predefined reference patterns is fitted to the measured pattern using a least squares calculation. Because the full diffraction pattern is used for quantification this method is less sensitive to peak overlap. The method can be used to differentiate between crystalline forms and to estimate the crystallinity of a sample that is mainly amorphous. We present the application of a full-pattern quantitative method for the analysis of Saquinavir free base.

Saquinavir is a protease inhibitor that prevents the proliferation of the human immunodeficiency virus (HIV). The worldwide first HIV protease drug contains crystalline Saquinavir mesylate (INVIRASE). Later amorphous Saquinavir free base was developed in order to improve bioavailability (FORTOVASE). Using X-ray powder diffraction the (pseudo)polymorphic forms of Saquinavir free base are distinguishable. To assure optimum performance of the active pharmaceutical ingredient analytical methods have been developed to prove the content of crystalline components.

Keywords: pharmaceuticals, polymorphism, quantification

P.08.11.4

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Effect on Additive Structure on Crystal Nucleation: Sulfathiazole

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Crystal nucleation events are notoriously susceptible to influence by extraneous molecular specie. Researchers Blagden, Davey *et al* have shown that in the presence of small quantities of the *N*-acetyl precursor to sulfathiazole selective nucleation of the metastable polymorph sulfathiazole can be achieved [1]. It was proposed that the difference in the hydrogen bonding at the sulfathiazole aniline moiety which particularly distinguishes form I from the other three polymorphs. In form I, only one of the aniline hydrogens is utilised while in forms II, III and IV both are used. It was proposed that the *N*-acetyl derivative is capable of entering the interwoven hydrogen bonded chain network without disrupting the structure, while incorporation into crystal nuclei of forms II, III and IV prevents further development of the hydrogen bonding network of these forms.

A feature of the above hypothesis worth further examination is the toleration of the replacement of an amine proton with the considerably more sterically demanding acetyl group. We have investigated the effect of various sulfathiazole *N*-substituents, in particular the effect of groups which are less (e.g. *N*-formyl,) or more (e.g. *N*-pivaloyl,) sterically demanding than N-acetyl. Additives of 'polymeric' design with the potential for increased efficacy have also been investigated, where design of the additives is based on consideration of the crystal structures of the polymorphs under study.

[1] Blagden N., Davey. J., Rowe R., Roberts R., *Int. J. Pharm.*, 1998 **172**, 169-177.

Keywords: polymorphism, crystallization, crystal nucleation

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Polymorphism Dependent Crystalline Photochromism of Salicylideneanilines

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Some salicylideneanilines show crystalline-state photochromism. The reversible color change from yellow to red upon irradiation by UV light is the result of the photo-isomerization from the enol to the *trans*-keto form, which is explained as an intra-molecular proton transfer followed by a crank-shaft-motion type conformational change. The red-colored crystal fades to yellow by a thermal process.

The salicylideneaniline derivative *N*-3,5-di-tert-butylsalicylidene-3-carboxyaniline has three polymorphs: the α phase (pale yellow needle), the β phase (yellow plate), and the γ phase (orange block). Only the α and β forms are photochromic, whereas the γ form is thermochromic. X-ray crystal structure analyses of these three forms revealed the significant differences in dihedral angles in these molecules. The large dihedral angle in the α and β forms makes the enol conformation (yellow) unstable, which explains why the yellow to red photochromic reaction occurs easily.

In order to investigate the large difference in the lifetime of the red *trans*-keto conformation in the α (17min.) and β forms (780min.), the crystal structure of the irradiated (red-colored) crystal was analyzed. Newly established inter-molecular hydrogen bonds were observed in this red-colored β form but not in the red-colored α form. This result indicates that the inter-molecular hydrogen bond is stabilizing the red *trans*-keto conformation and preventing it from converting to the yellow enol conformation.

Keywords: polymorphism, photochromism, hydrogen bonding

P.08.13.1

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The Nature of the HB. 1. HB Empirical Rules from Crystal Structure Correlations

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HB is a D•–•H---:A three-centre-four-electron proton-shared interaction characterized by an extreme variability of HB properties (energy, geometry, shape of the proton-transfer pathway, electrostatic/ covalent nature) even for a same D…A couple of donor and acceptor atoms. Not surprisingly, its complete rationalization has turned out to be a formidable problem. This communication shows that the partial results obtained by systematic CSD screening over the years can now be unified to give a coherent interpretation of all factors determining HB strength in any molecular system. It is shown that all HBs can be reduced to only six specific molecular patterns, the six Chemical Leitmotifs (CL), out of which *four* have the curious property of turning *weak, long and proton-out-centred HBs of electrostatic nature* into *strong, short and proton-centred ones classifiable as 3-center-4-electron covalent bonds*, and *the last two* are deputed to form the moderately strong σ-cooperative …O-H…O-H…O-H… bonds typical of water or the almost infinite variety of weak HBs.

CLs are interpreted in terms of differences of proton affinities (PA) or acid-base dissociation constants (pK_a) of the HB donor and acceptor group, showing that all HB phenomenology can be reduced to a more basic "PA/pK_a Equalization Principle" stating that the HB properties are completely determined by the differences of these quantities (PA or pK_a) and that the strongest possible HB can only be associated with the conditions ΔPA or ΔpK_a = 0.

Keywords: hydrogen bond, PA/pKa equalization, chemical leitmotifs

P.08.13.2

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The Nature of the HB. 2. Predicting HB Strength by the pKa Slide Rule

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All HBs between neutral molecules are to be considered acid-base equilibria, R-D-H---:A-R ⇔ R-D$^-$---H-A$^+$-R, and their strength is determined by the difference ΔpK_a = pK_{AH}(R-D-H) – pK_{BH}(R-A-H$^+$), the HB becoming the stronger the smaller ΔpK_a is. In fact, the limit ΔpK_a = 0 corresponds to the condition by which the proton is equally shared by the two groups so that the HB is transformed from a weak electrostatic interaction into a strong proton-centred 3-centre-4-electron R-D$^{1/2-}$---H---$^{1/2+}$A-R covalent bond. The *a priori* appraisal of ΔpK_a is therefore a promising method for predicting HB strengths among organic compounds provided the pK_a values of the interacting molecules are known. This communication presents for the first time detailed lists of pK_{AH} and pK_{BH} values covering most classes of organic compounds and arranges them in an unique chart, called the *pK_a slide rule*, that makes it possible to predict the approximate strength of the HBs formed by any couple of organic HB donors and acceptors by simple inspection. Previsions obtained through the *pK_a slide rule* are compared with the results of diffraction experiments through an extensive search of all reasonably accurate R-O-H---:NR$_3$ ⇔ R-O$^-$---H-N$^+$R$_3$ HBs present in the CSD and subdivided in

chemical groups (10 of donors and 14 of acceptors). It is shown that many HBs are *intrinsically weak* because of impossible pK_{AH}/pK_{BH} matching and that strong HBs can be obtained only by combining donor and acceptor molecules for which the $\Delta pK_a \approx 0$ condition is actually accessible.

Keywords: hydrogen bond, PA/pKa equalization, pKa slide rule

P.08.13.3

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Proton Migration in Hydrogen Bonded Donor-Acceptor Complexes

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Intermolecular hydrogen bonding plays an important role in forming anisotropic interactions in condensed systems, and subtle competition between H-bond acceptors/donors can lead to dramatically different solid-state structures. There is significant national and international research effort directed at the study of hydrogen bonding in the solid state. Much of this work has focussed on the *static* structures adopted by molecular hydrogen-bonded systems, but the importance of hydrogen atom migration through hydrogen bonds between molecules has also been identified. It is becoming increasingly apparent that the positions of the protons involved in hydrogen bonds are highly susceptible not only to chemical environment, but also to the effects of temperature and pressure.

A collaborative project has been set up with the aim of preparing molecular adducts in which a proton migrates between the donor and acceptor species as temperature and/or pressure is varied. In this poster we will describe our experimental techniques [1] and present results for some of our variable temperature studies of the 1:1 salt formed between 2-iodoaniline and picric acid [2].

[1] Parkin A., Harte S.M., Goeta A.E., Wilson C.C., *New J. Chem*., 2004. [2] Tanaka M., Matsui H., Mizoguchi J., Kashino S., *Bull. Chem. Soc. Jpn*, 1994, **67**, 1572-1579.

Keywords: hydrogen bond, intermolecular interactions, variable temperature

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Multi-temperature Neutron & X-ray Studies of Hydrogen Bonded Molecular Complexes

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X-ray single crystal diffraction is a commonly used technique in many structural chemistry laboratories to find the structure of large and small molecules. However, neutron diffraction, although less readily accessible, is more sensitive to the determination of detailed hydrogen atom parameters, and this is of particular importance in hydrogen-bonded systems. By application of a multi-temperature approach to both these techniques, it is possible to study in detail the temperature-dependent behaviour of the hydrogen atoms within these hydrogen bonds. Features such as proton disorder and migration can be frequently observed.

Both X-ray and neutron multi-temperature single-crystal data has been collected on the molecular complex of isonicotinamidium formate. Neutron data were collected at four temperatures (40K, 100K, 150K, 200K) on the SXD instrument at ISIS, and X-ray data were collected on a laboratory diffractometer at 50K intervals from 100K-300K.

We will present the initial analysis of the neutron data, including some discussion of the inherent difficulties in processing such datasets and some of the early use in the chemical crystallography area of the new SXD2001 software developed for the instrument, which we are helping to test. We will also present how these initial neutron results compare with the X-ray data.

Keywords: neutron crystallography, hydrogen bonds, variable temperature

P.08.13.5

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Proton Sponges of 1,2-bis(di-*R*-aminomethyl)benzene Type

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The pK_a values for 1,2-bis(di-*R*-aminomethyl)benzenes (DRAMB) are much higher than for DMAN, 1,8-bis(dimethylamino)naphthalene, the classic proton sponge. On protonation a strong intramolecular N-H···N H bond is formed. The molecule of DRAMB can adopt four idealized conformations with the following symmetries: (i) C_{2v}, (ii) C_2, (iii) C_s-mirror plane in the benzene ring, (iv) C_s-mirror plane normal to the benzene ring. The C_{2v} symmetry is achieved by symmetric disposition of the alkyl groups above and below the benzene ring with the N atoms exactly in the ring plane, and with the lone pairs oriented away from or towards the aromatic ring. In both conformations, the monoprotonated $DRAMBH^+$ cation cannot form an intramolecular N···H···N bond. Conformation (ii) is characterized by location of the N atoms on the opposite sides of the benzene ring. Formation of a twofold-symmetric intramolecular N···H···N bonds is possible but the proximity of the N atoms in short bridges causes large steric effects even in simple system, such as DMAMB (M=CH_3). Form (iii) is compatible with intermolecular N-H···X hydrogen bonds. Form (iv), with the N atoms on one side of the aromatic system, is optimal for minimization of steric hindrance and for the formation of a short intramolecular H bond. A $DMAMBH^+$ cation with exact C_s-symmetry (iv) is observed in the ClO_4^- salt. Pseudo C_s cations are found in the crystals of $DMAMBH^+{\cdot}NO_3^-$ and $DEAMBH^+{\cdot}ClO_4^-$ (E=ethyl). For bulkier substituents (*R*=propyl, butyl) the symmetry of the bis(aminomethyl)benzene moiety is closer to C_s.

Keywords: proton sponges, N-H···N hydrogen bond, conformation

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Ordering of Hydrogen Bonds in High-pressure Low-temperature Ices

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We have studied the near *K*-edge structure of oxygen in liquid water and ices III, II, and IX at 0.25 GPa and several low temperatures down to 4 K using inelastic x-ray scattering at 9884.7 eV with a total energy resolution of 305 and 175 meV [1]. It is found that the ordering of the oxygen network from the liquid phase to ice III causes only a small decrease of the preedge intensity, whereas the ordering of the hydrogen bonds in the proton-ordered lattice of ices II and IX dramatically reduces the preedge intensity, which is interpreted as a result of the diminishing number of uncoordinated hydrogen bonds in ices II and IX. Some preedge intensity remains, however, in the latter phases unexpectedly according to previous first principles calculations [2]. Our density functional theory calculations of the near-edge X-ray absorption spectrum for ice IX indicate that the remaining intensity may be due to the influence of the local electronic structure by the Madelung potential of the crystal lattice. Substantial changes of the near *K*-edge spectra from ice IX have also been observed below 50 K.

[1] Cai Y.Q., et al., *Phys. Rev. Lett.*, 2005, **94**, 025502. [2] Myneni S., et al., *J. Phys. : Condens. Matter*, 2002, **15**, L213.

Keywords: hydrogen bonds, electronic structure, X-ray inelastic scattering