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Controlling molecular tautomerism through supramolecular selectivity†

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We have isolated the stable as well as the metastable tautomers of 1-deazapurine in the solid state by exploiting principles of supramolecular selectivity in the context of cocrystal design.

All molecules capable of tautomerism can present multiple chemical expressions towards their surroundings. Consequently, properties such as acidity, hydrophobicity or polarity can vary considerably between different tautomers of the same compound.[1] Since hydrogen atoms are difficult to locate using X-ray diffraction techniques, prototropic tautomers[2,3] have often been overlooked or even miss-assigned. The problem of ''tautomeric blindness'' has adversely affected many hierarchies of structural sciences from small molecule crystal structures to biological macromolecules, including DNA.[4]

Whilst many compounds may tautomerize in solution, they are almost invariably frozen into a particular tautomeric form once they aggregate in a solid. In fact, 99.5% of tautomeric molecules only exhibit one tautomeric form in the crystalline state,[5] and this usually corresponds to the most stable tautomer (except when the tautomeric energy differences are small, <5 kJ mol^{-1}).[6] In those rare cases where higher-energy tautomers are observed,[7] tautomeric energy differences almost never exceed the interaction energy of a strong hydrogen bond.[5] It appears that the less stable a tautomer is, the more challenging its isolation becomes within a crystalline phase. For example, it has taken 137 years to discover and characterize the most stable polymorph of barbituric acid, a polymorph containing the considerably higher-energy enolic tautomer.[8]

A change in polymorphic structure[5,9] or a change in lattice components[10] may, in some cases, induce a change in the observed tautomeric form of a compound. Whilst relatively little control can be gained over the way in which a compound chooses to crystallize by itself, the introduction of additional components into the lattice opens up a range of new possibilities. The aim of this contribution is to demonstrate how it is possible to command molecular tautomerism by exploiting concepts of supramolecular selectivity in the context of cocrystal design.[11,12] To demonstrate the fundamental principles of our approach, we chose imidazo[4,5-*b*]pyridine, 1-deazapurine (1-DAP), as a model compound. 1-DAP can exhibit two different tautomers: 3H and 1H (Fig. 1). Tautomer 3H is always more stable than the 1H tautomer, even in markedly different polarizable environments (Fig. 1 and Table S1, ESI†).

In order to sample the likely aggregation modes of both tautomers of 1-DAP, we used computational methods (CrystalPredictor)[13] to generate $Z' = 1$ crystal structures of both tautomers. Computer generated crystal structures containing the 3H tautomer revealed a preference of 3H-1-DAP to form hydrogen bond dimers (Fig. 2, left). Computer generated crystal structures containing the 1H tautomer revealed a preference of 1H-1-DAP to form catemeric motifs (Fig. 2, right). In these aggregation modes, both tautomers end up with one unused basic nitrogen atom (the imidazole nitrogen for the 3H tautomer and the pyridine nitrogen for the 1H tautomer).

In order to extract a desirable tautomer from solution and into the solid state, regardless of its relative stability, we opted for a strategy based on molecular-recognition driven cocrystallization whereby the face of a specific tautomer is selectively

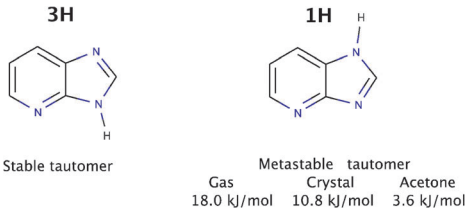

Fig. 1 3H and 1H tautomers of 1-DAP. Relative tautomeric energies were calculated at the CCD/aug-cc-pVTZ level of theory in the gas-phase and using a Polarizable Continuum Model (ESI†).

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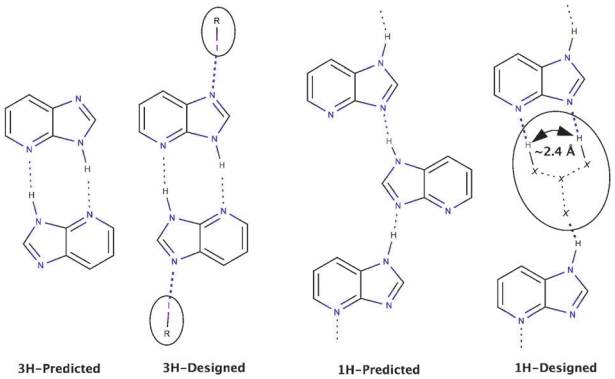

Fig. 2 Predicted aggregation modes of 1-DAP in the 3H and 1H tautomers and supramolecular synthons proposed for their selective isolation.

matched with a complementary molecule. First, to selectively isolate the more stable 3H tautomer, we decided to cocrystallize 1-DAP with a molecule capable of interacting strongly with the available imidazole nitrogen atom in the 3H tautomer without perturbing the hydrogen-bond dimer. We chose a halogen-bond donor since such a molecule should interact favourably at the 3H imidazole nitrogen with a lower probability of disturbing the 3H dimer or the 1H catemeric motif (Fig. 2). Consequently, we employed two well-established halogen-bond donors (I1 & I2) as selective cocrystal formers for the 3H tautomer (Fig. 3, left). Second, to selectively isolate the metastable 1H tautomer, we needed a cocrystallizing agent capable of forming two coplanar hydrogen bonds (both as donors) separated by a distance of ~2.4 Å (the distance between the imidazole and the pyridine basic nitrogen atoms in the 1H tautomer) with an accessible hydrogen-bond acceptor at the opposite end of the molecule (Fig. 2, right). Such a partner should selectively interact with the 1H tautomer by inserting itself in the catemeric motif, while leaving the 3H tautomer unperturbed. A search of the Cambridge Structural Database for such molecular topologies resulted in several possible candidates including urea derivatives (ESI†). Since metastable tautomers are usually more difficult to crystallize than stable tautomers, an extensive library of diphenyl ureas (U1–U14) was used as a source of selective cocrystal formers for the 1H tautomer (Fig. 3, right).

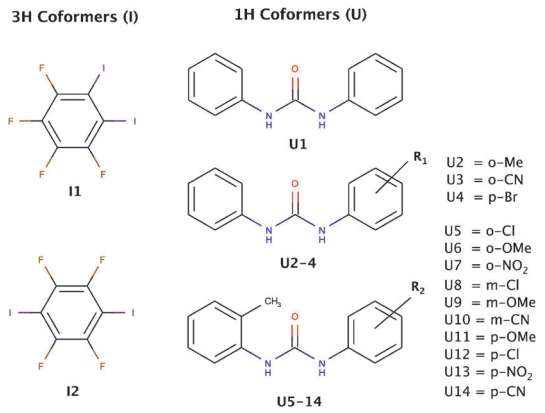

Fig. 3 Cocrystal formers used for the selective crystallization of the stable 3H tautomer (left) and the metastable 1H tautomer (right) of 1-DAP.

1-DAP and the coformers were either synthesized or purchased as detailed in the ESI.† Cocrystal formation was attempted by grinding 1 : 1 solid mixtures of 1-DAP and the coformer (I/U) in the presence of a few drops of acetone. New forms were identified using PXRD and FTIR, and single crystals were obtained *via* slow evaporation from acetone solutions. Eight new solid forms were produced by grinding, six of which were characterized using single crystal XRD (1-DAP cocrystals with I1, I2, U1, U3, U4 and U13).

All cocrystals obtained in this study contained the desired tautomeric forms as well as the intended supramolecular synthons. In the two cocrystals of 1-DAP with the coformers I1 and I2, tautomer 3H is present (Fig. 4, left). As intended, the 3H dimer (held together by two N–H···N hydrogen bonds) is intact, leaving the halogen-bond donor to engage the peripheral nitrogen atom, which results in discrete tetrameric supermolecules in both structures (the second halogen atom in each *I* coformer does not display any significant intermolecular interactions). In the four cocrystals of 1-DAP with the urea coformers U1, U3, U4 and U13, the desired meta-stable tautomer 1H is indeed obtained (Fig. 4, right). As intended, the urea coformer inserts itself in the original catemeric motif through two hydrogen bonds at one end and one hydrogen bond at the opposite end of the molecule (Fig. 4, right) and in each case the primary motif is an infinite chain of alternating urea-1H building blocks. The success rate for crystallizing the less-stable 1H tautomeric form was 43% (6/14) as indicated using infrared spectroscopy on all solid products (ESI†).

Energies of the main dimers in these cocrystals were calculated and are summarized in Table 1 for two representative cocrystals of each type. Dimer energies were calculated by fully geometry optimizing the experimental crystal structure of the cocrystal using VASP[14] (PBE[15] DFT functional with Grimme's[16] van der Waals corrections, PBE-d) and then performing a single point energy calculation of the isolated dimer of interest and a full geometry optimization of the isolated monomers using the same model. The energy difference between the dimer and the monomers corresponds to the reported dimer energy in Table 1. In the cocrystals containing the 3H tautomer, 3H is involved in two main dimer interactions: (i) with another 3H molecule of -97 kJ mol^{-1} (involving two hydrogen bonds) and (ii) with a *I* molecule of -37 kJ mol^{-1} (involving a strong halogen bond). In the cocrystals containing the 1H tautomer, 1H is involved in two main interactions with *U* of ~ -80 kJ mol^{-1} (involving two hydrogen bonds) and ~ -48 kJ mol^{-1} (involving an additional hydrogen bond). Each 1-DAP coformer interaction present in these cocrystals is far more stabilizing than the tautomeric energy of the 1H tautomer itself (Fig. 1), hence, it is not surprising that supramolecular interactions can provide an effective way of controlling tautomeric forms. Overall, the interactions involving the 3H and the 1H tautomers of 1-DAP are very similar in both types of cocrystals. However, whilst in the 3H:I cocrystals the motifs are isolated (a tetramer unit), in the 1H:U cocrystals they extend infinitely as part of a catemer motif.

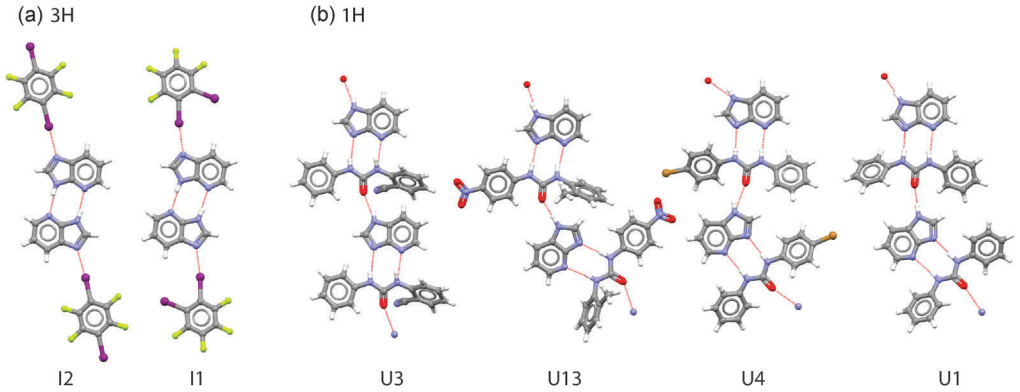

Fig. 4 Motifs found in the 1:1 cocrystals of (a) 1-DAP as the stable 3H tautomer with I2 and I1 and (b) 1-DAP as the metastable 1H tautomer with U3, U13, U4 and U1.

Table 1 Dimer energies (kJ mol^{-1}) between one molecule of 1-DAP and its two closest neighbours in four relevant cocrystals

	Dimer interacting through	
Cocrystal	Two hydrogen bonds (3H–3H)	One halogen bond (3H–I)
3H:I1	−96.5	−36.5
3H:I2	−98.1	−37.9
	Two hydrogen bonds (1H–U)	One hydrogen bond (1H–U)
1H:U1	−74.0	−48.3
1H:U13	−86.1	−47.3

To understand the overall stabilities of the systems, one needs to compare the lattice energies of the cocrystal structures with respect to the lattice energies of the single component crystal structures.[17–19] Lattice energies for the cocrystals 3H:I2 and 1H:U1 and the coformers I2 and U1 were calculated by geometry optimizing the experimentally known crystal structures with VASP (PBE-d). The lattice energy of pure 1-DAP was taken from the most stable crystal structure generated computationally and energy minimized using the same method.‡ The cocrystallization energy was calculated as the difference between the lattice energy of the cocrystal and those of the single component crystal structures. For both cocrystals 3H:I2 and 1H:U1, the cocrystallization energy was found to be negative, −9 and −6 kJ mol^{-1} respectively. A negative cocrystallization energy indicates that cocrystal formation is driven by an enthalpic gain. The energy gain afforded through the formation of the 1H:U1 cocrystal, however, is less stabilizing (−6 kJ mol^{-1}) than the energy gain afforded through the formation of the 3H:I2 cocrystal (−9 kJ mol^{-1}), perhaps, amongst other contributions, because of the higher tautomeric energy of the former.

In summary, we have been able to extract desired molecular tautomers into the solid state using supramolecular selectivity driven by both hydrogen and halogen bond based interactions. This study illustrates how relative stabilities of tautomers can drastically change with a change of environment and how, by controlling the environment, it is possible to deliberately isolate a desired tautomer. The concepts illustrated in this contribution may prove very useful for the design of new materials containing rare tautomeric forms, which are likely to exhibit very different physical properties. This should be of interest to many research areas dealing with the solid-state properties of high-value active ingredients and materials.

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Notes and references

‡ This structure was later found to correspond to the crystal structure observed experimentally.[20]

1 Y. C. Martin, *J. Comput.-Aided Mol. Des.*, 2009, **23**, 693–704.
2 A. Katritzky, M. Karelson and P. Harris, *Heterocycles*, 1991, **32**, 329–369.
3 J. Elguero, A. R. Katritzky and O. V. Denisko, in *Advances in Heterocyclic Chemistry*, ed. A. R. Katritzky, Elsevier Academic Press Inc., San Diego, 2000, vol, 76, pp. 1–84.
4 J. Elguero, *Struct. Chem.*, 2012, **23**, 297–300.
5 A. J. Cruz-Cabeza and C. R. Groom, *CrystEngComm*, 2011, **13**, 93.
6 A. J. Cruz-Cabeza, A. Schreyer and W. R. Pitt, *J. Comput.-Aided Mol. Des.*, 2010, **24**, 575–586.
7 M. R. Chierotti, L. Ferrero, N. Garino, R. Gobetto, L. Pellegrino, D. Braga, F. Grepioni and L. Maini, *Chem.–Eur. J.*, 2010, **16**, 4347–4358.
8 M. U. Schmidt, J. Bruening, J. Glinnemann, M. W. Huetzler, P. Moerschel, S. N. Ivashevskaya, J. van de Streek, D. Braga, L. Maini, M. R. Chierotti and R. Gobetto, *Angew. Chem., Int. Ed.*, 2011, **50**, 7924–7926.
9 J. Elguero, *Cryst. Growth Des.*, 2011, **11**, 4731–4738.
10 M. Tutughamiarso and E. Egert, *Acta Crystallogr., Sect. B*, 2012, **68**, 444–452.
11 C. B. Aakeröy, A. M. Beatty and B. A. Helfrich, *Angew. Chem., Int. Ed.*, 2001, **40**, 3240–3242.
12 G. R. Desiraju, *Angew. Chem., Int. Ed.*, 2007, **46**, 8342–8356.
13 P. G. Karamertzanis and C. C. Pantelides, *J. Comput. Chem.*, 2005, **26**, 304–324.
14 G. Kresse and J. Hafner, *Phys. Rev. B*, 1993, **47**, 558; G. Kresse and J. Hafner, *Phys. Rev. B*, 1994, **49**, 14251; G. Kresse and J. Furthmüller, *Comput. Mater. Sci.*, 1996, **6**, 15–50.
15 J. P. Perdew, K. Burke and M. Ernzerhof, *Phys. Rev. Lett.*, 1996, **77**, 3865–3868.
16 S. Grimme, *J. Comput. Chem.*, 2006, **27**, 1787–1799.
17 A. J. Cruz-Cabeza, G. M. Day and W. Jones, *Chem.–Eur. J.*, 2008, **14**, 8830–8836.
18 A. J. Cruz-Cabeza, S. Karki, L. Fábián, T. Friščić, G. M. Day and W. Jones, *Chem. Commun.*, 2010, **46**, 2224–2226.
19 H. C. S. Chan, J. Kendrick, M. A. Neumann and F. J. J. Leusen, *CrystEngComm*, 2013, **15**, 3799–3807.
20 L. Dymińska, A. Gagor, M. Maczka, Z. Węgliński and J. Hanuza, *J. Raman Spectrosc.*, 2010, **41**, 1021–1029.