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A mayor obstacle for the prediction of the crystal structures of organic molecules is the discrepancy between the small size of typical lattice energy differences and the limited accuracy of force fields or pure density functional theory (DFT) calculations. We present a hybrid method for the calculation of accurate lattice energy differences that combines DFT calculations using the VASP program with empirical Van der Waals (VdW) potentials.

The key to success is the careful adjustment of the empirical potentials, in particular in the region of intermediate interatomic distances, where both the DFT component and the VdW component yield a significant contribution to the total interaction energy. We have fitted the empirical parameters for H, B, C, N, O, S, F, Cl and Br to molecular C_6 coefficients and to the unit cells of low temperature crystal structures. The unit cell volumes and the cell lengths are typically reproduced to within 1%.

Energy ranking studies have been conducted for a variety of molecules, including acetylene, ethylene, ethane, methane, acetic acid, urea, paracetamol and several molecules from the first two CCDC blind tests on polymorph prediction. The experimental low temperature crystal structures are generally found as the most stable predicted crystal structures. In several cases, the most stable packing motif is expressed in more than one space group, giving rise to tiny energy differences of less than 1kcal/mol per molecule.

Keywords: polymorphs, lattice energy, modeling

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Exploring Polymorphism: the Case of Benzene

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Crystal structure prediction is one of the most challenging problems in theoretical chemistry. The standard approaches focus on the minimization at T=0 of lattice energies. Here instead we concentrate on the finite temperature, finite pressure Gibbs free energy, thus fully accounting for entropic effects. This is achieved by combining the Parrinello-Rahman variable cell approach with metadynamics[1], a novel powerful sampling method. We apply this scheme to an old and difficult problem, the prediction of benzene polymorphs[2]. Only the knowledge of the molecular structure and a reasonable intermolecular potential are necessary. We find seven stable crystalline structures of benzene. Comparison with the experimental data shows an unambiguous correspondence between our structures and those revealed by Raman spectroscopy and X-ray diffraction, so that for the first time the benzene phase diagram appears to be completely accessible. These results demonstrate that metadynamics is a powerful tool that shows definite promise for solving the problems of crystal structure prediction or search for polymorphs and suggest that the smoothness of the free energy surface, as compared to the enthalpy surface, may facilitate the task even when using extremely accurate force fields.

[1] Laio A., Parrinello M., *PNAS*, 2002, **99**, 12562-12566. [2] Raiteri P., Martoňák R., Parrinello M., *Angew. Chem. Int.Ed.*, *in press.*

Keywords: molecular dynamics, free energy, crystal structure prediction

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Progress in Crystal Structure Prediction for Diastereomeric Salts

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The development of a methodology that will allow the prediction of the structure and relative stability of diastereomeric salt pairs could have an immense impact in the manufacture of chemical entities in optically pure form as it will assist the design of separation processes based on diastereomeric resolution. The solubility differences of the diastereomeric pair is an important determinant for the resolution efficiency of the resolving agent and can be estimated *via* lattice (free) energy calculations.

This paper develops an approach to the crystal structure prediction of such systems based on global lattice energy optimisation. To alleviate the mathematical complexity of the solution space due to the presence of two entities in the asymmetric unit, the search is guided by a statistical analysis of the Cambridge Structural Database for common coordination environments. A distributed multipole model for the dominant electrostatic interactions and high level *ab initio* calculations for the intramolecular contributions allow the quantitative calculation of the relative stabilities of the p- and n-salt for a given resolving agent.

The methodology is successfully applied in the case of 1-phenylethylammonimum-2-phenylpropanoate. All experimentally determined known forms and their relative stabilities are predicted.

Keywords: diastereomeric, resolution, prediction

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Inorganic Structure Prediction with GRINSP

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The computer program GRINSP (Geometrically Restrained INorganic Structure Prediction) [1], allows to explore the possibilities of occurence of 3, 4, 5 and 6-connected 3D networks. Hypothetical binary models (as well as known frameworks) are produced with exclusive connections of polyhedra by corners, such as $[MX_3]$ triangles in M_2X_3 formulation, $[MX_4]$ tetrahedra in MX_2 (zeolites or dense SiO_2 polymorphs), $[MX_5]$ polyhedra in M_2X_5 and finally $[MX_6]$ octahedra in MX_3 polymorphs. Moreover, hypothetical ternary $M_aM'_bX_c$ compounds are built up by combinations of either two different polyhedra or two different cations adopting the same coordination but with two different radii. The cost function is based on the agreement of the model interatomic distances with ideal distances provided by the user. The Monte Carlo algorithm explores randomly a range of cell parameters. First are found rough structure candidates, selected after the verification of the expected geometry, and then are optimized the cell parameters and the atomic coordinates. A satellite software (GRINS) can use the predicted models and produces the characteristics of isostructural compounds which would be obtained by cationic substitutions. CIF files (>1000) of hypothetical boron oxyde polymorphs (including nanotubes), zeolites, fluoroaluminates, borosilicates, titanosilicates, gallophosphates, are available at the PCOD (Predicted Crystallography Open Database) [2].

[1] a) Le Bail A., *J. Appl. Cryst*.,*submitted*; b) http://www.cristal.org/grinsp/ [2] http://www.crystallography.net/pcod/

Keywords: structure prediction, inorganic compounds, Monte Carlo treatment

MS77 PERSPECTIVE OF NEUTRON CRYSTALLOGRAPHY AT HIGH POWER SOURCES

Chairpersons: Masatoshi Arai, Ian Anderson

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Prospects for Neutron Diffraction under Extreme Pressure Conditions

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The Spallation Neutron Source currently under construction at Oak Ridge National Laboratory in the United States is due to receive first neutrons in the spring of 2006. In this talk the current state of the

neutron instrument suite will be highlighted with particular emphasis on performance parameters of the diffraction instruments. The instrument parameters of the Spallation Neutrons And Pressure (SNAP) instrument will include a discussion of planned micro-diffraction capabilities. Specifically, recent progress in micro-focused neutron beams demonstrates that neutron diffraction from sub 100 micron samples held within 'more standard' opposed gem anvil cells (e.g. DACS) might be feasible. Beams focused to 90 x 90 microns have been demonstrated to produce at least an order of magnitude increase in flux at the focal spot. This technique does not significantly increase beam divergence. Recent neutron diffraction results from single crystal micro-samples (300 microns) mounted on fibers and micro samples (200 microns) under pressure in opposed gem anvil pressure cells will be presented.

Keywords: neutron diffraction, instrumentation, high pressure

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ISIS Crystallography on TS-II: what can we do with 60 kW?

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European facilities in general and ISIS in particular are facing a major challenge from the construction of a new generation of pulsed neutron sources in the US and Japan. Although the European research community must warmly welcome these developments, it is nevertheless crucial for us to maintain a leadership role, if not in sheer flux, at least in the creative development of new neutron instruments and techniques and in the operation of a cutting edge science program.

The construction of the Target Station II at ISIS will enable us to extend pulsed neutron crystallography to cover a much wider domain of momentum transfer Q. A combination of high peak flux and state-of-the-art target, guide and instrumentation design will result in world-leading performances, in spite of the fact that the integrated power of the source is only a fraction of that at SNS and J-PARC.

The new diffractometer WISH at the ISIS TS-II will further push the envelope of low-Q crystallography. WISH is primarily designed for powder diffraction at long d-spacing on magnetic and large-unit-cell systems, with the option of enabling single-crystal and polarized beam experiments.

The conceptual design for a new single-crystal diffractometer for large molecule crystallography and structural biology will also be presented. Although the instrument design is quite different from comparable instruments at high-repetition rate sources (such as the SNS), detailed Monte Carlo simulations have shown that this machine will have excellent performances overall, and will be particularly competitive for medium-resolution crystallography on small samples.

Keywords: neutron diffraction, instrumentation, ISIS

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Hydrogen and Hydration Sensitive Structural Biology

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It is well known that neutron diffraction provides an experimental method of directly locating hydrogen atoms, but unfortunately, to date, there are relatively few examples of neutron crystallography in biology since it takes a long period of time to collect a sufficient number of Bragg reflections. The recent development of a neutron imaging plate (NIP) became a breakthrough event in neutron protein crystallography [1]. At the Japan Atomic Energy Research Institute (JAERI), we have constructed several high-resolution neutron diffractometers dedicated to biological macromolecules (called BIX-type diffractometers), which gives several interesting results regarding hydrogen positions and hydration in proteins and oligomer DNA.

However, neutron protein crystallography still remains an intensity limited technique. Recently next generation spallation neutron sources, such as J-PARC (Japanese proton accelerator research complex) and SNS (Spallation neutron source in USA), are being constructed and several protein crystallography diffractometers will be installed there. Then about two orders of magnitude gain in neutron intensity would be expected and neutrons absolutely expand the field of structural biology. In this microsymposium, the future prospect for neutron protein crystallography will be discussed.

[1] Niimura N., et al, *Nucl. Instrum. Method. Phys. Res*., 1994, **A349**, 521-525.

Keywords: neutron diffraction, hydrogen, bio-macromolecules

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Shaping the Future of Neutron Powder Diffraction

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Neutron powder diffraction is recognized as a powerful technique to clarify the relationship between the crystal structure and the properties of functional materials. Its application fields have been expanding in materials science, and prominant results obtained across a large number of diverse disciplines. New neutron powder diffractometers (NPD's), in various stages of construction at new facilities in Europe, Australia, the US and Asia, will exceed the present limits of application, and stimulate the existing 60 NPD's in the world. Some of these new diffractometer projects including the ones in Japan will be presented and the prospects for new scientific impact will be discussed.

Keywords: neutron powder diffraction, materials science, structure-properties relationship

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Neutron Protein Crystallography (nPX) Development: reaching yet higher Molecular Weight Capability

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The unique property of the neutron scattering interaction with deuterium being as strong as C, N, O means that medium resolution crystal structure studies can discern the hydrogenation and hydration of a protein structure. We have used the Institut Laue Langevin (ILL) LAue DIffractometer 'LADI' to compare with Ultra-high resolution X-ray PX to define such details of the lectin concanavalin A [1] and performed a 15K nPX analysis of concanavalin A structures, then a 15K to 293K comparison [2]. This latter study [2] also brings time-resolved freeze trapping nPX studies as a potential for the future. New nPX instruments at LANSCE-USA, the ILL, ISIS 2 UK (proposed), SNS-USA (under construction) and SNS-Japan (under construction) will further expand the capabilities including into yet higher molecular weight protein complexes and protein DNA complexes. We will review our contribution to the nPX developments [3] and also we offer new simulations addressing the category of non-crystallographic symmetry cases where we show that even higher molecular weight can be examined in nPX studies of deuterium atom placement.

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Keywords: neutron protein crystallography, synchrotron radiation, hydrogens and hydration in proteins