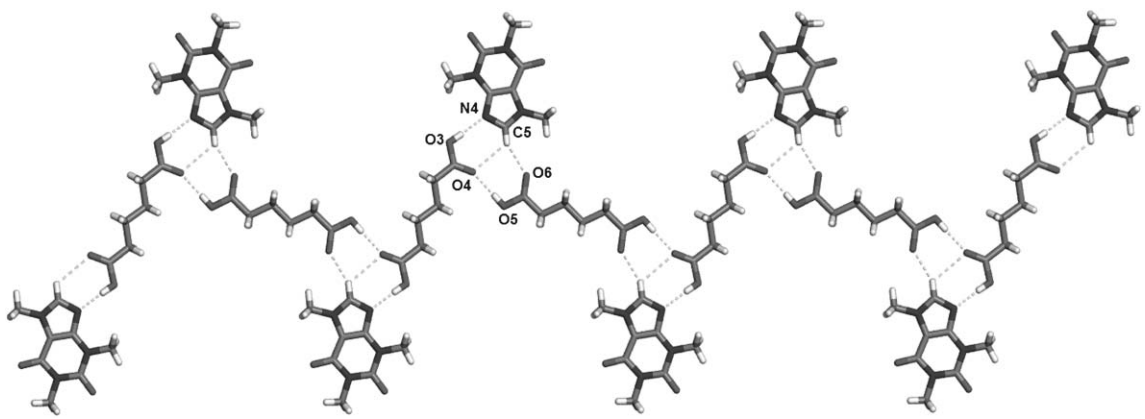


Fig. 3 A view of caffeine–adipic acid trimers along the crystallographic plane (1 −2 0). The trimers are linked *via* hydrogen-bonded adipic acid molecules into molecular tapes.

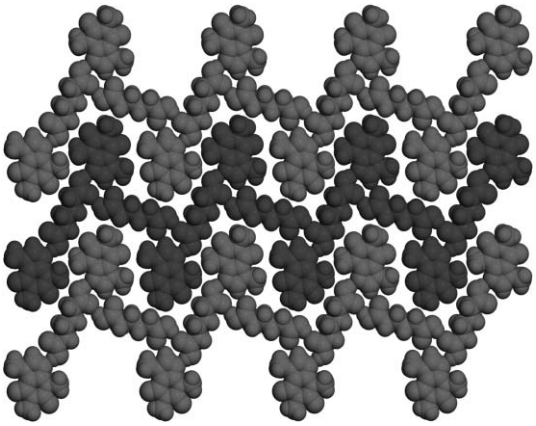


Fig. 4 The "zipper" arrangement of the caffeine–adipic acid molecular tapes.

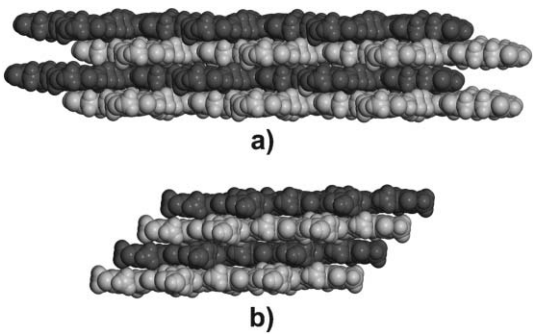


Fig. 5 A space-filling model of four layers of compound **1** stacked in an ABAB manner viewed along the crystallographic planes: (a) (2, 1, −2) and (0, −1, 0); (b) (2, 1, −2) and (0, 0, −1).

Table 1 Selected hydrogen-bond parameters of compound **1** (Å, °)[a]

D–H···*A*	*d*(H···*A*)/Å	*d*(D···*A*)/Å	*θ*(D–H···*A*)/°
O3–H3···N4	1.87	2.6850(12)	178
O5–H5···O4	1.93	2.7453(12)	172
C5–H5a···O6	2.26	3.1138(17)	153
C10–H10b···O1(A)	2.51	3.2353(16)	132

[a] Symmetry operator used to generate equivalent O1(A) atom: $-x + 1, -y, -z + 1$.

together by C10–H10b···O1 hydrogen bonds (Fig. 5). The selected hydrogen-bond parameters are listed in Table 1.

As in the majority of adipic acid containing crystal structures deposited in the CSD, adipic acid in the co-crystal **1** exhibits an outstretched chain-like conformation (in only 5 of 30 adipic acid containing crystal structures does the adipic acid exhibit a non-outstretched chain conformation).‖

In conclusion, we have discovered the "hidden" co-crystal of caffeine and adipic acid. Although the validity and the efficiency of our slurry co-crystal screening method have been demonstrated previously with sixteen reported co-crystal systems,[10] the discovery of this "hidden" co-crystal further establishes the significance of this novel co-crystal screening method. When searching for co-crystals, it is now possible to rapidly determine whether they exist without extensive crystallization trials that are time and labor intensive. The effort that is preserved can be re-directed toward exploring more potential co-crystal formers, which will ultimately result in improved success rate in our search for co-crystals.

Notes and references

‡ Acetonitrile was selected based on two considerations: (1) it is poor hydrogen-bonding solvent, therefore, tends not to interfere with the interactions between the two co-crystallization components in solution. Meanwhile, it is a polar solvent that tends to provide solvency for many organic compounds. (2) Solubility measurements indicate that acetonitrile provides similar solubility for both caffeine and adipic acid, therefore, offers optimal conditions for co-crystal formation.

§ Single crystals of compound **1** were prepared by solvent evaporation method. Caffeine (19.4 mg) was mixed with adipic acid (14.6 mg). A small portion (2 ml) of acetonitrile was added to the solid mixture. The suspension was heated until the caffeine and adipic acid were completely dissolved. The solution was kept at 348 K for 10 min, filtered and left to evaporate slowly at 298 K. Crystals suitable for single-crystal X-ray diffraction were obtained after five days.

¶ *Crystal data* for **1**: $C_8H_{10}N_4O_2{\cdot}C_6H_{10}O_4$, M_r = 340.34, triclinic, space group $P\bar{1}$, a = 9.5480(16), b = 9.5862(16), c = 9.6682(16) Å, α = 82.705(3), β = 87.649(3), γ = 67.236(2)°, V = 809.4(2) Å^3, Z = 2, D_c = 1.397 g cm^{-3}, μ = 0.110 mm^{-1}, T = 293(2) K, total of 9608 collected reflections, 3877 unique reflections (R_{int} = 0.0690), 3433 observed reflections [$I > 2\sigma(I)$], R_1(obs) = 0.0418, wR_1(obs) = 0.1195, R_2(all) = 0.0454, wR_2(all) = 0.1223. CCDC 616820. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b611749j

‖ Searches to determine the number of (a) caffeine containing co-crystals and (b) adipic acid (also adipate) containing entries in the CSD were performed on CSD version 5.27 using ConQuest version 1.7. The CSD was searched without any single filter in place.

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