lytic-like protease. In contrast, the high-resolution crystal structures of another prokaryote serpin, tengpin, reveals that the serpin domain of this molecule folds spontaneously and rapidly to most stable (i.e. relaxed) conformation. This is an exciting result, since tengpin represents the first serpin identified to date that obeys Anfinsen's conjecture. Furthermore, the X-ray crystal structures of tengpin reveals the structural basis for a novel mechanism for loop-C-sheet serpin-polymerisation. Analysis of the structural data provides striking insight into the mechanism of serpin metastability and the structural basis for serpin polymerisation.

[1] a) Irving J.A., et al., *Structure 2003*; b) Fulton K.F., et al., *J Biol Chem*, 2005.

Keywords: serpin, folding, polymerisation

MS03 CHIRAL AND NON-CENTROSYMMETRIC STRUCTURES

Chairpersons: Shiv P. Halasyamani, Reiko Kuroda

MS03.24.1

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Spontaneous Resolutions in Halogen Bonded Fluorinated Networks

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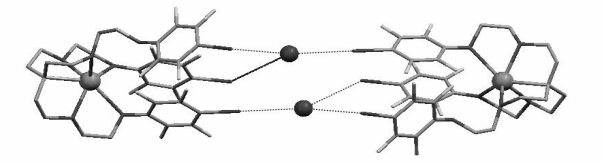
Halogen bonding is an efficient tool for self-assembling halo-perfluorocarbons (PFC) and hydrocarbons (HC) [1]. Its particular ability to control spontaneous resolution in hybrid PFC-HC systems has been discovered only recently [2]. Up to now we observed spontaneous resolutions in four cases affording chiral cocrystals, space group $P2_12_12_1$. Three of them involved long-chain iodo-PFC's (C_8-C_{10}) with either QUATS or *N,N,N',N'*-tetramethyl-*p*-phenylendiamine as bases. Their different features with regard to the segregation behaviour and the conformation of the PFC chains will be outlined. The X-ray structure of a chiral alkali halide complex **1** (Figure) involving a tripodand will also be presented.



1

[1] Metrangolo P., Neukirch H., Pilati T., Resnati G., *Acc. Chem. Res.*, 2005, *in press.* [2] Neukirch H., Guido E., Liantonio R., Metrangolo P., Pilati T., Resnati G., *Chemm. Commun.*, 2005, 1534.

Keywords: halogen bonding, chiral resolution, molecular cocrystals

MS03.24.2

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Invariom Modeling for Improving Absolute Structure Determination

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A reliable determination of the Flack parameter [1] for structures of organic molecules, containing only the elements H, C, N, and O usually fails. The reason for this is the very weak anomalous signal obtained from the light atoms [2]. Recently we have introduced invariom [3] and here we try to improve the absolute structure determination by replacing the independent atom model with the aspherical invariom scattering model. The determination of the Flack parameter was included in the program XDLSM [4]. Alternatively, its calculation has been attempted via a hole-in-one procedure. A precise data set on a steroid compound was collected using copper radiation and CCD detection, and first results are reported.

[1] Flack H. D., *Acta Cryst*., 1983, **A39**, 876. [2] Flack H. D., Bernardinelli G., *J. Appl. Cryst.*, 2000, **33**, 1143. [3] Dittrich B., Koritsanszky T., Luger P., *Angew. Chem. Int. Ed.*,2004, **43**, 2718. [4] Koritsanszky T., Richter T., Macci P., Gatti C., Howard S., Mallinson P.R., Farrugia L., Su Z.W., Hansen N.K., *XD*, Freie Universitat Berlin, Berlin, 2003.

Keywords: Invarioms, Flack parameter refinement, chiral structures

MS03.24.3

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Optical Topographies of Chiral Structures

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Can optical rotatory power, a phenomenon typically associated with chirality or handedness, be used as a contrast mechanism in microscopy? Chiroptical imaging techniques have not heretofore been implemented. This neglect has created a hole in the science of molecular chirality, particularly with respect to complex, heterogeneous, organized media. We built a circular extinction imaging microscope to examine chromophores in anisotropic hosts. With this instrument, images of crystals were made via two mechanisms, intrinsic circular dichroism (CD) and a new effect that was discovered and called anomalous circular extinction (ACE). Through these new chirality "spectacles" we have observed left and right handed twinning in crystals of a dye that was masked by all previous methods of analysis, Figure 1 [1]. However, when turned onto unusual dyed crystals, we observed optical effects that mimic those due to chirality.

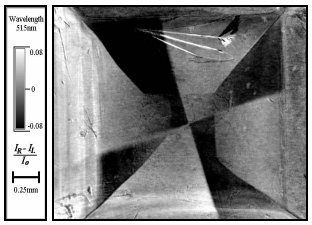

Figure 1. Circular Dichroism in 1-8-Dihydroxyanthraquinone.

[1] Claborn K., Puklin-Faucher E., Kurimoto M., Kaminsky W., Kahr B., *J. Am. Chem. Soc.*, 2003, **125**, 14825-14831.

Keywords: chirooptical properties, circular dichroism measurement, dyes

MS03.24.4

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Nonlinear Optical Properties of Chiral Polymers and Systems

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We present the nonlinear optical properties of different thin film films of chiral (conjugated) polymers. These systems exhibit large magnetic dipole nonlinearities, in some cases larger than the effects linked to electric dipole interactions. The nonlinear optical effects observed indicate the links between magnetic hypersusceptibilities and chirality. We also investigated supramolecular assemblies of helicenes where the nonlinear optical effects are exclusively described by electric dipole interactions. In the crystalline liquid state the chirality, as expressed by nonlinear CD effects, of these helicene assemblies could be switched by the application of an electric field.

Keywords: polymers, chirality, nonlinear optics

MS03.24.5

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Some Reminiscences of Non-centrosymmetric Structures

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In the "neanderthal" age of crystallography, a light atom non-centrosymmetric crystal was usually relegated to the skeleton collection of unsolvable structures. The development of MULTAN

and its increasingly sophisticated successors has made consideration of centrosymmetricity essentially a non-issue in structure solution and refinement.

Nevertheless, the question of the relationship between molecular symmetry and crystallographic symmetry remains one of considerable importance, especially with regard to crystal engineering and the interest in engineering non-centrosymmetric crystals, for instance for the generation crystals exhibiting non-linear optical effects.

Kitaigorodskii [1] claimed that centrosymmetric molecules essentially universally crystallize in centrosymmetric space groups. However, many molecules lacking a center of symmetry also tend to crystallize in centrosymmetric space groups, e.g. $P2_1/c$, P1-bar, C2/c, etc. While chiral molecules must crystallize in chiral space groups, it is not clear why some achiral molecules also do so. In the case of polymorphic systems some members may be centrosymmetric and others non-centrosymmetric, providing clues as to how one might achieve a desired either one of the situations.

This presentation will include a number of examples from our own work, in addition to some possible strategies for the generation of centrosymmetric or non-centrosymmetric structures.

[1] Kitaigorodskii A.I., *Organic Chemical Crystallography*, Consultants Bureau, New York, 1961.

Keywords: polymorphism, polar crystal, crystallization conditions

MS04 POLYMORPHISM

Chairpersons: Shiv P. Halasyamani, Reiko Kuroda

MS04.24.1

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Modifying Nucleation Kinetics of Polymorphic Crystals in Bulk and Emulsion States

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This paper discusses thermodynamic and kinetic influences on nucleation processes of polymorphic crystalline systems in bulk and emulsion states in comparative ways. Three main characteristics may be revealed in the crystallization processes in emulsion droplets: (1) reduction in nucleation rate caused by thermodynamic and kinetic effects, (2) interfacial crystallization caused by molecular interactions between interfacial membrane and the solute molecules, and (3) droplet-droplet interactions of two kinds; dilution of solute/solvent molecules which are slightly soluble in the continuous phase, and partial coalescence of the particles after crystallization. Based on recent experimental work of melt crystallization of long-chain lipophilic materials in oil-in-water emulsion droplets, we discuss the polymorphic crystallization behavior related to the reduction in nucleation rate and the interfacial crystallization.

Keywords: polymorphism, nucleation kinetics, emulsion

MS04.24.2

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Controlling Crystal Polymorphism: from Stability Prediction to Crystallization Process Design

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Investigations of crystal polymorphism are usually conducted early in drug development to optimize the physical properties of a pharmaceutical solid. Although the thermodynamically most stable crystal form is generally selected for a drug product, controlling polymorph appearance must be accomplished through careful evaluation of both thermodynamic (tendency toward the formation of more stable polymorphs) and kinetic parameters (which lead to the formation of metastable polymorphs) in the crystallization process. The first step in designing a crystallization process should be to evaluate the thermodynamic stability relationship(s) (monotropy or enantiotropy), i.e., free energy differences (ΔG), between the polymorphs as a function of temperature. A number of tools (including, but not limited to, DSC analysis of pure and eutectic melting, solubility, intrinsic dissolution, solution calorimetry and slurry bridging) can be used collectively to assess ΔG over a wide range of temperatures. While qualitative approaches, which yield the sign of ΔG only, are useful for assessing the risk of unwanted phase transformations, quantitative studies allow for the thermodynamic transition temperature of enantiotropic polymorph pairs and differences in important physical properties (solubility, intrinsic dissolution rate) to be predicted. A number of factors, including structural similarities between crystal polymorphs, comparable thermodynamic stability, ease of crystal nucleation, and overlap of occurrence domains (metastable zones), have been shown to contribute to poor polymorph selectivity during crystallization. All of these factors must be considered in implementing strategies to control polymorph appearance.

Keywords: polymorph, crystallization, stability

MS04.24.3

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Crystal Structure Prediction: Theory, Applications and Challenges

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Although crystal structure prediction from first principles is now less controversial and more mainstream than when the first applications were reported in the early 1990's, it is debatable whether it is possible to reliably predict the observable polymorphs of simple organic molecules.

In this contribution, the theory of crystal structure prediction will be reviewed and illustrated with recent application examples (e.g., [1, 2]), including the three so-called 'blind tests' organised by the Cambridge Crystallographic Data Centre [3].

Despite significant progress since the early 1990's, many challenges still remain, such as the treatment of flexible molecules and the accurate description of polymorphic stability [4]. Related areas of research that merit particular attention are the simulation of crystal nucleation and the consideration of kinetics in crystal growth simulations [5]. The latest research aims to address the fundamental question why certain polymorphs crystallise and grow, whereas other structures, which are predicted to be thermodynamically stable, cannot be obtained experimentally.

[1] Leusen F.J.J., *Crystal Growth & Design*, 2003, **3**, 189–192. [2] Price S.L., *Advanced Drug Delivery Reviews*, 2004, **56**, 301–319. [3] Motherwell W.D.S., et al., *Acta Crystallographica B*, 2002, **58**, 64 –661. [4] Brodersen S., Wilke S., Leusen F.J.J., Engel G.E., *Physical Chemistry Chemical Physics*, 2003, **5**, 4923–4931. [5] Bennema P., et al., *Crystal Growth & Design*, 2004, **4**, 905-913.

Keywords: polymorphism, crystal modelling, molecular mechanics

MS04.24.4

Acta Cryst. (2005). A**61**, C12-C13

Polymorphism in Co-Crystals and Pharmaceutical Co-Crystals

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Pharmaceuticals are perhaps the most valuable materials known to mankind and there are important intellectual property, regulatory and efficacy implications if one is able to discover new compositions of matter for active pharmaceutical ingredients (API's). Emphasis will be placed on pharmaceutical co-crystals,[1] a long known but little explored alternative to the three accepted forms of API (polymorphs, solvates, salts).

The presentation will detail how one can exploit the principles of crystal engineering to design and generate novel pharmaceutical co-crystal phases that contain one or more API's. Examples to be presented will include well-known API's such as aspirin, ibuprofen, carbamazepine and piracetam. CSD surveys and structural and physical studies on new co-crystals will be presented in order to address the relative stability of pharmaceutical co-crystal phases with