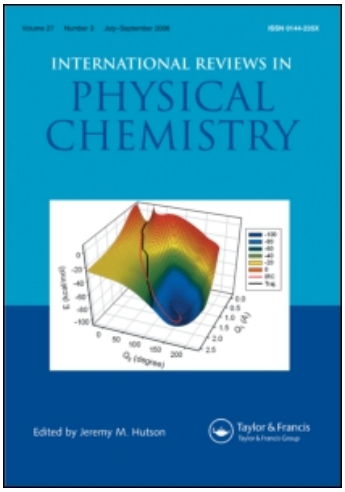

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Experimental and theoretical studies of organic molecules and crystals

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A review is given of some applications of X-ray crystallography to chemical processes in the organic solid state, of molecular mechanics to the minimization of strain energy in crowded molecules, and of studies on the mutual interaction of molecular and crystal potential fields.

1. Molecules and crystals

In 1961, one could read, in the preface of a book entitled *X-ray Analysis of Organic Structures* (Nyburg 1961), the following sentence: 'X-ray structure analysis is essentially a branch of physics and one which involves an appreciable amount of mathematics. Thus it is difficult for the chemist, and in particular, the organic chemist and biochemist to understand how X-ray structure analyses are carried out'. Twenty-five years later this opinion, if still entirely endorsable for the first part, sounds a little strange in a chemical and biochemical world whose literature is teeming with reports of X-ray structure analyses. Indeed, by one of those unpredictable turns which scientific ideas take independently of their fathers, von Laue's 1912 suggestion that a copper sulphate crystal would be a perfect grating for X-ray diffraction has in fact opened the way to the structural approach to modern chemical and biochemical thinking. Of course this by no means implies that chemists have taught themselves the physics of X-ray diffraction—they found it much more convenient to have it taught to computers, and companies now sell software packages that produce beautiful, detailed and almost three-dimensional pictures of complex molecules at the touch of a finger.

The ideal companion to X-ray structure analysis, in times when *ab initio* calculations were just a dream, was molecular structure analysis by the strain energy method. Under the guidance of Massimo Simonetta, the authors have dealt with both in the days when the calculation of the strain energy for a ten-atom molecule or of a few structure factors for a crystal was still quite a feat, and the visualization of structural results meant hours of painstaking battles with China ink and fountain-pens. Today, all this is taken care of by computers in seconds, and crystal and molecular structure analysis has become a mature discipline—actually, it has become a tool, the most popular and compelling argument in the discussion of chemical problems. How this tool has been used in recent years in our laboratory is illustrated in this review by a few examples.

2. Molecules in crystals

If it is agreed that scientific research must be an amusing and rewarding intellectual exercise, then it is clear that routine X-ray molecular structure analysis no longer qualifies. There must be some chemical purpose when undertaking such an analysis—crystal disorder, an unusual crystal packing, a temperature-dependent solid-state

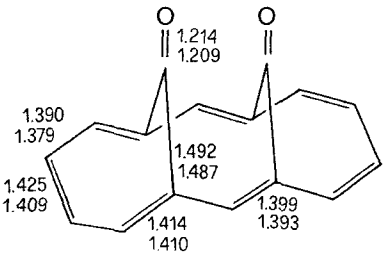


Figure 1. Bond lengths (Ångström units; averaged over C_{2v} symmetry; uncorrected for thermal libration) in syn-1,6:8,13-biscarbonyl[14]annulene (typical σ values are 0·002). For each couple the upper value is at 15 K, and the lower at room temperature. Owing to extensive thermal motion, the room temperature bond lengths appear much shorter than at 15 K.

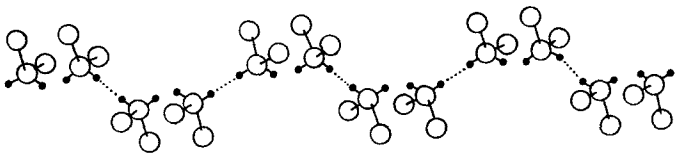


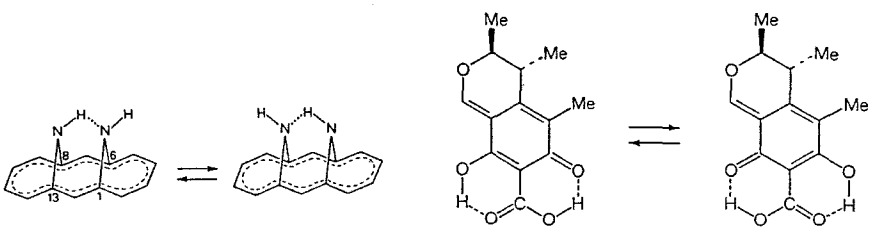
Figure 2. Ribbons of syn-1,6:8,13-diimino[14]annulene in the crystal. Bridge hydrogens are shown in two disordered positions (black dots), and dotted lines pass through crystal symmetry elements. For clarity, only bridge and bridgehead atoms are shown.

process. In fact, temperature control is what mainly turns X-ray crystallography from an analytical technique into a true branch of physical chemistry.

The effect of temperature changes on the accuracy of structure determination is illustrated in figure 1. Data were collected for syn-1,6:8,13-biscarbonyl[14]annulene at room temperature (Destro and Simonetta 1977) and at $15 \pm 0{\cdot}5$ K (Destro and Gavezzotti 1987; copper sphere data, Mo radiation, $R = 3{\cdot}4\%$ for reflections with $I > 3\sigma(I)$).

X-ray analysis can provide direct structural evidence for chemical changes, like tautomerism and its temperature dependence. Proton exchange is an example of such a process. The crystal of syn-1,6:8,13-diimino[14]annulene, **1**, contains infinite ribbons of molecules along the (001) direction, and peaks in difference Fourier maps show the occurrence of both proton orientations (Destro *et al.* 1985). Since impossibly short intermolecular H...H contacts would result across symmetry elements (figure 2) by occupation of both sites at the same time, it is clear that what the X-rays see is some sort of spatially averaged, or more likely time-averaged, picture. CP-MAS n.m.r. spectra are being taken to distinguish between these two possibilities.

An example of freezing-out of the equilibrium is provided by the case of citrinin, **2**, where difference Fourier maps



1 **2**

at 290 K show double peaks for the hydroxyl H atoms, the *p*-quinone form exceeding the other tautomer by 60–40%. At 147 K, the refinement of the X-ray structure unequivocally indicated that only the *p*-quinone form is present (Destro and Marsh 1984). Figure 3 shows the difference Fourier maps at the two temperatures.

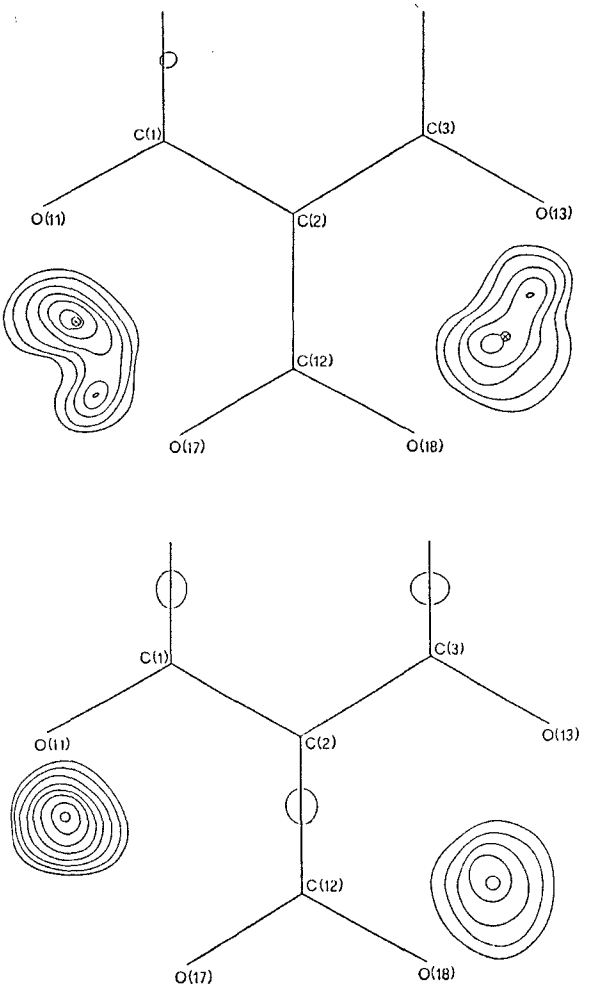


Figure 3. Difference Fourier synthesis in the crystal of compound **2**, at room temperature (top) and at 147 K (bottom). Only the lower part of the molecule is shown.

3. Molecular and crystal potential fields

Historically, molecular structure analysis came after crystal structure analysis, but logically the molecular structure must be understood before the effects of crystal packing on it can be analysed. Like anything belonging to the atomic world, molecular structure is dictated by the laws of quantum mechanics, in which no forces or trajectories are admissible. Molecular spectra are then interpreted as the result of

transitions between quantum states. But vibrational spectra are susceptible to a more immediate interpretation, in terms of the motion of atomic masses against restoring forces:

$$F = -kx = m\ddot{x} \tag{1}$$

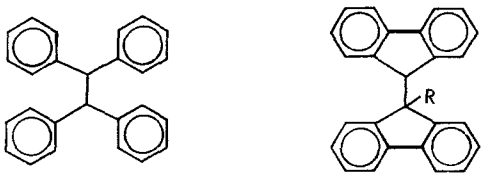
Equation (1) is the harmonic approximation to these motions, and can be solved to yield frequencies if the force constants are known, or force constants if frequencies are taken from infrared spectra. It is natural to work backwards from this and to imagine the molecule as immersed in a self-potential, U:

$$F = -dU/dx \qquad U = 1/2kx^2 \tag{2}$$

Chemical and structural meaning can be attached to the numbers, k, which describe the relative stiffness of atomic motions in molecules. The function U can be speculated upon, and other ingredients may be added, like dispersion–repulsion interatomic contributions, permanent-charge electrostatic contributions, or π-electron energy contributions. The molecule will be at equilibrium when

$$dU/dx = 0 \tag{3}$$

so the whole structure-finding exercise amounts to collecting the proper numbers k, other constants for the parametric expressions of the terms in the potential, and in searching for the set of molecular coordinates for which (3) is satisfied.



3 R = H
4 R = $C(CH_3)_3$

Figure 4. Phenyl-substituted ethane and back-clamped equivalent (the clamping bonds are the heavier lines).

Table 1. Experimental and calculated values for the central C–C bond length in phenyl-substituted ethanes (in Ångström). Refer also to figure 4.

Compound	Experimental value†	Calculated value	
		Hounshell *et al.* (1977)	Favini *et al.* (1981 b)
3	1·542	1·543	1·545
4	1·585	—	1·572
1,1,1-triphenylethane	1·553	—	1·560
1,1,1,2-tetraphenylethane	1·567	—	1·571
Pentaphenylethane	1·606	1·595	—
Hexaphenylethane	—	1·639	—

† From X-ray studies, as quoted in Favini *et al.* (1981 b).

Figure 4 shows some examples of molecular systems to which the method can still be comfortably applied with present-day computing means. The results of molecular mechanics calculations (Favini *et al.* 1981 b) are compared in table 1 with those from X-ray studies. The key parameter is the central C–C (ethane) bond length: heavy substitution at both ends lengthens this bond, but back-clamping (figure 4) brings it back to a free-ethane-like value. Calculated and experimental values for this parameter agree to a surprising accuracy.

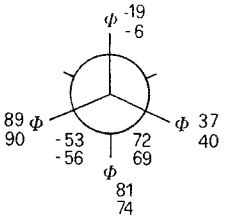


Figure 5. Torsion angles in 1,1,1,2-tetraphenylethane (degrees); of each pair of values the upper is calculated, the lower is experimental. Φ symbolizes a phenyl group; numbers near this symbol are torsion angles around C_{et}–C_{Φ} bonds, other numbers are C_{Φ}–C_{et}–C_{et}–C_{Φ} angles.

Quite different is the behaviour of torsion angles (figure 5), whose variation is along 'softer' molecular bending modes. Calculated and experimental values here disagree, and the suspicion arises that this may be due to crystal packing forces. But just how strong has to be the pull from these forces to induce a molecular distortion? This is not a trivial question, and only order-of-magnitude answers can be proposed (Bianchi *et al.* 1986). Let $E_n(R)$ be the amount of packing energy (see next section) due to atom n in the molecule, as a function of the radial distance, R, from it. This can easily be calculated by breakdown of the total lattice packing energy into atomic contributions and into contributions from spherical shells around each atom. Then the quantity

$$F_n(R) = -dE_n(R)/dR \tag{4}$$

is a rough estimate of the crystal force at atom n. For organic crystals, F_n turns out to be $\sim 10^{-1}$ kcal mol Å^{-1}, while bond stretching force constants are two to three orders of magnitude larger. On the other hand, the force constants for torsional displacements are of the same order of magnitude as F_n.

From the above one should deduce that bond lengths are unaffected by crystal potential effects. Nevertheless, a molecule like 11-methyl-11-cyano[10]annulene (figure 6) has four values for the transannular C_1–C_6 bond length (between 1·623 and

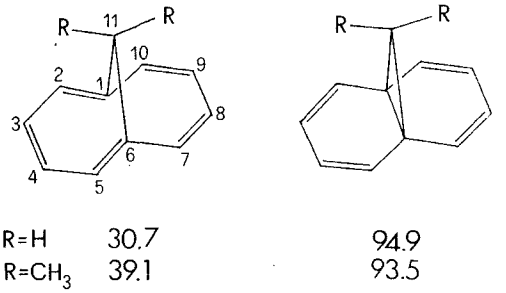


Figure 6. Strain energies (kcal mol^{-1}) in 1,6-methano [10] annulenes, for the annulenic (left) and norcaradienic (right) forms.

Table 2. Bond lengths (Å) and angles (degrees) in 1,6-methano[10]annulene (figure 6, R = H, annulenic form).

Parameter	Calculated (Favini *et al.* 1981 a)	Experimental (Bianchi *et al.* 1980)
C_1–C_2	1·401	1·405
C_2–C_3	1·404	1·377
C_3–C_4	1·416	1·418
C_1–C_{11}	1·472	1·485
C_1–C_2–C_3	121	123
C_2–C_3–C_4	128	127
C_2–C_1–C_{10}	125	127
C_2–C_1–C_{11}	117	117
C_1–C_{11}–C_6	99	98

1·851 Å) in different crystal structures. Clearly, C_1–C_6 is a sort of soft molecular bond. When one tries to correlate the F_1 and F_6 of equation (4) with the bond length, however, nothing consistent is found. The reason is that the molecular distortion which describes the conformational change is not localized over the 1–6 bond stretch, but is presumably spread over all atoms in the molecule, and so is the 'pull' which causes the transannular bond to vary.

Molecular mechanics, for the annulenic systems, gives two distinct minima, one for the open- and the other for the closed-bond system, but is hardly able to give insight on the interconversion path. It does however reproduce satisfactorily the molecular dimensions (table 2), and also reproduces the trend in stability of annulenic vs. norcaradienic forms (see figure 6) (Favini *et al.* 1981 a).

4. Crystal mechanics

In condensed phases an organic molecule experiences a potential field which is generated by its neighbours, and which, to a first approximation, good in principle only for apolar substances, is given by

$$E = \sum_i \sum_j A \exp(-BR_{ij}) - CR_{ij}^{-6} \tag{5}$$

where i runs over atoms in the molecule, and j labels the surrounding molecules. One can immediately see how the breakdowns mentioned in the foregoing section are to be done.

It is amazing how much sound information can be extracted from this handy, easily computer-programmable formula. It can be used to predict equilibrium crystal structures, just as the molecular self-potential is used to calculate equilibrium molecular structures; but a skilful application will also give insight into dynamical processes. An article in this issue (C. M. Gramaccioli 1987) is devoted to lattice dynamics based on this potential. Here we mention that it also describes quite well motions that drive the molecules far from equilibrium positions in the crystal. In fact, the solid state is not quite a 'thermal death' world, and much interesting chemistry happens there (Gavezzotti and Simonetta 1982, 1987 a, b). Solid-state processes

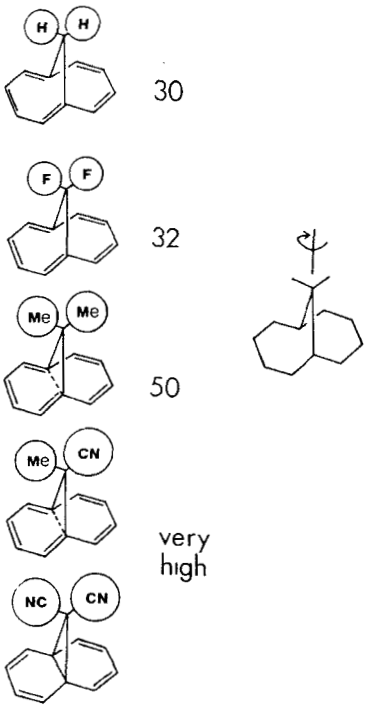


Figure 7. Barriers to molecular rotation (kcal mol^{-1}) in the crystal for substituted annulenes. Circles are intended to give a hint of substituent bulk.

develop their own structure–activity relationships: take, as the simplest example, rigid-body molecular rotation, which is widespread in organic crystals, and often a harbinger of mesogenic power. Figure 7 shows the relationship between the calculated barrier to rotation in the crystal and the bulk of the bridge substituents. Notice that the methano- and difluoro-derivatives show the same behaviour although their crystal structures are quite different, while the dimethyl and methylcyano derivatives behave differently although their crystal structures are isomorphous. Thus, the ease of rotation is a molecular, rather than a crystal property (Bianchi *et al.* 1986).

Finally, organic crystals do react. The potential in equation (5) can be used to predict the motions of the reacted fragments in their crystal cage (an extreme solvent effect). For example, the position of CO_2 molecules after the reaction

$$R-C\begin{matrix}=O & O=\\ -O & O-\end{matrix}C-R' \rightarrow R+R'+2\ CO_2$$

was found in this way (Bianchi and Gavezzotti 1986, Gavezzotti 1987).

5. Conclusion

We have outlined a few examples of how structural analysis can be used in chemistry. This has been the lifelong business of Massimo Simonetta. Rather than conclusions, this article is meant to offer perspectives and opportunities for the future.

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