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Investigating Weak Interactions in Pharmaceutical Co-Crystal Systems
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Pharmaceutical co-crystallisation is emerging as a possible alternative to polymorphs, salts and solvates in the modification of an active pharmaceutical ingredient (API) during dosage form. It may alter the physico-chemical properties of the API (e.g. melting point and solubility), and also have intellectual property implications.

Traditionally, co-crystallisation research has involved robust synthons with strong interactions and rarely involved pharmaceutically acceptable co-crystallising agents and conditions. Our current work has focused on the co-crystallisation of sulfathiazole with sugar excipients, [1], where moderate to weak interactions were expected to dominate.

Co-crystallisation was investigated by solution and solid-state methods (including solvent mediated grinding). Co-crystallisation of sulfathiazole with lactose, mannitol and sorbitol was unsuccessful from solution or the solid-state. However, sulfathiazole-glucose co-crystals were produced from ethanol and propanol solutions.

[1] Gavan P.T., Blagden N., Seaton C.C., Grimsey, I.M., Marshall, P., *CrystEngComm.* , 2005, *submitted*.
Keywords: cocrystals, weak interactions, pharmaceuticals

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Design and Synthesis of Co-crystals: From Molecular Sense to Supramolecular Sensibility
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What is most likely going to happen when a homogeneous solution containing two different molecular solutes is allowed to evaporate to dryness? Unless a chemical reaction driven by the formation of covalent bonds takes place between the two solutes one would, as a rule, expect the appearance of two separate molecular solids. This is a manifestation of the inherent structural selfishness of molecules, something that is relied upon every time recrystallization is employed as a method of purification. Recrystallization processes are essential in most covalent synthetic procedures and are performed on a regular basis in every synthetic laboratory. In the supramolecular laboratory, however, the very same process also provides an opportunity to move in the opposite direction – a co-crystallization is a deliberate attempt at bringing together different molecular species in one crystalline lattice without making or breaking covalent bonds. Recrystallization and co-crystallization processes are, in essence, only distinguishable by their intents. The goal of the former is a homomeric product, the goal of the latter is a heteromeric product. Since the odds are stacked firmly in favor of a homomeric product, how do we go about developing reliable and versatile synthetic methods for the directed assembly of co-crystals? This presentation will attempt to answer the question by outlining several modular hydrogen-bond driven strategies for the design and synthesis of binary and ternary supermolecules and co-crystals.
Keywords: hydrogen bond, cocrystals, molecu1ar recognition

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Crystal Engineering of Arylammonium Perhalometallates
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The ultimate aim of crystal engineering is the design of crystal structures, and as a result, materials with desired properties. A fundamental requirement of crystal engineering is the understanding of the role of non-covalent interactions occurring in the solid-state structure.

A number of crystal engineering studies have focused on the identification of interaction synthons in compounds of the type LMX_4 where L is the 4,4'-bipyridinium cation [1] or the pyridinium cation [2].

This study focuses on the identification of non-covalent interactions in a family of primary arylammonium perhalometallate organic-inorganic hybrid materials. A number of novel crystal structures, some isostructural, will be reported.

The hydrogen bonding- and aromatic interactions present in these crystal structures will be highlighted, and their influence on the molecular packing illustrated. Crystal engineering synthons will be identified, and compared to synthons identified in related structures.

[1] Gillon A.L., Orpen A.G., Starbuck J., Wang X., Rodriques-Martin Y., Ruiz-Perez C., *Chem. Comm*., 1999, 2287-2288.
[2]Felloni M., Huberstey P., Wilson C., Schroder M., *CrystEngComm*., 2004, **6**, 87-95.
Keywords: non-covalent interactions, organic-inorganic hybrids, crystal engineering

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Towards Electrochemical Artificial Muscles: A Supramolecular Machine Based on One-dimensional Copper-containing Organophosphonate System
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The development of artificial system is a field which is currently being intensively explored. In particular, interest is being focused on transition-metal-containing system. In our laboratory, we have created a new supramolecular machine, exhibited reversible electromechanical actuators based on sheets of water-soluble one-dimensional copper-centred enthylenephosphonate (1DOP-Cu) chains, described for the first time. Like natural muscles, the macroscopic sheet actuators are composed of mats of individual nanofiber bundles joined by mechanical entanglement and pi-pi interaction forces along the crystallographic a-axis. The lithium inserted state, upon electrochemical charge injection into 1DOP-Cu, exhibits a reversible contraction/ stretched process by oxidizing or reducing the copper center to Cu(II) or Cu(I) whose coordinated geometries will be changed at will by a redox process, as characterized by x-ray diffraction patterns, solid state NMR, and XANE spectra.

[1] Gu G., Schmid M., Chiu P. W., Minett A., Fraysse J., Kim G. T., Roth S., Kozlov M., Muñoz E., Baughman R. H., *Nature materials*, 2003, **2**, 316. [2] Fu S. J., Cheng C. Y., Chen W. H., Lin K. J., Kao H. M., *Angew. Chem. Int. Ed*, 2004, **43**, 4186.
Keywords: copper, artificial muscles, supramolecular chemistry

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Molecularly Designed Functional Materials; Can We Really Control their Supramolecularity?
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Supramolecular chemistry can be simply defined as the chemistry of multicomponent molecular assemblies in which the component structural units are typically held together by a variety of weaker (noncovalent) interactions (chemistry beyond molecules). A specific example of such supramolecules is inclusion compounds. Inclusion Compounds are formed by the noncovalent insertion of *guest* molecules into the *host* lattice during the crystallization process.

Supramolecules present great potential industrial applications in separation of isomers, purification of solvents, drug delivery, catalysis, molecular recognition and many other fields. Recently, we have been working on design and synthesis of new host molecules such as V-shape diquinolines and arene derivatives and investigating their self assembly as well as their potential applications. Although the

chemical modifications of the molecular structures are very reliable and accessible, prediction of the supramolecular behavior is not always easy and in some cases can be very complex.

In this paper, examples of these new hosts will be presented as well as their design and synthesis procedures. Furthermore, the crystal structures of some of these new inclusion compounds will be described in detail.

[1] Alshahateet S. F., Bishop R., Scudder M. L., Hu C. Y., Lau E. H. E., Kooli F., Judeh Z. M. A., Chow P. S., *CrystEngComm.* , 2004, *submitted*. [2] Alshahateet S. F., Bishop R., Craig D. C., Scudder M. L., *Cryst. Growth Des*., 2004, **4**(4), 837-844. [3] Bishop R., Scudder M. L., Rahman A. M. M., Alshahateet S. F., Craig D. C., *Molecular Crystals & Liquid Crystals*, 2005, *accepted*.

Keywords: inclusion compounds, host, crystal structure

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Interactions of Supramolecular Synthons Formed by Secondary Propargylic Alcohols

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Chiral secondary propargylic alcohols are used in the enantioselective synthesis of natural products and as synthetic precursors of several optically active compounds. Secondary propargylic alcohols with aryl substituents possess three important functional groups: the hydroxyl group, the π system of the alkyne moiety, and a variety of aryl rings that can be involved in π˜ π stacking as well as other interactions. The combination of the three functional groups attached to one chiral carbon makes secondary propargylic alcohols well suited for applications in supramolecular chemistry and crystal engineering [1-3].

The competition between O-H…O hydrogen bonds and weaker interactions such as C-H…π and π˜ π stacking leads to the formation of a diverse set of synthons, including non-planar hexamers. The cooperativity between intermolecular forces is essential for the stabilization of these synthons.

[1] Desiraju G.R., *Angew. Chem. Int. Ed. Engl.*, 1995, **34**, 2311. [2] Bilton C., Howard J.A.K., Madhavi N.N.L., Nangia A., Desiraju G.R., Allen F.H., Wilson C.C. , *Acta Cryst.*, 2000, **B56**, 1071. [3] Madhavi N.N.L., Desiraju G.R., Bilton C., Howard J.A.K., Allen F.H. , *Acta Cryst*., 2000, **C56**, 1359.

Keywords: supramolecular chemistry, crystal engineering, organic molecule

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Stereochemistry in Crystal Engineering

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Molecular recognition by hydrogen bonding between organic molecules has been explored in supramolecular chemistry to a great extent. [1,2] Most of the recognition motifs are however two-dimensional in nature. By employing organic compounds in the context of supramolecular chemistry and utilizing their chiral attributes the three-dimensional nature of intermolecular hydrogen bonding may be revealed.

This project, to date, has been focused on the design and synthesis of sulfides, sulfoxides and sulfones. Sulfoxides are ideally suited as a recognition motif as they are extremely polar and have the potential to participate in hydrogen bonding. The intrinsic chirality at sulfur introduces the three-dimensional nature of the study. The effect of the oxidation state of sulfur on the hydrogen bonding array is also investigated, along with other substituent effects.

[1] Desiraju G.R., *Angew. Chem. Int. Ed. Engl.*, 1995, **34**, 2311. [2] Weiss H.C., Boese R., Smith H.L., Haley M.M., *Chem. Commun.*, 1997, 2403.

Keywords: hydrogen bonding, chirality, sulfur

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Ringing the Changes with Tetrazole: Hydrogen Bonding Studies

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Tetrazoles are acidic heterocycles and used in angiotensin II receptor antagonists for the treatment of high blood pressure. The binding mode is still controversial [1], as yet the only published crystal structure of a tetrazole-protein complex shows close contacts between two of the tetrazole nitrogen atoms and two lysine residues within the enzyme binding site. [2]

Tetrazoles are used as bioisosteric replacements for carboxylic acids in modern drug design. Transmembrane receptors are notoriously difficult to study, so model systems can provide further insight into non-covalent binding interactions.

This work describes the hydrogen-bonding patterns seen for readily available ionic model complexes, developing earlier studies of hydrogen-bonding tetrazolate anion [3] and illustrate how the tetrazole, or simple derivatives bind to acetamidine (arginine model), propranolol (an antihypertensive drug) and spermine (a natural hormone). These will be compared with analogous carboxylic acid complexes to provide insight into the hydrogen bonding interactions favoured by tetrazoles as well as difference in binding properties.

[1] Noda K., Saad Y., Kinoshita A., Boyle T. P., Graham R. M., Husain A., Karnik. S. S., *J. Biol. Chem*., 1995, **270**, 2284. [2] Goldgur Y., Craigie R., Cohen G. H., Fujiwara T., Yoshinaga T., Fujishita T., Sugimoto H., Endo T., Murai H., Davies D. R., *Proc. Natl. Acad. Sci. USA*, 1999, **96**, 13040. [3] Peters L., Fröhlich R., Boyd A. S. F., Kraft A., *J. Org. Chem*., 2001, **66**, 3291.

Keywords: drug binding, hydrogen bonding, heterocyclic compounds

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Structure of *N,N*-dimethylaminopyridinium *L*-malate

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The crystal structure of a new *L*-malic acid salt, N,N- dimethyl-aminopyridinium *L*-malate has been determined at room temperature using single crystal X-ray diffraction techniques. The space group is orthorhombic $P2_12_12_1$ with lattice parameters a= 7.461(1), b= 7.945(1) and c= 20.774(4)Å. Similarly to other *L*-malic salts, the malate anions form hydrogen-bonded head-to-tail (carboxylic and carboxylate groups) infinite chains parallel to the [100] crystal direction. On the other hand, the dimethylaminopyridinium cations are arranged with their mean plane approximately perpendicular to the [100] crystal direction. The N-H group of every cation forms two hydrogen bonds with oxygen atoms of different anion chains connecting *L*-malate chains along the [010] crystal direction. The whole crystal packing can be viewed as parallel two-dimensional hydrogen-bonded molecular arrangements perpendicular to the [001] direction. As in other *L*-malic salts, preliminary measurements show optical second-harmonic generation.

Keywords: nonlinear optical materials, molecular crystals, crystal engineering

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Complexes of Non-chiral Surfactant Molecules with Chiral and Racemic Compounds

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