KY.NT.14 THE ROLE OF CRYSTALLOGRAPHY FOR BETTER HIGH Tc SUPERCONDUCTORS. Catherine Chaillout, Laboratoire de Cristallographie, CNRS-UJF, BP 166, 38042 Grenoble Cedex 09, France

Since 1986, a large number of high Tc superconducting cuprates of general formula $A_mM_2R_{n-1}Cu_nO_x$ have been discovered. Their structure consists in the stacking of (AO), (MO), (R), and (CuO_2) layers along the c-axis, where A= Bi ,Tl, Hg, Cu, or C, M= Sr, or Ba, R=Ca or a rare earth cation. The superconducting transition temperatures obtained for the more recently discovered phases are among the highest, namely 135K at ambient pressure and ≈164K under ≈35 GPa for the third member of the Hg-based phases.

This lecture will emphasize the role that crystallography can play in the study of these phases and in the search for new superconducting compounds with possibly higher T_c's.

Examples will be taken mainly in the Hg-based and oxycarbonates phases, to illustrate the influence of the oxygen stoichiometry, the cation substitution,.. on the physical properties. The role of pressure, either in the synthesis, or for the structure determination will be also discussed.

Some time will be devoted to the way the observations of structural defects can yield to the synthesis of new phases. The example of $Hg_2Sr_2YCu_2O_x$ will be given.

All along this lecture, we will insist upon the necessity to use simultaneously different techniques such as diffraction, absorption, and microscopy in order to get the relationships between the local structure and the physical properties. This is due to either the complex structural arrangements, or the preparation method of the samples such as the pressure-induced synthesis.

KY.NT.15 THE CRYSTAL PACKING OF ORGANIC SMALL MOLECULES. A.Gavezzotti, Dipartimento di Chimica Strutturale e Stereochimica Inorganica, Universita' di Milano, Milano, Italy

An overview of the structural and thermodynamic aspects of the crystal packing of organic small molecules (up to 100 atoms) will be given, along the following lines. 1) Geometry: correlations between molecular structure and crystal structure descriptors; long-range order and space group symmetry. 2) Energies: atom-atom potentials, and their optimization for molecular crystals using structural and thermodynamic data; thermodynamics of sublimation and melting. 3) Studies of intermolecular recognition at the elementary molecular level: computer simulation and possible relevance to crystal nucleation. 4) Computer generation of crystal structures, and their energy ordering; polymorphism. 5) Crystal structure prediction assisted by partial diffraction data; why the need for well grown single crystals will be reduced in the near future. 6) Kinetic and thermodynamic obstacles preventing the completely ab initiodetermination of organic crystal structures by computer simulations.

Related literature

- Gavezzotti, A. PROMET(5): A Program for the Generation of Possible Crystal Structures from the Molecular Structure of Organic Compounds, Mark 5 version, University of Milano, 1995 (available from the author upon request). See also: Gavezzotti, A., *J. Am. Chem. Soc.* 1991,113,4622; Williams, D.E., PCK83, QCPE Program 548, Chemistry Department, Indiana University, Bloomington, 1983.
- Gavezzotti, A.; Filippini, G. *J. Phys. Chem.* 1994,98,4831.
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KY.NT.16 THE INTEGRATION OF STRUCTURE-BASED DRUG DESIGN & COMBINATORIAL CHEMISTRY FOR EFFICIENT DRUG DISCOVERY. F. Raymond Salemme, 3-Dimensional Pharmaceuticals, Inc., Eagleview Corporate Center, 665 Stockton Drive, Suite 104 Exton, PA 19341

Structure-Based drug design allows the atom by atom modification of drugs leads whose binding to a receptor target can be directly visualized using x-ray crystallography. Although structure-based design has become increasingly widely used in pharmaceutical discovery owing to improved technology for rapid 3D structure determination of drug-ligand complexes, key technical issues have emerged which limit process efficiency. Specifically, the picture provided by the protein-ligand 3D structure tells the "how" but not the energetic "why" of ligand binding. This situation basically reflects the physical complexity that underlies the change in free energy accompanying ligand binding, which involves a multiplicity of factors including changes in ligand bonding [with both solvent water and the target protein], changes in ligand conformation or flexibility, changes in ligand polarization, as well as corresponding changes in the target protein. The accurate estimation of how these changes will occur and manifest themselves in the binding energetics for a given ligand is beyond the capabilities of currently available computational methods, although some success is possible in estimating the effects of small structural perturbations. Studies of complexes formed between streptavidin and a variety of ligands, where high resolution x-ray crystallographic results were complemented with detailed thermodynamics measurements of ΔH and ΔS, provide illuminating examples in this context. Still, from a practical standpoint, investigators have typically found it necessary to carry out the iterative synthesis and structural analysis of an extensive series of compounds to empirically define the important aspects of ligand binding energetics and refine the properties of the target ligand.

An alternative to the serial approach to structure-property refinement involves the development of methods for parallel synthesis of compounds that meet specific geometric requirements of a target receptor binding site. Custom chemical scaffolds can be designed that are directed to fit a particular receptor binding site and that can be synthetically elaborated through combinatorial reaction with commercially available reagents. Although such targeted combinatorial schemes can produce libraries of drug-like compounds with thousands to millions of members, parallel automated synthesis methods are presently capable of synthesizing libraries containing on the order of a hundred discrete compounds. This practical limitation on synthetic throughput motivates the development of effective computer search strategies that can iteratively define and refine the selection of sub-libraries that will best investigate the structure-property relationships for a given library-target combination. This has been achieved through the computer generation of large "virtual" libraries of synthetically accessible compounds which are designed to explore specific features suggested from a 3D structural model and/or other SAR features thought to be important in the ultimate development of a successful drug [e.g. features relating to bioavailability, toxicology, etc.]. Computer codes are then used to select library sub-sets for rounds of automated chemical synthesis and bioassaytesting. Test data resulting after each round are used both as selection criteria for additional 3D target-ligand structure determinations, and to iteratively refine molecular properties using more traditional SAR methods. In many cases, extensive 3D structural data generated from a chemically "easy" combinatorial library can be combined with elements of pure structure-based designs to rapidly develop novel compounds. This integrated approach will be described in the context of developing and refining libraries of potent and specific protease inhibitors.

Ref: Crystallographic and Thermodynamic Comparison of Natural and Synthetic Ligands Bound to Streptavidin, P.C. Weber, J.J. Wendoloski, M.W. Pantoliano, and F.R. Salemme (1992) J. Amer. Chem. Soc., 114:3197-3200