From molecular sociology *via* structural chemistry to functional materials

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1. Introduction[1]

Co-crystals represent solids where bulk physical properties may be amenable to fine-tuning by making modular and controllable alterations to the crystalline lattice that "houses" an active molecular species. The links between crystal structure and solid-state properties offer opportunities for improving processing, performance and shelf-life of a wide range of specialty chemicals. Consequently, an ability to control and change the crystalline environment of a material without altering molecular properties would be of considerable significance to manufacturers and consumers alike. However, if co-crystals are to make a transition from a mostly academic pursuit into widely applicable technologies, key questions regarding their synthesis need to be addressed and the implied challenges therein must be overcome. In short, how do we cultivate versatile synthetic procedures that reproducibly deliver multi-component products with structural and stoichiometric consistency?

2. Hydrogen-bond directed assembly of co-crystals

In order to develop versatile supramolecular synthetic strategies that can be applied in hydrogen-bond (HB) driven assembly[2] of co-crystals it is necessary to identify building blocks that display reliable binding preferences in the presence of a range of chemical functionalities. We may realize this goal by allowing custom-designed ditopic molecules (with two different HB donors/acceptors) to react with probe molecules in order to identify a ranking of synthons within a structural "competition", Figure 1.

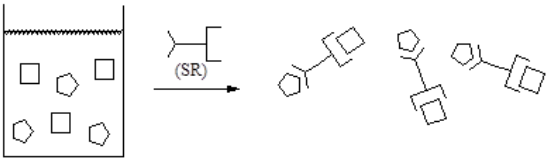

Figure 1. A one-pot supramolecular reaction between two different molecules and a ditopic supramolecular reagent (SR) resulting in 1:1:1 ternary supermolecules.

2.1 Supramolecular strategy and covalent building blocks

The success of 'conventional' covalent synthesis is often measured in terms of selectivity, versatility, and yield, and the quality of a supramolecular reagent can be assessed along similar lines. First, "selectivity" translates to the ability to assemble supermolecules with predictable connectivity based upon principles of molecular recognition. Second, "versatility" means that the supramolecular reagent should be able to operate effectively under different reaction conditions (*e.g.* change in solvents and temperature). Third, "yield", in a supramolecular sense, translates to frequency of occurrence of a particular synthon in the presence of potentially disruptive intermolecular interactions. With this in

mind, we can evaluate any crystal engineering strategy geared towards the assembly of heteromeric crystalline solid using quantitative and transferrable metrics.

2.2 How do we design, engineer and build a molecular crystal?

A central aspect of crystal engineering, which in itself can be viewed as a sub-discipline of supramolecular chemistry, concerns the construction of crystalline materials from discrete molecular building blocks using non-covalent interactions.[3,4] An overriding goal for such efforts is to acquire and develop reliable and practical means for the synthesis of molecular materials with specific and tunable properties.[5] For example, we may want to design materials that can perform chemical separations, or that have non-linear optical,[6] magnetic,[7] or catalytic properties.[8] In order to obtain non-linear optical materials, individual molecules must be organized in a non-centrosymmetric arrangement with appropriately aligned dipole moments, for magnetic materials they must be positioned so that communication between spins is facilitated and optimized, and for chemical separations the host-material must be able to selectively entrap molecules or ions. In other words, if we wish to build functional materials, we must be able to control *how* molecular building blocks can be assembled into architectures with desirable connectivity and precisely defined metrics. Supramolecular synthesis is a pro-active process – molecular building blocks are typically designed such that directional intermolecular interactions are expressed in terms of specific structural consequences and it may therefore be more appropriate to describe targeted supramolecular synthesis as "directed assembly" instead of "self-assembly".

3. Energetic materials

Supramolecular synthesis of solid-state architectures, crystal engineering, is achieved by directional and site-specific intermolecular interactions.[9] Since our first paper on co-crystals was published in 1996,[10] we have developed robust and transferable practical strategies for the synthesis of co-crystals of molecules containing a wide-range of chemical functionalities,[11] and we have also demonstrated how physical properties of active ingredients can be 'dialed-in' through a careful selection of co-crystallizing agents based on extensive synthetic, structural, and spectroscopic efforts.[12] In this section we will shift our focus onto functionalities that impart function and performance of energetic materials. When it comes to the deliberate design and construction of co-crystals of energetic materials, the synthesis is primarily dictated by the intermolecular chemistry of nitro and, to a lesser extent, amino groups. Unfortunately, the $-NO_2$ moiety is one of the least active chemical functionalities from the point of view of non-covalent interactions. In fact, nitro groups are frequently thought of as nothing more than a space-filling entity without an ability to influence solid-state assembly in a meaningful or predictable manner.[13] Although, examples of co-crystals of energetic materials have been reported,[14] we do not yet have access to versatile and reliable synthetic strategies for the targeted assembly of co-crystals, new solid forms, of energetic materials of strategic and commercial importance.

Ethylenedinitramine (**EDNA**) is a known energetic material which requires attention partly due its chemical instability originating with its two highly acidic protons. In order to stabilize EDNA, a co-crystallization approach targeting the acidic protons using a series of co-crystallizing agents with suitable hydrogen-bond acceptors was employed.[15] A systematic co-crystallization study of **EDNA** demonstrated that the acidic protons in the energetic material can be successfully targeted with suitable hydrogen-bond acceptors.

Six of the eight co-crystals synthesized were characterized using single-crystal diffraction and the outcome was predictable supramolecular motifs based upon N-H···N and N-H···O structure-directing hydrogen bonds. The co-formers also act as "supramolecular protecting groups" resulting in a reduced chemical instability/corrosiveness which is otherwise detrimental to the storage and processability of **EDNA**. The co-crystal of **EDNA** and 1,2-bis(4-pyridyl)¬ethylene was recognized as a more thermally stable alternative to **EDNA** while the co-crystal of **EDNA** and pyrazine N,N'-dioxide showed comparable detonation strengths (and improved chemical stability) compared with EDNA. The co-crystal of EDNA and 4,4'-bipyridine was found to be about 50% less impact sensitive than pure EDNA. Thermal properties impact sensitivity, and detonation velocities and pressure could also be modified and altered with a degree of predictability since the structural consistency throughout this series unearthed some correlations between molecular structure/property of the pure co-former and the energetic properties of the resulting co-crystal. This clearly suggests that systematic co-crystallizations may allow us to fine-tune properties that are important for storage, handling, and processing, with minimal negative impact on the performance of the targeted substance.

4. Synthesis and solubility of co-crystals of pharmaceuticals

The vast majority of active pharmaceutical ingredients (API's) exists as solids at room temperature and the particular solid form defines many of the API's physical properties such as solubility, thermal and mechanical stability, and particle morphology (which influences downstream processability and formulation). Furthermore, the API's physicochemical properties also govern pharmacokinetic (PK) properties such as bioavailability, absorption, and distribution. A major challenge in this field is the lack of versatile technologies that can alter/improve key physicochemical properties of API's, and while there are many drug-delivery technologies that can lengthen the time a drug remains in the human body or how it is delivered, there are few options to control solubility. Particle size reduction may improve the kinetic solubility of the API in some cases, however it may also introduce additional technical challenges, such as agglomeration and instability, in formulation and manufacturing as well as higher cost in production. Instead, it would be more beneficial if properties such as solubility or chemical stability of the solid-form of the API could be engineered at the molecular level[16] access to such expertise and technologies would have dramatic and long-term impact on the pharmaceutical industry.

Herein[17] we present a systematic structure-property study of a series of co-crystals of hexamethylenebisacetamide, **A**, a compound capable of inhibiting the proliferation of lung cancer cells, and which is also being used in the treatment of myelodysplastic syndrome (MDS) and resistant acute myelogenous leukemia (AML).[18] Our strategy was to synthesize infinite API···diacid···API···diacid chains using the well-known COOH···py hydrogen-bond based synthon,[19] and these chains were subsequently going to be arranged into 2-D layers as a result of API-based self-complementary amide···amide hydrogen bonds.[20] All diacids used in this study, Figure 5, are generally regarded as safe by FDA. The main objectives of this study are (i) to determine if we can synthesize a series of co-crystals with the desired structural consistency; (ii) to establish how well thermal stability can be correlated with the nature of the co-crystallizing agent and; (iii) to establish how well solubility can be correlated with the nature of the co-crystallizing agent.

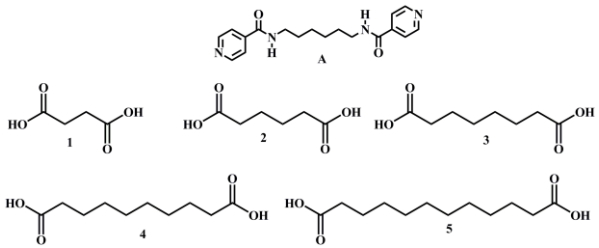

Figure 5. Target API and dicarboxylic acids.

Co-crystallization reactions were carried out between **A** and **1-5**, and IR spectroscopy was used to screen all resulting solids for co-crystal formation. We were also able to grow crystals suitable for single crystal X-ray diffraction of all products. In **A1** (the 1:1 co-crystal of **A** and **1**) a primary interaction between the pyridyl moiety and carboxylic acid was observed resulting in 1-D chains which, in turn were organized into layers via interchainhydrogen bonds. Similar structures were obtained with all diacids and these also contain 2-D layers generated via self-complementary amide···amide hydrogen bonds, Figure 6.

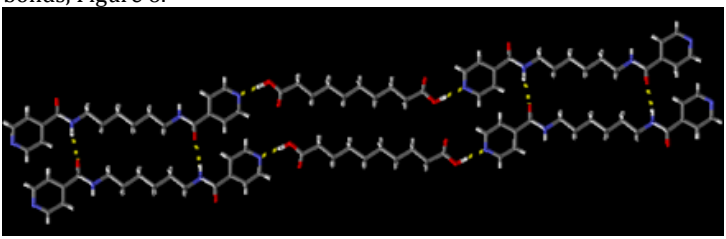

Figure 6. 2-D sheet in **A4** generated through O-H···N and N-H···O hydrogen bonds.

Having achieved the required structural consistency, we subsequently examined whether the thermal stability of these co-crystals could be correlated with any molecular feature of the five co-crystallizing agents, Fig. 7. The data clearly show that the melting points of these five crystalline solids are directly related to the melting points in the dicarboxylic acids.

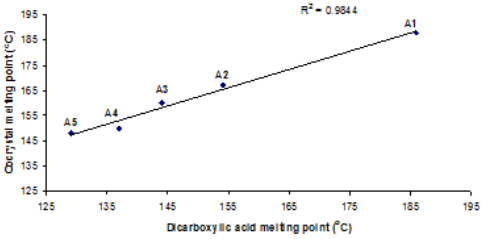

Figure 7. Thermal stabilities for **A1-A5.**

Thermal stability is an important issue but solubility is a key factor, and we therefore also determined the aqueous solubilities for **A1-A5,** Figure 8.

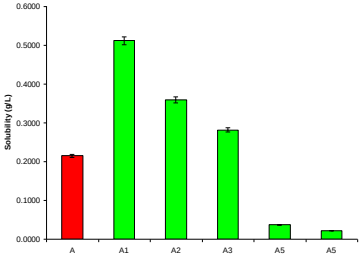

Figure 8. Aqueous solubilities of **A** and **A1-A5.**

Although the solubilities of the five co-crystals of the API do not produce a linear correlation as was the case with the thermal stabilities, the trend in physico-chemical properties of the co-crystals can certainly be rationalized in terms of the aqueous solubilities of the dicarboxylic acids. The co-crystals of the longer chain diacids, which are less polar and more hydrophobic in nature, show decreased aqueous solubility compared to that of the API itself.

6. Endnote

By addressing specific questions about how relatively simple molecules prefer to bind to each other, we will attempt to establish reproducible and reliable links between molecular function and directed non-covalent synthesis. The ability, (a) to position molecules exactly where we want them to be; (b) to construct heteromolecular architectures with desirable metrics; and (c) to translate intermolecular communication into blueprints for materials design and for constructing viable biological mimics, represent significant long-term goals of interest to a wide range of scientists.

References

1. Aakeröy, C.B., *Acta Crystallogr. Sect. B.* **2015**, *71*, 387-391; Aakeröy, C.B., Wijethunga, T.K., Benton, J., Desper, J., *ChemComm*. **2015**, *51*, 2425 – 2428; Aakeröy, C.B., Wijethunga, T.K., Desper, J., Đaković, M., *Cryst. Growth Des.,* **2016**, *16*, 2662–2670; Aakeröy, C.B., Spartz, C.L., Dembowski, S., Dwyre, S., Desper, J., *IUCrJ*, **2015**, *2*, 498-510.
2. Braga, D.; Desiraju, G.; R.; Miller, J. S.; Orpen, A. G. Price, S.L. *CrystEngComm*, **2002**, *4* 500-509; Angeloni, A.; Crawford, P.C.; Orpen, A.G.; Podesta, T.J.; Shore, B.J. *Chem. --A Eur. J*. **2004**, *10*, 3783-3791
3. J.-M. Lehn, *Angew. Chem. Int. Ed. Engl.* **1990**, *29,*1304; G.R. Desiraju, *Crystal Engineering: The Design of Organic Solids*, Elsevier, Amsterdam, **1989**. J.W. Steed, J.L. Atwood, Supramolecular Chemistry: An Introduction, J.Wiley & Sons, Chichester, **2000**.
4. Aakeröy, C.B., *Acta Crystallogr.* **1997**, *B53,* 569.
5. Desiraju, G.R., *Nature* **2001**, *412*, 397; Coronado, E., Galan-Mascaros, J.-R., Gomez-Garcia, C.J., Laukhin, V. *Nature* **2000**, *408,* 447.
6. Muthuraman, M., Masse, R., Nicoud, J.-F., Desiraju, G.R., *Chem. Mater.* **2001**, *13*, 1473; König, O., Burgi, H.-B., Armbruster, T., Hulliger, J., Weber, T. *J. Am. Chem. Soc.* **1997**, *119*, 10632.
7. Kahn, O., *Acc. Chem. Res.* **2000**, *33*, 1; Miller, J.S., *Inorg. Chem.* **2000**, *39*, 4392.
8. Aoyama, Y., *Topics Curr. Chem*. **1998**, *198*, 131; Bassani, D.M., Darcos, V., Mahony, S., Desvergne, J.-P., *J. Am.Chem. Soc.* **2000**, *122*, 8795.

9. Aakeröy, C.B.; Chopade, P.D.; Ganser, C.; Desper, J**.,** *Chem. Commun***., 2011,** *47***,** 4688-4690**;** Aakeröy, C.B.; Desper, J.; Fasulo, M.; Hussain, I.; Levin, B.; Schultheiss, N. *CrystEngComm*, **2008**, *10*, 1816-1821; Aakeröy, C.B. Desper, J., Helfrich, B.A., Metrangolo, P., Pilati, T., Resnati, G., Stevenazzi, A., *Chem. Commun*, **2007**, 4236-4238; Desiraju, G.R.;, *Angew. Chem. Int. Ed.,* **2007,** *46***,** 8342–8356; Moulton, B.; Zaworotko, M.J. *Chemical Reviews*, **2001**, *101*, 1629-1658; Thomas, J.M., *CrystEngComm.,* **2011**, *13*, 4304-4306.
10. Aakeröy, C.B.. Cooke, T.I.. Nieuwenhuyzen, M. *Supramolecular Chemistry*, **1996**, *7*, 153-156.
11. Aakeröy, C.B, Beatty, A.M., Nieuwenhuyzen, M.; Zou, M. *Tetrahedron*, **2000**, *56*, 6693-6699; Aakeröy, C.B, Beatty, A.M.; Helfrich, B.A.; *Angew. Chem. Int. Ed. Engl*. **2001**, *40*, 3240-3242; Aakeröy, C.B; Beatty, A.M; Helfrich, B.A.; *J. Am. Chem. Soc*.; **2002**, *124*, 14425-14432. Aakeröy, C. B.; Beatty, A. M.; Helfrich, B. A.; Nieuwenhuyzen, M.; *Cryst. Growth Des*.; **2003**; *3*, 159-165; Aakeröy, C.B; Salmon, D.J. *CrystEngComm*, **2005**, *7*, 439-448.
12. Aakeröy, C.B.; Forbes, S., Desper, J, *J. Am. Chem. Soc*., **2009**, *131*, 17048-17049; Aakeröy, C.B.; Fasulo, M.E., Desper, J., *Molecular Pharmaceutics*, **2007**, *4*, 317-322; Aakeröy, C.B.; Grommet, A. B., Desper, J, *Pharmaceutics* **2011**, *3*, 601-614; Aakeröy, C.B.; Forbes, S.; Desper, J. *CrystEngComm*, **2012**, *14*, 2435 - 2443.
13. Robinson , J.M.A..; Philp, D., Harris, K.D.M.; Kariuki, B.M., , *New J. Chem.*, **2000**,*24*, 799-806.
14. Aakeröy, C.B.; Rajbanshi, A.; Desper, J., *ChemCommun*, **2011**, *47*, 11411 – 11413.
15. Aakeröy, C.B., Wijethunga, T.K., Desper, J., *Chem. Eur. J.* **2015**, *21*, 11029 – 11037.
16. Aakeröy, C.B.; Forbes, S.; Desper, J. *CrystEngComm*, **2012**, *14*, 2435 – 2443; Aakeröy, C.B.; Grommet, A. B., Desper, J, *Pharmaceutics,* **2011**, *3*, 601-614.
17. Aakeröy, C.B.; Forbes, S., Desper, J., *J. Am. Chem. Soc*., **2009**, *131*, 17048-17049.
18. (a) Andreeff, M.; Stone, R.; Michaeli, J.; Young, C.W.; Tong, W.P.; Sogoloff, H.; Ervin, T.; Kufe, D.; Rifkind, R.A.; Marks. P.A. *Blood*, **1992**, 80, 2604-2609; (b) Callery, S.P.; Egorin, M.J.; Geelhaar, L.A..; Nayar B.S. *Cancer Res.*, **1986**, 46, 4900-4903; (c) Siegel, D.S.; Zhang, X.; Feinman, R.; Teitz, T.; Zelenetz, A.; Richon, V.M.; Rifkind, R.A.; Marks, P.A.; Michaeli, *J. Proc. Natl. Acad. Sci. USA*, **1998**, 95, 162-166.
19. (a) Shan, N.; Zaworotko, M.J. *Drug Discovery Today*, **2008**, 11, 440-46, (b) Aakeröy,C.B.; Beatty, A. M.; Helfrich, B. A.; Nieuwenhuyzen, M. *Cryst. Growth Des*. **2003**; *3*, 159-165; (c). Aakeröy,C.B.; Desper, J.; Helfrich, B. A. *CrystEngComm*, **2004**, *6*, 19-24; (d) Aakeröy,C.B.; Desper, J.; Urbina, J.F. *Cryst Growth&Design,* **2005**, *5*, 1283-1293.
20. Lauher, J.W.; Fowler, F.W.; Goroff, N.S. *Acc. Chem. Res*., **2008**, *41*, 1215-1229