corrected rather easily by changing the residue name, deleting surplus atoms or editing the LINK or CONECT records. Other problems, however, require more sophisticated methods to fix them. To fix e.g. stereochemistry problems, atoms have to be relocated. In some instances, e.g. when wrong stereochemistry is involved in glycosidic linkages, entire residues might have to be rearranged, which involves refinement of the 3d structure. Here, we present an approach to combine a tool for carbohydrate validation (pdb-care [3], www.glycosciences.de/tools/pdb-care/) with the modeling software WHAT IF [4] (swift.cmbi.ru.nl/whatif/) and the refinement tool PDB-redo [5] (www.cmbi.ru.nl/pdb_redo/) to enable a (semi-)automatic correction of erroneous carbohydrate structures in PDB entries.

[1] Crispin M, Stuart DI, Jones EY (2007) Nat Struct Mol Biol. 14, 354
[2] Lutteke T, Frank M, von der Lieth CW (2004) Carbohydr Res. 339, 1015-1020
[3] Lutteke T, von der Lieth CW. (2004) BMC Bioinformatics 5, 69
[4] Vriend, G. (1990) J Mol Graph. 8, 52-56.
[5] Joosten, R.P., Vriend, G. (2007) Science, 317, 195-196

Keywords: fefinement, validation, glycoproteins

P03.02.11

Acta Cryst. (2008). A**64**, C221

A molecular dynamics approach to equilibrium structures in crystals

Anthony M Reilly, Derek A Wann, Carole A Morrison, David WH Rankin
University of Edinburgh, School of Chemistry, West Mains Road, Edinburgh, Midlothian, EH9 3JJ, UK, E-mail：anthony.reilly@ed.ac.uk

The equilibrium structure of a crystal represents the system in a theoretical vibrationless state at the absolute minimum of its potential-energy surface. Such structures can be compared directly between different phases and polymorphs and with theoretical calculations. Structures determined using X-ray and neutron-diffraction experiments are time-averaged over all of the molecular vibrations occurring in the crystal. If these motions are anharmonic or curvilinear then the time-averaged and equilibrium structures will differ. There remains no general and simple method for removing the structural inconsistencies that result. We have recently developed a new method using molecular dynamics (MD) simulations that allows experimental positions to be corrected to equilibrium positions. The corrections are determined by taking the differences between theoretical equilibrium structures and time-averaged structures obtained from MD trajectories. The application of the method to the crystal structure of nitromethane using an empirical force field will be detailed. Comparisons will be made with literature X-ray and neutron data sets. Thermal motion is incorporated into the crystal-structure refinement process using the Debye-Waller factor, which is the Fourier transform of an atom's vibrational probability density function. This probability function is typically assumed to be a trivariate Gaussian and yields the ubiquitous probability ellipsoids. The MD simulations allow us to determine the true function numerically. In the case of nitromethane this leads to highly curved probability functions for the H atoms.

Keywords: thermal motion, molecular dynamics simulations, Debye-Waller factor

P03.02.12

Acta Cryst. (2008). A**64**, C221

Restrained anisotropic refinement with SHELXL

Andrea Thorn, George M. Sheldrick
University of Goettingen, E-mail：andrea.thorn@web.de

The successful refinement of macromolecular crystal structures usually requires the use of restraints based on our knowledge of similar structures. Whereas geometrical restraints are relatively well understood and quantified, there is still much room for improvement of the restraints applied to the atomic displacement parameters (isotropic and anisotropic temperature factors). We are currently investigating a variety of potential restraints and other features with a view to making the SHELXL program for crystal structure refinement more suitable for the refinement of macromolecular structures at modest resolution. The step from isotropic to anisotropic refinement increases the number of parameters refined by more than a factor of two and often results in over-fitting of the data. A good approach to this problem is the use of TLS constraints (Schomaker & Trueblood, 1968; Winn, Isupov & Murshudov, 2001) because, as usually implemented, the number of extra parameters is limited to 20 per 'rigid' domain. However, it is not always easy to subdivide a macromolecular crystal structure into suitable domains and an atom may not be in more than one domain at the same time. A flexible alternative is to extend the rigid bond restraints by Rollett (1970) and known as the DELU restraint in SHELX, to much greater distances (say 6-8 Å) than normally employed. Didisheim and Schwarzenbach (1987) showed that in the limit of very tight restraints this asimptotes to the TLS model. The main technical problem in the implementation of such 'TLS restraints' for large structures is finding the appropriate atom pairs efficiently, since this needs to be performed each refinement cycle and should take symmetry equivalents into account.

Keywords: restrained refinement, anisotropic atomic displacement parameter, macromolecular structure

P03.04.13

Acta Cryst. (2008). A**64**, C221–222

Computational chemistry approach to polymorphism of aspirin

Shigeaki Obata, Hitoshi Goto
Toyohashi University of Technology, 1-1, Hibarigaoka, Tempaku-cho, Toyohashi, Aichi, 441-8580, Japan, E-mail：obata@cochem2.tutkie.tut.ac.jp

It is strongly expected that practical techniques on computational analysis of molecular crystal structures can provide knowledge for molecular designs of functional materials or drugs, and for crystallographic studies of solid state phenomena, such as nucleation, growth, polymorphism, and phase transition. To cope with the expectations, we have been developing a computational chemistry system (CONFLEX/KESSHOU) to crystallographic analysis and prediction of conformational and packing polymorphism based on rational evaluations for many energy minima of crystal structures and their dynamical behaviors. In this conference, as an extension of CONFLEX/KESSHOU, we propose our computational investigation for the recent topic on the aspirin crystal polymorphism [1-3]. In order to quantitatively elucidate this polymorphic transition between form I and form II without purported ambiguity, we have calculated energy minimum crystal structures by using CONFLEX/KESSHOU crystal calculations. In comparison with their free energies of two polymorphic forms at room temperature and 100 K, the predominant stability of form I has been computationally ascertained as well

as the experimental. Potential energy map of the phase transition between form I and II is also evaluated to demonstrate the dynamical behaviors of aspirin polymorph. It is indicated that activation energy required for the polymorphic transition is small enough to be able to overcome the energy barrier at room temperature.

[1] C. Ouvrard, S. L. Price, Cryst. Growth Des. 2004, 4, 1119.
[2] P. Vishweshwar, J. A. McMahon, M. Oliveira, M. L. Peterson, M. J. Zaworotko, J. Am. Chem. Soc. 2005, 127, 16802
[3] A. D. Bond, R. Boese, G. R. Desiraju, Angew. Chem. Int. Ed. 2007, 46, 615, 618

Keywords: drug polymorphism, crystal structure analysis, phase transitions

P03.04.14

Acta Cryst. (2008). A**64**, C222

Effects of initial conformations of small ligands on computational docking accuracies

Akifumi Oda[1], Ohgi Takahashi[1], Noriyuki Yamaotsu[2], Shuichi Hirono[2]
[1]Tohoku Pharmaceutical University, 4-4-1, Komatsushima, Aoba-ku, Sendai, Miyagi, 981-8558, Japan, [2]Kitasato University, 5-9-1, Sirokane, Minato-ku, Tokyo, 108-8641, Japan, E-mail：oda@tohoku-pharm.ac.jp

Computational ligand docking is one of the most important techniques of Structure-Based Drug Design, which makes the most of 3D-structures of drug target proteins determined by experimental studies, such as NMR or crystallographic analyses for the drug discovery and development. In this study, the effects of initial conformations of ligands on computational docking were investigated, and appropriate settings of conditions for computational docking were determined. Five types of initial conformations were prepared, and docking calculations were carried out by using each conformation as inputs. Furthermore, several settings of docking parameters were used (default, accurate, high throughput, etc), and robust settings for various initial structures were investigated. GOLD and eHiTS were used as docking software, and structurally known protein-ligand complexes were used as test set. Root mean square deviations between computational and experimental structures (RMSD) were adopted for criteria for evaluations, and the docking pose with RMSD < 2.0 Å were defined as “reasonable poses”. When at least one of the generated poses by a docking trial was reasonable, the trial was defined as “success”, and when the top ranked pose, i.e. the pose with the lowest binding free energy, was reasonable, the trial was defined as “top pose success”. The search abilities of docking were evaluated by “success rate” and “top pose success rate”. As the results, bad initial conformations, which were much different from crystal ligand structures, cause the worst success rate and the worst top pose success rate in all initial conformations. Comparing GOLD and eHiTS, eHiTS was better than GOLD to obtain reasonable poses regardless of rankings, but GOLD was better to obtain reasonable top poses.

Keywords: computer-aided drug design, conformational analysis, protein-ligand complexes

P03.04.15

Acta Cryst. (2008). A**64**, C222

Trypanosoma cruzi DHOD structure-based design of 5-halogen and 5-alkyl orotate derivatives

Daniel K. Inaoka[1], Lee Nayoung[2], Kimitoshi Sakamoto[1], Hironari Shimizu[1], Tomoo Shiba[3], Genji Kurisu[3], Takeshi Nara[4], Takashi Aoki[4], Masayuki Inoue[2], Kiyoshi Kita[1], Shigeharu Harada[5]
[1]The University of Tokyo, Biomedical Chemistry, 7-3-1, Hong, Bunkyo-ku, Tokyo, 113-0033, Japan, [2]Department of Medicinal Chemistry, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan, [3]Department of Life Sciences, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan, [4]Department of Molecular and Cellular Parasitology, Juntendo University, 2-1-1, Hongo, Bunkyo-ku, Tokyo, 113-8421, Japan, [5]Department of Applied Biology, Kyoto Institute of Technology, Goshokaido-cho, Matsugasaki, Sakyo-ku, Kyoto, 606-8585, Japan, E-mail：danielkeninaoka@yahoo.co.jp

Trypanosoma cruzi (*T. cruzi*) is the pathogen of Chagas’ disease and affects approximately 16 to 18 million people in Latin America. *T. cruzi* produces succinate as the main end product of respiration, even though it uses the TCA cycle and the aerobic respiratory chain. Fumarate reductase (FRD), which catalyzes the last step in succinate fermentation, is the key enzyme in the energy metabolism and a promising drug target for some parasites such as Ascaris suum, Leishmania donovani and *T. cruzi*, because human hosts do not possess FRD. It has been noted that FRD in mitochondria and glycosomes of T. brucei and *T. cruzi* uses NADH as the electron donor. On the other hand, we identified a novel type of FRD in the cytoplasm of T. cruzi that uses dihydroorotate as the electron donor, and characterized this enzyme as the dihydroorotate dehydrogenase (DHOD). Since DHOD is the fourth enzyme of de novo pyrimidine biosynthetic pathway, the enzyme may play an important role not only in succinate fermentation but also in de novo pyrimidine biosynthesis. In this study, we have determined the first complete set of structures of TcDHOD in the native form and in complexes with all physiological substrates and products. In addition, we found a parasite-specific pocket near the 5th carbon of the bound orotate. In order to design specific inhibitors, 5-halogen (Cl, Br and I) and 5-alkyl (vinyl and 3,3-dimethyl-but-1-enyl) orotate derivatives, whose substituent groups were aimed for filling the pocket, were synthesized and the structures of DHOD complexed with these compounds were also determined.

Keywords: *trypanosoma cruzi*, energy metabolism, fumarate reductase, dihydroorotate dehydrogenase, drug design, parasite

P03.05.16

Acta Cryst. (2008). A**64**, C222−223

First principles study of composition fluctuation and residual strain in InGaN/GaN MQW

Kiichiro Mukose, Noriyuki Uehara, Akihiko Sakamoto, Yu Yoshioka, Masatoshi Sano
Tokyo University of Science, Faculty of Engineering, 1-3 Kagurazaka, Shinjuku-ku, Tokyo, 162-8601, Japan, E-mail：mukose@ee.kagu.tus.ac.jp

The quantitative relations between mechanical properties and the composition fluctuation in InGaN films are studied theoretically. In the ternary alloy InGaN, the indium composition has been known to show spatial inhomogeneity in various growth conditions. This composition fluctuation has been considered to form the quantum disk structures in InGaN quantum wells those influence the spontaneous emission rate in light emitting devices. To investigate the mechanical properties of the structures theoretically, a new method based on first principles calculation was used in this study. The simulation models of InGaN films contain triangular pillar-shaped cells, where the composition ratio, the strain and the stress in the each cell follow an equation of state which has been determined by ab initio electronic structure calculations. The quantitative