Carboxamide–pyridine *N*-oxide heterosynthon for crystal engineering and pharmaceutical cocrystals†

L. Sreenivas Reddy, N. Jagadeesh Babu and Ashwini Nangia*

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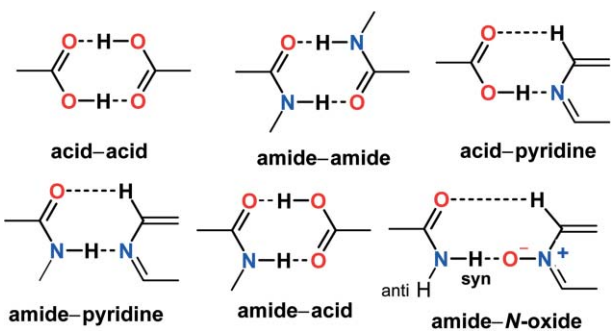
The novel carboxamide–pyridine *N*-oxide synthon, sustained *via* N–H···O$^-$ hydrogen bonding and C–H···O interaction, is shown to assemble isonicotinamide *N*-oxide in a triple helix architecture and the same heterosynthon is exploited to synthesize cocrystals of barbiturate drugs with 4,4′-bipyridine *N*,*N*′-dioxide.

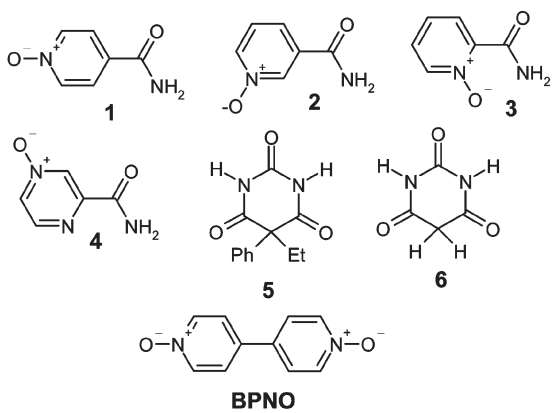
Pharmaceutical cocrystals—defined as hydrogen-bonded complexes between an active pharmaceutical ingredient (API) and a benign solid component—are crystalline phases developed for superior efficacy, solubility and stability in drug formulation.[1] Desiraju[2] defined supramolecular synthons as recurring hydrogen bond and/or intermolecular interaction patterns for crystal engineering. Zaworotko and co-workers[1] sub-classified them as homosynthons or heterosynthons depending on whether the interacting complementary functional groups are the same or different (Scheme 1). Carboxylic acids and carboxamides have traditionally been used in crystal design[3] *via* the dimer synthon. The remarkable success of the acid–pyridine synthon[4] for controlling the supramolecular architecture and in providing access to binary/ternary cocrystals shows the considerable potential of heterosynthons in chemistry, particularly acid–amide.[5] We report preliminary results on a novel amide–*N*-oxide heterosynthon by taking advantage of the strong N–H···O$^-$ hydrogen bond.

A necessary condition for heterosynthon assembly is that hydrogen bonding between the dissimilar functional groups should be stronger than homo-aggregation. The amide–pyridine motif‡ appeared unsuited because hydrogen bond acceptor strength of pyridine N is slightly less than amide C=O, though at times they may be comparable (*e.g.* isonicotinamide dimorphs),[6] whereas pyridine *N*-oxide (N$^+$–O$^-$) is a stronger acceptor because of its anionic character. For example, pK_{HB} values of pyridine, amide and *N*-oxide in increasing basicity order are 1.86, 1.96 and 2.70,[7] and moreover electrostatic surface potential (ESP) charges at N, O and O$^-$ atoms parallel the above trend.§ A related observation that pyridine *N*-oxide is able to disrupt the urea α-network[8] encouraged us to oxidize some common pyridine amides to the corresponding *N*-oxides (Scheme 2) and analyze their crystal packing.¶



Scheme 1 Some examples of homosynthons and heterosynthons.

In the crystal structure of isonicotinamide *N*-oxide **1** (space group $Pna2_1$) the carboxamide *syn* NH hydrogen bonds to pyridine *N*-oxide *via* N–H···O$^-$ interaction (1.89 Å, 168.4°). The auxiliary C–H···O interaction (2.25 Å, 156.8°) in the amide–*N*-oxide synthon is significant because the two functional groups are roughly coplanar (O–N–O$^-$–C torsion angle ~12°). Participation from the *anti* N–H···O$^-$ hydrogen bond (1.95 Å, 161.9°) results in a remarkable triple helical architecture in *N*-oxide **1** (Fig. 1). Its non-centrosymmetric packing is consistent with a two-fold higher SHG response compared to urea (Nd^{3+}-YAG laser at 1064 nm). Triple helices are a useful target in supramolecular networks[9] because of potential application in non-linear optics. Nicotinamide *N*-oxide **2** has linear tapes of amide–*N*-oxide (1.93 Å, 164.9°; 2.43 Å, 134.5°) connected *via anti* N–H···O$^-$ (1.88 Å, 159.8°) to produce inversion-related helices in $P2_1/n$ space group. Because of intramolecular *anti* N–H···O$^-$ bonds (1.73 Å, 141.2°) in picolinamide *N*-oxide **3**, *syn* NH groups aggregate *via* the amide dimer (1.95 Å, 173.2°). All hydrogen bond parameters are listed in ESI.†



Scheme 2 The carboxamide–pyridine *N*-oxide heterosynthon is present in crystals **1**, **2**, **4** and cocrystals **5**, **6** with BPNO.

School of Chemistry, University of Hyderabad, Hyderabad, 500 046, India. E-mail: ashwini_nangia@rediffmail.com; Fax: 91 40 23011338
† Electronic supplementary information (ESI) available: Table of hydrogen bonds, IR stretching frequency of N–H group, and computation of hydrogen bond energy in crystals. See DOI: 10.1039/b515510j

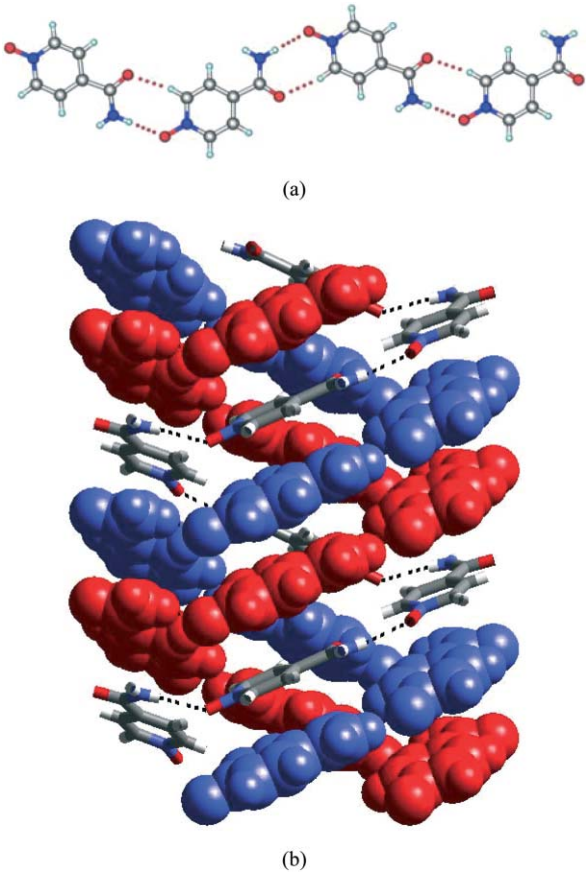


Fig. 1 (a) N–H···O$^-$/C–H···O interaction in the amide–*N*-oxide heterosynthon. (b) Triple helix in the non-centrosymmetric structure of isonicotinamide *N*-oxide **1**. Helices are made up of alternating *syn* and *anti* NH donors bonding to the *N*-oxide acceptor.

Pyrazinamide polymorphs exhibit different variations of N–H···O and N–H···N hydrogen bonds.[10] Oxidation of the sterically exposed and more reactive pyridyl group with H_2O_2–AcOH afforded pyrazinamide-4-*N*-oxide **4**. Symmetry independent molecules form linear tapes of the amide–*N*-oxide synthon (Fig. 2) which further extend into 2D sheet *via* N–H···O, C–H···O and C–H···N interactions in the $P\bar{1}$ space group.

After successfully evaluating the robustness of our novel heterosynthon in multi-functional molecules, we attempted cocrystallization of two different components with carboxamide and pyridine *N*-oxide functional groups. The amide–*N*-oxide heterosynthon was tested in barbiturate drugs because (1) barbiturates are known to be polymorphic,‖[11] (2) polymorphic compounds with several H bond donor/acceptor groups (*e.g.* isonicotinamide, pyrazinamde) tend to cocrystallize readily,[6] and (3) cocrystals offer a practical solution to controlling polymorphism in pharmaceuticals.[12] Dissolution of an equimolar mixture

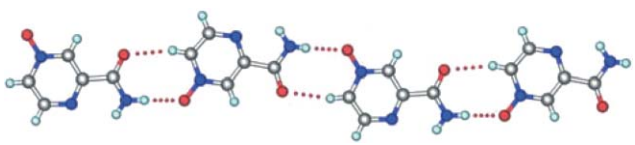


Fig. 2 1D tape in pyrazinamide *N*-oxide **4** assembled *via* amide–*N*-oxide heterosynthons between symmetry independent molecules.

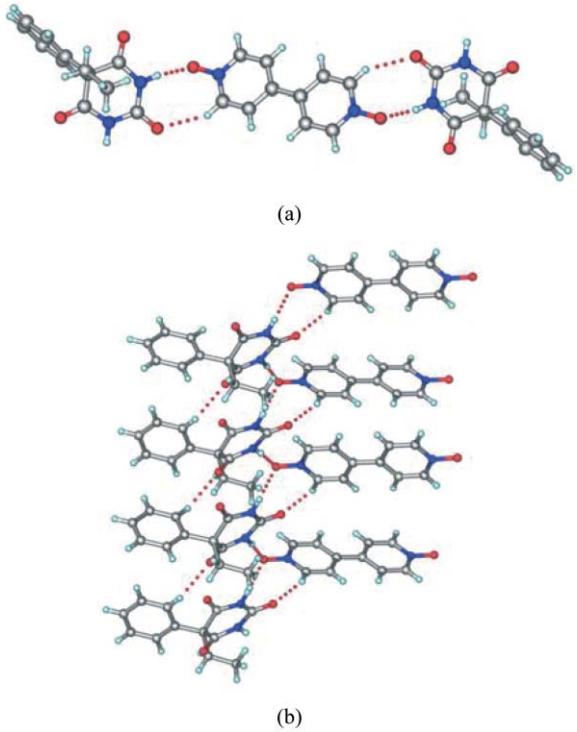


Fig. 3 (a) Binary aggregate of phenobarbital **5** and bipyridine *N*,*N*′-dioxide. (b) Helical array of molecules in the cocrystal. Hydrogen bonding is shown on one side of BPNO (resides on the inversion center) for clarity.

of phenobarbital and 4,4′-bipyridine *N*,*N*′-dioxide (BPNO) in MeOH by warming and cooling to room temperature afforded single crystals of the binary aggregate **5**·$(BPNO)_{0.5}$ suitable for X-ray diffraction ($P2_1/c$ space group). CONH groups of two molecules of **5** are connected to each *N*-oxide part of BPNO in a bifurcated motif leading to a helix (Fig. 3) stabilized by distinct occurrences of the amide–*N*-oxide heterosynthon, one of which is a single interaction (1.78 Å, 173.3°) and the other a two-point motif (1.81 Å, 162.5°; 2.28 Å, 151.0°). The cocrystal of barbituric acid and BPNO includes a water molecule during crystallization from MeOH to give **6**·BPNO·H_2O. The crystal structure has linear tapes of alternating amide–*N*-oxide synthons and its hydrated motif in *Pbca* space group (Fig. 4). Water molecules bridge adjacent layers of molecules. Why the ratio of barbituric acid to BPNO is 2:1 with **5** but 1:1 with **6** is difficult to say, however different stoichiometries have been noted in barbiturate–aza-heterocycle cocrystals.[13] The formation of binary bulk phases was found to be about 50% complete after 30 min of ball mill grinding by powder X-ray diffraction. In solid-state IR spectra the N–H

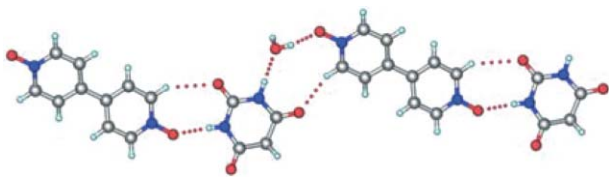


Fig. 4 Barbituric acid·BPNO·H_2O has both amide–*N*-oxide and its hydrate motif. Amide–acid heterosynthon and its hydrated motif were recently reported in carbamezapine–4-aminobenzoic acid cocrystal.[5]

stretching frequency is systematically shifted to lower ν_s values by 50–100 cm^{-1} compared to that in amides, confirming complex formation (see ESI†). A logical follow up to the 'proof of concept' model cocrystals of **5** and **6** would be to synthesize binary cocrystals of barbiturates and other amide-containing drugs, such as carbamezapine, piracetam, pyrazinamide, with GRAS (generally regarded as safe) components. Another lead is to cocrystallize *N*-oxide functional group drugs[14] with pharmaceutically acceptable carboxamides.[15] An advantage with the amide–*N*-oxide heterosynthon is that H bonding is sufficiently different from that in the amide dimer, and this should result in unexpected functions and properties of cocrystals.

Hydrogen bond preferences and synthon energy calculations suggest that amide *N*-oxides should be less prone to polymorphism compared to amide pyridines. Polymorphism in isonicotinamide[6] and pyrazinamide[10] may be understood from different occurrences of N–H···O and N–H···N hydrogen bond synthons, perhaps due to the comparable acceptor strength of amide C=O and pyridine N groups. On the other hand, the strong N–H···O^- H bond controls crystallization in amide–*N*-oxides. The two-point amide–*N*-oxide heterosynthon is worth 11–12 kcal mol^{-1} with an enthalpic advantage, ΔE_{HB}, of ~3.0 kcal mol^{-1} over homosynthon aggregation,† a value that is comparable to the energy gain in acid–pyridine and amide–acid heterosynthons (ΔE_{HB} 2.0–4.0 kcal mol^{-1}).[16] We argue that formation of the amide–*N*-oxide heterosynthon is kinetically preferred because the strongest H bond donor (amide NH) will readily approach the strongest acceptor (pyridine *N*-oxide),[17] a hypothesis that is in agreement with the frequency of acid–pyridine and amide–acid heterosynthons in the CSD (91 and 47%).** When kinetically formed synthons are also thermodynamically favored, polymorphism is hardly likely under normal *P*/*T* conditions because the global free energy minimum structure will be much lower in energy than other possible metastable polymorphs.[18] Of course, here we are analyzing only the hydrogen bond contribution to the lattice energy and polymorphism could well be possible through different arrangements of the same heterosynthon, or through differences in close packing of layers/hydrophobic groups or different molecular conformations but the same heterosynthon. A thorough screening of amide–*N*-oxide crystals is currently under way to ascertain these possibilities.

To summarize, the novel carboxamide–pyridine *N*-oxide heterosynthon is designed by exploiting the better acceptor strength of anionic oxygen and shown to result in helical motifs, a sought after architecture in crystal design. Notably, the amide–*N*-oxide heterosynthon dominates over the amide dimer homosynthon and should have a high probability of occurrence in crystal structures, except when it is in competition with intramolecular H bonding. This heterosynthon will provide a different set of molecules to answer the frequently-asked billion-dollar question in pharmaceutical R&D: do API cocrystals tend to be less polymorphic than pure compounds?

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Notes and references

‡ The Cambridge Structural Database, www.ccdc.cam.ac.uk, August 2005 update, recorded 4 hits of amide–pyridine motif (N–H···N 2.5–3.5 Å, C–H···O 3.0–4.0 Å) in 84 accurately determined organic crystal structures ($R < 0.10$, 3D coordinates, no errors, no ions, not polymeric), giving an occurrence probability of 5%. This value is too low in competition with amide dimer and catemer synthons (35 and 18%).[5] CSD refcodes of the 4 hits are EHOWIH02, NICOAM01, PEBMAK, SEKDOB. The amide–pyridine *N*-oxide synthon is absent up to the current CSD version.

§ Calculated in Spartan 04, www.wavefun.com, HF/6-31G**. Isonicotinamide: N −43.7, O −47.4; isonicotinamide *N*-oxide: O^- −53.3, O −43.1. ESP charges are in kcal mol^{-1} and more negative potentials indicates a better acceptor atom. See ESI† for H-bond energy calculations.

¶ Crystal data for amide *N*-oxides **1–4**, **5**·$(BPNO)_{0.5}$ and **6**·BPNO·H_2O are given in ESI.† Amide NH and H_2O protons were refined isotropically and CH protons were fixed in SHELX refinement. Hydrogen bond geometries reported are of neutron-normalized H atom positions. CCDC 288479–288484. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b515510j

‖ Phenobarbital has 13 forms, barbital four and barbituric acid two.

** Here too, strongest donor to strongest acceptor pairing prevails in acid–pyridine O–H···N and acid–amide O–H···O H bonds.

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