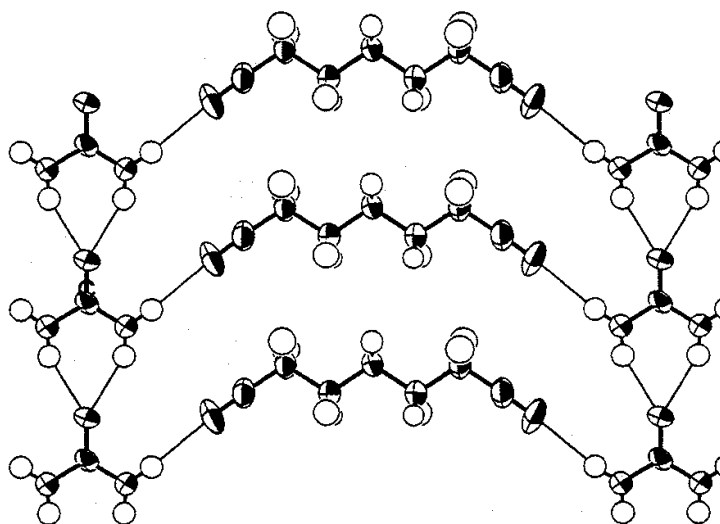
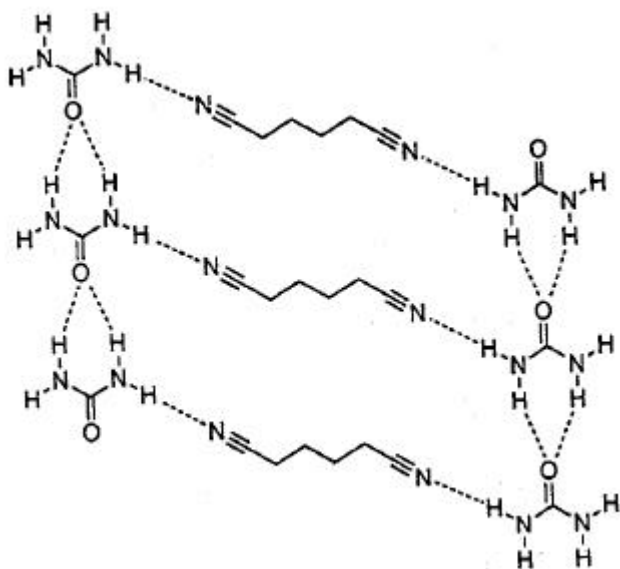


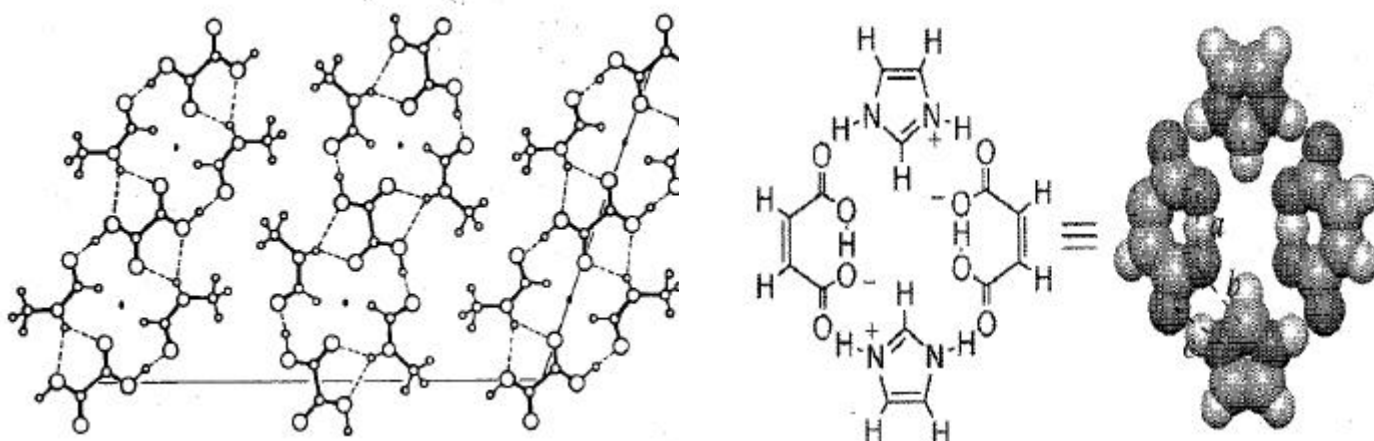
Crystal Engineering: Co-crystals

A Proposal to the ISIS Facility of the Rutherford Appleton Laboratories by
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Co-crystals are used to reveal specific recognition motifs such as those proposed for rational drug design [1] and crystal engineering applications [2]. The ongoing issue in this discussion is the interplay between the recognizable features of hydrogen bonding distances and angles and the less well-defined issue of crystal packing interactions. Strong H-bonds can produce loose structures (ice, urea); close packing may result in deformed H-bonds. Another issue in this area is the extent to which the properties of an individual component of a molecular crystal can be considered as a unit whose properties are unaffected by the presence of the neighbors. Intermolecular interactions may result in observable structural changes but force constants as revealed by vibrational spectra are usually much more sensitive to very small structural changes below the resolution of x-ray methods. These small structural changes may correspond to rather large changes in charge distributions and thus in cohesive energies. A theoretical treatment that correctly describes the structure and dynamics of such a system forms the basis for understanding the cohesive energy.

Co-crystal systems also provide interesting cases for evaluation of methods for simulating the vibrations of solids at both an empirical and ab initio level because they provide opportunity for study of the individual components independent of the co-crystal. Some species such as urea form co-crystals with a variety of other substances and so can be investigated in a variety of environments. Further flexibility is provided by the fact that many components of co-crystal forming substances have both exchangeable hydrogens (usually involved in hydrogen bonds) and non-exchangeable hydrogens which can be replaced by deuterium synthetically. If this is done for both species there results six materials of the type (AH) \cdots H(BH), (AH) \cdots D(BH), (AD) \cdots H(BH), (AH) \cdots H(BD), (AD) \cdots H(BD) and (AD) \cdots D(BD). All of these materials should have spectra that are simultaneously described by the same empirical force field or by an ab initio treatment of a cluster model with interchange of D for H atoms but keeping the same force constants.





Three examples of co-crystals are shown above. These are adducts formed by α,ω -dinitriles and urea [3], the complex of N-methylformamide and oxalic acid [4] and the ionic complex imidazolium hydrogen malate [1]. The first two are examples of a larger class of materials. Reference [4] gives 25 examples. All of these chosen cases form two-dimensional sheets containing all of the inter-molecular hydrogen bonds. Another example is the 1:1 complex of diacetamide with acetamide [5]. The hydrogen bonds are much stronger interactions than van der Waals forces in terms of resistance to deformation and result in much closer dynamical coupling of the units. Our recent work has shown that treatment of clusters in such crystals provides a good description of the INS spectra. In this set of examples the last one contains a closed unit of four components and the N-methylformamide/oxalic acid co-crystal forms a linear chain arrangement with the methyl groups on the edges. These arrangements further simplify computations. The α,ω -dinitrile/urea co-crystals can probably be modelled as in terms of a linear trimer of hydrogen bonded urea units with dinitrile units hydrogen bonded to the central urea. The dynamics of the central unit is then used to calculate the spectrum.

[1] Baures, P., "Heterocyclic HIV-1 Protease Inhibitors", *Organic Letters* 1, 249 (1999).

[2] *Chemistry of Materials*, Volume 6, Number 8. This issue contains many examples.

[3] Hollingsworth, Mark D.; Brown, Michael E.; Santarsiero, Bernard D.; Huffman, John C.; Goss, Christopher R. Template-Directed Synthesis of 1:1 Layered Complexes of α,ω -Dinitriles and Urea: Packing Efficiency versus Specific Functional Group Interactions. *Chem. Mater.* (1994), 6, 1227.

[4] Leiserowitz, L.; Nader, F. The molecular packing modes and the hydrogen-bonding properties of amide:dicarboxylic acid complexes. *Acta Crystallogr. Sect. B* (1977), B33(9), 2719.

[5] Matias, Pedro M.; Jeffrey, G. A.; Ruble, John R.. Structures of the E,Z-(cis-trans) isomer of diacetamide and the 1:1 complex with acetamide at 123 K: ab-initio molecular orbital calculations on the Z,Z (trans-trans), E,Z (cis-trans) and E,E (cis-cis) isomers of diacetamide. *Acta Crystallogr. Sect. B: Struct. Sci.* (1988), B44, 516.