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

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

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

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

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

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

Crystal Structure Prediction: Theory, Applications and Challenges

Frank J. J. Leusen, *Institute of Pharmaceutical Innovation, University of Bradford, BD7 1DP, United Kingdom.* E-mail: f.j.j.leusen@bradford.ac.uk

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

emphasis upon their reduced tendency to exhibit polymorphism.

[1] Almarsson Ö., Zaworotko M.J., *Chem. Commun*., 2004, 1889-1896.
Keywords: solid-state chemistry, crystal engineering, co-crystals

MS04.24.5
Acta Cryst. (2005). A**61**, C13
An Exploration of Polymorphism in Molecular Crystals Using High Pressure
Colin R. Pulham[a], Francesca P.A. Fabbiani[a], David R. Allan[a], Alistair J. Davidson[a], W.G. Marshall[b], Simon Parsons[a], [a]*School of Chemistry and Centre for Science at Extreme Conditions, The University of Edinburgh, Scotland, UK.* [b]*ISIS Neutron Facility, Rutherford Appleton Laboratory, UK.* E-mail: C.R.Pulham@ed.ac.uk

The application of high pressure to simple molecular compounds is proving to be a powerful method for exploring the polymorphic behaviour of these compounds [1]. Direct compression of either single crystals or powders, and crystal growth from the melt are two methods that have been used to prepare new polymorphs of compounds that have been structurally characterised by X-ray and neutron diffraction. Recent examples include sulfuric acid monohydrate, thiourea dioxide, and acetamide. The development of methods for *in situ* high-pressure growth of single crystals from solution has allowed a much wider range of compounds to be studied including pharmaceuticals (e.g. paracetamol, piracetam), and has enabled us to prepare new solvates [2]. We have also demonstrated how metastable polymorphs and solvates can be prepared under pressure with subsequent recovery of bulk quantities at ambient pressure, and how pressure can be used to screen compounds for polymorphism and solvate formation.

[1] Fabbiani F. P. A., Allan D. R., Dawson A., David W. I. F., McGregor P. A., Oswald I. D. H., Parsons S., Pulham C. R., *Chem. Commun*, 2003, 3004. [2] Fabbiani F. P. A., Allan D. R., David W.I.F., Moggach S.A., Parsons S., Pulham C. R.,*CrystEngComm*, 2004, **6**, 504.
Keywords: pharmaceuticals, high pressure, polymorphs

MS05 STRUCTURAL PHASE TRANSITIONS

Chairpersons: Juan Manuel Perez-Mato, Ulrich Bismayer

MS05.24.1
Acta Cryst. (2005). A**61**, C13
Structural Transitions in Perovskites: Successes of a Group Theoretical Approach
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The author has made extensive use of group theory, as implemented in computer program ISOTROPY (http://physics1.byu.edu/~stokesh//isotropy.html), to underpin the study of structural variation and structural phase transitions in perovskites. A review of the work appears in the literature [1].

The approach will be illustrated for the double perovskites, $A_2BB'X_6$, where alternation of *B*-site cations is coupled with the ubiquitous BX_6 octahedral tilting. The symmetries of the cation ordering, in-phase and out-of-phase tilting are identified, respectively, with irreducible representation R_1^+, M_3^+, R_4^+ of the parent space group $Pm\bar{3}m$. Program ISOTROPY is used to enumerate the structures and possible phase transitions [1]. The results have guided recent structure determinations of Sr_2YNbO_6 and Sr_2YTaO_6 [2], as well as detailed studies of temperature-induced transitions in $BaBiO_3$ and Ba_2BiSbO_6.

In another development [3], we used ISOTROPY to assist in constructing the free energy expansion for a combination of Jahn-Teller distortion (Γ_3^+)and octahedral tilting (R_4^+) in $PrAlO_3$. We proposed a mechanism for the coupling of J-T distortion to the octahedral tilting via a common tetragonal strain - such a mechanism can account for the three phase transitions observed.

[1] Howard C.J., Stokes H.T., *Acta Cryst.*, 2005, A**61**, 93. [2] Howard C.J., Barnes P.W., Kennedy B.J., Woodward P.M., *Acta Cryst.* B, submitted. [3] Carpenter M.A., Howard C.J., Kennedy B.J., Knight K.S., *Phys. Rev. B*, submitted.
Keywords: group theory, phase transitions, perovskites

MS05.24.2
Acta Cryst. (2005). A**61**, C13
Phase Transitions in Relaxor Ferroelectric Based Solid Solutions
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The phase diagrams of solid solutions of lead based complex perovskite relaxors with $PbTiO_3$ contain a morphotropic phase boundary (MPB) similar to that observed in the well known $Pb(Zr_xTi_{1-x})O_3$ (PZT) ceramics. This talk focuses on our recent work on the structural changes as a function of composition and temperature in one such system i.e., $(1-x)Pb(Mg_{1/3}\ Nb_{2/3})O_3$-x $PbTiO_3$ (PMN-xPT). Our results show [1, 2] that unlike the PZT system, the MPB composition range ($0.26<x<0.35$) in the PMN-xPT contains two monoclinic phase regions with Cm and Pm space groups, giving rise to two peaks in the variation of the physical properties with composition. Temperature dependent dielectric, piezoelectric resonance frequency, polarization and powder diffraction studies reveal several other interesting features: (i) relaxor nature of the transitions from the rhombohedral and the two monoclinic phases to the cubic phase, (ii) non-relaxor nature of the tetragonal to cubic transition, (iii) a transition from the tetragonal to the monoclinic Pm phase below room temperature, (iv) the monoclinic to cubic transition via an intermediate tetragonal phase above room temperature and (v) elastic instability associated with transitions between two ferroelectric phases. The role of polarization rotation and elastic matching at various phase boundaries will be discussed in relation to the high piezoelectric response of PMN-xPT in the MPB regions.

[1] Singh A.K., Pandey D., *Phys. Rev. B*, 2003, **67**, 064102. [2] Singh A.K., Pandey D., Zaharko O., *Phys. Rev. B*, 2003, **68**, 172103.
Keywords: relaxor ferroelectrics, monoclinic phases of PMN-xPT, MPB

MS05.24.3
Acta Cryst. (2005). A**61**, C13
The Phase Diagram of $Ca_{2-x}Sr_xRuO_4$: Crystal Structure and Physical Properties
Markus Braden[1], Oliver Friedt[1,2], Olaf Schumann[1], Joerg Baier[1], Paul Steffens[1], Markus Kriener[1], Thomas Lorenz[1], Francoise Bouree[2], Gilles Andre[2], Arsene Gukasov[2], Paolo G. Radaelli[3], Satoru Nakatsuji[4], Yoshiteru Maeno[4], [1]*II. Physikalisches Institut, Universität zu Köln, Zülpicher Str. 77, 50937 Köln, Germany.* [2]*Laboratoire Leon Brillouin, CE-Saclay, Gif-sur-Yvette, Cedex.* [3] *ISIS Facility, Chilton, Didcot, Oxon OX11 0QX.* [4]*Department of Physics, Kyoto University, Kyoto 606-8502.* E-mail: braden@ph2.uni-koeln.de

The phase-diagram of $Ca_{2-x}Sr_xRuO_4$ has been studied by several diffraction techniques and by analysis of thermodynamic properties as function of concentration, temperature, pressure and magnetic field. The substitution of Sr through the smaller Ca induces a series of structural phase transitions with a strong impact on the physical properties. The spin triplet superconductor Sr_2RuO_4 exhibits an undistorted crystal structure, and the Mott-insulator Ca_2RuO_4 shows strong structural distortions characterized by tilting, rotating and flattening of the RuO_6-octahedra. For intermediate structural distortions samples stay metallic but with outstanding physical properties. Throughout the phase diagram we find a close coupling between the crystal structure on one side and magnetic and electronic behavior on the other side.

[1] Braden M., et al., *Phys. Rev. B*, 1998, **58**, 847. [2] Friedt O., et al., *Phys. Rev. B*, 2001, **63**, 174432. [3] Kriener M., et al., *cond-mat*/0408015, [4] Steffens P., et al., *cond-mat*/0502332.
Keywords: ruthenium oxide compounds, crystal lattice distortion, neutron diffraction