06–Crystallography of Organic Compounds

06.01 – Molecular Interactions in Organic Crystals

MS–06.01.01 GRAPH SET ANALYSIS OF HYDROGEN-BOND PATTERNS IN ORGANIC CRYSTALS. RECENT DEVELOPMENTS AND APPLICATIONS By. J. Bernstein* and L. Shimoni, Department of Chemistry, Ben-Gurion University of the Negev, Beer Sheva 84120, Israel and R.E. Davis, and N.-L. Chang, Department of Chemistry, University of Texas, Austin, TX 78712, U.S.A.

A number of recent papers have advocated the use of graph sets for the analysis of hydrogen-bonding patterns in organic crystals (Etter, M.C. *acc. Chem. Res.* **1990**, *23*, 120; Etter, M.C.; MacDonald, J.C.; Bernstein, J. *Acta Crystallogr.* **1990**, *B46*, 256), and these have already been applied to a variety of problems (for instance, Stainton, N.M., Harris, K.D.M.; Howie, R.A. *J. Chem. Soc. Chem. Comm.* **1991**, 1781; Aakeroy, C.B.; Hitchcock, P.B.; Seddon *J. Chem. Soc. Chem. Comm.* **1992**, 553; Stowell, J.G.;Toma, P.H.; Byrn, S.R. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 185; Lynch, D.E., Smith, G; Byriel, K.A.; Kennard, C.H.L. *J. Chem. Soc. Chem. Comm.* **1992**, 300).

In the course of a number of these works and in our own efforts to expand and apply these methods to different systems, a number of problems, misunderstandings and ambiguities have arisen in the earlier prescriptions we provided for determining the graph sets. In this presentation we will review the general rules for applying graph set analysis to hydrogen-bonded systems, point out a number of pitfalls to be avoided, and describe a number of the applications to systems which have not been previously analyzed by this method.

MS–06.01.02 INTRAMOLECULAR N-H---O=C HYDROGEN BOND FORMATION IN CONJUGATED SYSTEMS.
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N-H---O=C hydrogen bonds (hb) play an important role in determinig the conformation of the proteins and nucleic acids, and in establishing intra and inter-molecular interactions in molecular recognition systems. There is a large variety of arrangements having N-H---O=C hb which display different geometries and topologies (Taylor *et al.* (1984). *Acta Cryst.* **B40**, 280). Accordingly, it is clear that the hb strength inevitably depends on various factors such as crystal field environments, cooperative effects, presence of charges on the acceptor and donor atoms, *etc.* (Jeffrey & Saenger (1991). *Hydrogen Bonding in Biological Structures*, Berlin: Springer). Moreover, it has been recently reported that the most relevant effects on hb are produced, in non-charged systems, by the presence of π electron delocalization within the conjugated fragments containing the atoms involved in hb. The role of resonance on the hb strenghtening has been so far described mainly for β-diketone enol systems (Gilli *et al.* (1989). *J. Am. Chem. Soc.*, 111, 1023; Bertolasi *et al.* (1991). *J. Am. Chem. Soc.* 113, 4917; Gilli *et al.* (1993). *Acta Cryst.*, **B49**, in the press). Owing to the synergistic coupling between the strength of hydrogen bond and the entity of the conjugation on the O=C-C=C-OH fragment this phenomenon has been called Resonance Assisted Hydrogen Bonding (RAHB).
In analogy with β-diketone enol systems we have undertaken a study of the intramolecular RAHB effect on similar fragments such as enaminones O=C-C=C-NH and keto-hydrazones O=C-C=N-NH. The results show that in these systems the RAHB is reproduced with the following characteristics: the N---O distances decrease up to 2.51 Å, δ(H) nmr shifts may become as larger as 16 ppm, and the infrared ν(NH) stretching vibrations may drop from 3300 up to 2600 cm^{-1}. All experimental data, both spectroscopic and structural, are intercorrelated in agreement with the RAHB model.
This research is directed to the study of the mechanisms of formation of strong hydrogen bonds which are assisted by resonance particularly in connection with their presence in important biological systems, such as in the coupling of nucleic bases; moreover it is devoted to understand the more general phenomenon of the tautomerism which is present in many conjugated chemical systems and seems to be strongly dependent by the hb formation.

MS–06.01.03
A COMMON PACKING PRINCIPLE OF ACYCLIC SUGAR DERIVATIVES. By C. Andre´ & P. Luger, Institut f. Kristallographie, Freie Universität Berlin, Germany.

From the crystal structure of L-mannonic acid hydrazide a general phenomenological packing principle common to many acyclic sugar derivatives of different chirality could be derived for the first time. Amongst these compounds are *talo-*, *gluco-*, *galacto-*, *mannon-* and *arabino*-configured derivatives. Their crystal structures share a quadrilateral, homodromic hydrogen bond cycle of general connectivity O(x)...O(x+2)...O(x+3)....O(x+1)...O(x). Both directions within the cycle are realized. There is a relationship between the occurrence of this cycle and the conformational behaviour and the cell dimensions of the sugar derivative. The magnitude of one lattice axis depends on the length of the molecule, whereas the two others are both approximately 5 Å long; the lattices are nearly rectangular. The molecules involved in the cycle are related solely by lattice translations along these 5Å axes, no matter in which space group the sugar crystallizes. The spatial orientation of the hydroxylgroups forming the cycle is identical in all compounds.

MS–06.01.04 1,3-PARALLEL INTERACTIONS IN ALDITOLS ("SUGAR ALCOHOLS"): NEW INSIGHTS. By J. Kopf*[1] and P. Köll[2]; [1]Institut für Anorganische und Angewandte Chemie der Universität Hamburg, Martin-Luther-King-Pl. 6, D-20146 Hamburg, FRG; [2]Fachbereich Chemie der Universität Oldenburg, D-26111 Oldenburg, FRG.

Most of the crystal structures of the pentitols and hexitols have been determined (Jeffrey, G. A. and Kim, H. S., Carbohydr. Res., 1970, **14**, 207) at the end of the sixties, but some were left. From those previous structure determinations it was derived, that the conformation in the crystal is controlled by the "so-called" Hassel-Ottar effect (Jeffrey, G. A., Acta Cryst., 1990, **B46**, 89): Generally, a planar zigzag conformation in the carbon chain is expected, but in the case when the C(n)–OH and C(n+2)–OH bonds are arranged parallel in the straight-chain conformation, one or more of the C–C–C–C torsion angles adopt the *gauche* conformation to avoid this unfavorable 1,3-parallel interaction of O atoms (designated as O//O). This claimed general avoidance of O//O interactions (which resembles 1,3-diaxial interactions in the cyclic case) was incorrectly assigned to Hassel and Ottar who, indeed, were very cautious in speculations about the steric influence of such a geometry (Hassel, O. and Ottar, B., Acta Chem. Scand., 1947, 1, 929).

In continuation of our recently started research program (Kopf, J., Köll, P., Morf, M., Zimmer, B. and Jarchow, O., 1990, Abstract PS-05.04.25, IUCr XV, Bordeaux, France) we have determined the crystal and molecular structures of previously not treated pentitols, hexitols, heptitols and several higher alditols up to decitols including peracetylated derivatives in most cases. Contrary to the above mentioned assumptions, our investigations show that the avoidance of 1,3-parallel interactions between the heavy atoms O and C is not a dominating factor in determining the conformations of higher alditols in the solid state. Acetylated alditols in particular are able to adopt "unexpected" conformations. Examples of the structure determinations and further discussions will be given. First results of our respective work have been published already (Kopf, J., Bischoff, M. and Köll, P., Carbohydr. Res., 1991, **217**, 1; Kopf, J., Morf, M., Zimmer, B., Bischoff, M. and Köll, P., Carbohydr. Res., 1992, **229**, 17 and Köll, P., Morf, M., Zimmer, B., Kopf, J., Berger, A., Dax, K. and Stütz, A. E., Carbohydr. Res., 1993, in press).

MS-06.01.05 The Use of Composite Crystal-Field Environments Derived from Crystal Packing in Molecular Recognition and the 'De-NOVO' Design of Protein Ligands

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Information about intermolecular interactions and the mutual recognition of organic molecules can be obtained from their packing in the crystalline state. Structural data has been retrieved from the Cambridge Crystallographic Database [1] to compile composite crystal-field environments about different functional groups, which also occur in proteins and nucleotides. The spatial distribution obtained for these next-neighbor contacts can be used to map-out putative interaction or recognition sites, e.g. about amino acid residues oriented towards the binding site of a given protein. Although influenced by packing forces, these composite environments show systematic patterns which reflect preferred interaction geometries of the functional groups under consideration with their neighboring groups, e.g. hydrogen bonding partners. A detailed analysis reveals differences and similarities in the structural properties of these functional groups which allows guide-lines to be devised for the consequences of mutual functional group replacements. Similar, but substantially less detailed, distributions can be obtained from crystallographically determined ligand/protein complexes (Brookhaven File [2]) for the spatial orientation of ligand functional groups about amino acid residues. These demonstrate that the properties observed in low-molecular weight structures are also representative for the sought-after spatial orientation of interactions between ligands and their receptor proteins [3]. The crystallographically determined binding geometries of three inhibitor/enzyme complexes are compared with the distributions of putative interaction sites predicted from corresponding composite field environments. In some cases, the observed positions of ligand atoms interacting with the proteins coincide with a region which is also frequently occupied by similar bonding partners in organic crystal structures, however, interaction geometries are also found which fall close to the limits of the ranges observed in the small molecule reference data. The information contained in the different composite crystal-field environments can be translated into rules which serve as guide-lines for an automatic docking of small molecule fragments into the active site of proteins [4].

[1] Allen F.H., Kennard O., Taylor R., Acc. Chem. Res. (1983) 16 146
[2] Bernstein F.C., Koetzle T.F., Williams G.J.B, Meyer E.F. Jr., Brice M.D., Rodgers J.R., Kennard O., Shimanouchi T., Tasumi T., J. Mol. Biol. (1977) 112 535
[3] Klebe G., Mietzner T., (1993) in "Organic Crystal Chemistry" ed. Jones D.W., Oxford Univ. Press
[4] Böhm H.J., J. Comp.-Aided Mol. Des., (1992) 6 61-78 and 593-606

MS-06.01.06 KEY ROLE OF SPECIFIC INTERMOLECULAR INTERACTIONS IN FORMATION OF ORGANIC CRYSTAL STRUCTURES

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Some contacts of atoms (for ex., CN···Cl, O···C=O, I···I, CH···O) display properties, which could not be described by conventional additive models (such as van der Waals radii, transferable atom-atom potentials, superposition models of electron density, etc.). We call them specific intermolecular contacts (SIC). The rise of SIC is one of the important factors determining the structure of a molecular crystal. Different ways to take into account the influence of SIC on the packing of molecules were considered:
1) the addition of SIC energy for the refinement of depths of minima after the energy minimization by atom-atom potential method,
2) the use of the special potentials and/or virtual atoms,
3) the energy minimization under the condition of fixed SIC geometry,
4) a priori construction of packings which contain setted SIC to use the packing as a starting point in energy minimization.
An application of the last way for uracil and its derivatives gave us initial models which were very close to real structures.
The use of donor-acceptor approach based on localized orbitals interaction in the second order of perturbation theory allowed us to reproduce the surface of potential energy for Cl...Cl SIC (contrary to the electrostatic approach).

MS-06.01.07 STRUCTURES OF UNSTABLE INTERMEDIATES IN THE CRYSTALLINE STATE REACTIONS

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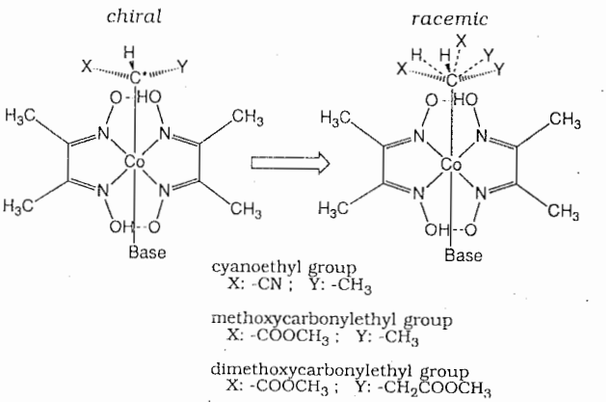
If the structural change in the process of reaction could be "observed" directly by X-ray analysis, the mechanism would be easily made clear. Such a reaction should proceed in a crystal with retention of crystallinity, which is called as crystalline state reaction.



cyanoethyl group
X: -CN ; Y: -CH_3

methoxycarbonylethyl group
X: -$COOCH_3$; Y: -CH_3

dimethoxycarbonylethyl group
X: -$COOCH_3$; Y: -CH_2COOCH_3