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Crystal Chemistry in Organic Solids

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I. Introduction

Studies of molecular structure have been traditionally carried out in all three states of matter—gaseous, liquid, and crystalline. On the other hand, chemical reactivity studies have focused on the two states that possess a relevant molecular freedom, relying on the principle that reaction requires mobility. Highly condensed media, in which the molecules are held in fixed orientations, however, display a selectivity that is unimaginable in solution or gas-phase experiments, while molecular motion in solids may not be so restricted as it might be thought.

A common view among chemists, and even X-ray crystallographers, is that a molecular crystal is made up of frozen chemical entities that can at most undergo very small translational and librational motions. This is because most of the solid-state investigation techniques, as well as the theoretical models for the interpretation of their results, see the molecules in such a way. There is on the contrary a vast selection of cases in which this still-life picture does not apply, and there is reason to suspect that the number of these cases might be higher than is actually reported, given the fact that many investigators regard large molecular motions in crystals as an unlikely nuisance. Also widespread among organic chemists is the idea that solid-state re-

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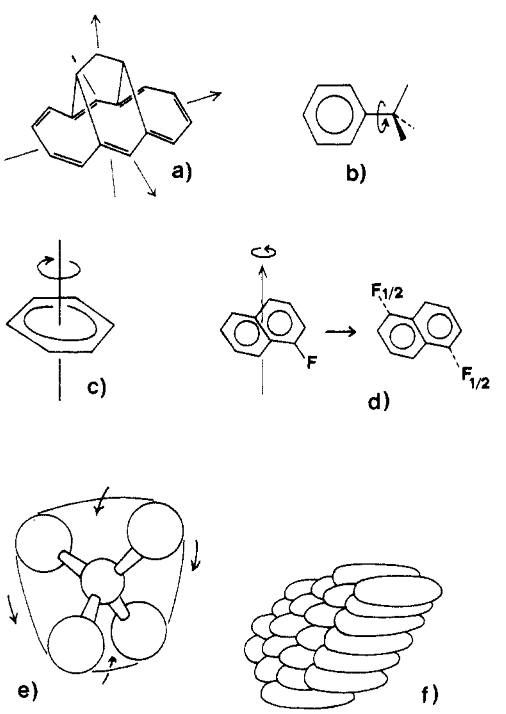


Figure 1. Types of molecular motions in crystals: (a) rigid-body libration around inertial axes; (b) methyl rotation; (c) reorientational jumps of the whole molecule, without production of disorder; (d) the same as (c) with production of a disordered crystal structure; (e) *tert*-butyl derivatives, globular molecules that may rotate in plastic phases; (f) schematic of a liquid crystal (only partial one- or two-dimensional order is preserved), with cylinder-shaped molecules.

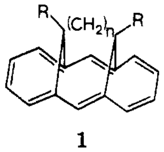
activity is virtually nonexistent and hardly worth investigating. Much information in this field is probably lost as crystals left alone for long periods and found altered or changed in color are discarded as deteriorated, while they might as well have undergone a remarkable solid-state process.

It is the purpose of this paper to (i) sketch briefly the main types of molecular processes in the solid state, (ii) review recent experimental findings, and (iii) describe some simple theoretical approaches useful in the rationalization of known experimental facts and in the prediction of possible crystal reactivity. The most important goal would be establishing the concept of organic crystal chemistry as a more challenging one than it is now in organic chemistry.

II. Molecular Processes in the Solid State

A. Thermal Libration

The atoms of a molecule in a crystal obviously undergo thermal motions. A case of particular interest is that of rigid molecules. Many molecular systems can be so classified; flat molecules like the benzenoid aromatics, and rigid-cage molecules as the bridged annulenes 1[1,2] (see also Figure 1a) are appropriate exam-



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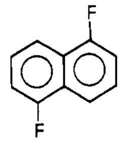
ples. The oscillations of rigid molecules in crystals are best described in terms of amplitudes of libration about and translation along inertial axes. In X-ray crystallography, a rigid-body analysis based on thermal motion ellipsoids has been developed.[3] The frequencies of lattice vibration modes can be measured in the far-infrared range. Even if they do not cause disruptions of the molecular or lattice edifices, such motions may be important to crystal chemistry, especially when their amplitude is unusually high. A sizeable translational amplitude in one particular direction may forecast large displacive motions at higher temperatures, or a large librational amplitude about an axis may correspond to an incipient rigid-body reorientation.[4] Librational energy profiles can be calculated and compared with root mean square librational amplitudes from X-ray analysis[5] (see also section IIIC).

B. Reorientations

There are cases in which the entire molecule or a particular group of atoms is allowed to undergo rotations or translations. As a first example we may mention methyl group rotation (Figure 1b); when the motion is not hindered by a substantial intermolecular potential, methyl groups can rotate in the crystal, since intermolecular constraints are not severe. The point is illustrated by compounds $(CH_3)_3CX$ (X = OH, SH, NCO, CHO, NH_2, OCH_3), where the barriers to methyl rotation range from 3.96 to 4.71 kcal/mol[6]—values that are quite close to the gas-phase ones. Substituted benzenes are good examples of almost free rotation of methyl groups; in hexamethylbenzene, the barrier is 1.9 kcal/mol at 75 K.[7] Depending on the relative population of molecules at rest and of rearranging molecules, the X-ray picture of rotating groups may be blurred. For instance, methyl H's in *N*-methylurea show as disordered in the crystal due to rotation.[8] On the other hand, in 1,1,1-triphenylethane the intramolecular barrier is high[9] and the position of H atoms is sharply detected in the crystal by X-rays.[10] A systematic investigation of the intermolecular potential in the rotation of methyl groups in organic crystals reveals barriers ranging from 0.2 to 11 kcal/mol.[11]

Flat molecules can undergo rotational rearrangements in the crystal, as does benzene, that rotates in its molecular plane (Figure 1c); many benzene derivatives follow this example, but also much larger molecules have been found to rotate in the crystal (see ref 12 and references therein), even at temperatures far below their melting points. The ability of X-rays to detect such motions is limited, though it is possible in some cases to analyze the unusual features that result (non-Bragg or diffuse scattering). The structure determination will show disorder if the jump frequency is in the correct range and the structures produced by rotation are distinguishable; thus, the benzene crystal, in which the molecules undergo 60° rotational jumps, does not show as disordered,[13] nor does 1,5-difluoronaphthalene (**2**),[14] in which the jumps are 180° ones in the molecular plane. 2-Fluoronaphthalene (**3**) jumps in the same fashion, but the crystal structure does show disorder in the position of the F atom[15] (see Figure 1d). Other cases of hindered rotation in the crystal are those of the cyclopentadiene units in ferrocene (**4**), whose structure is partially disordered at room temperature,[16] or of the benzene rings in dibenzenechromium (**5**).[17]

If the reorientational motions become quite easy and widespread, plastic crystals are produced which exhibit



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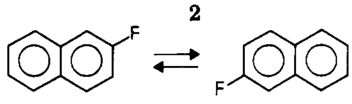

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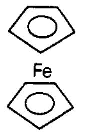

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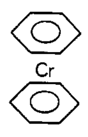

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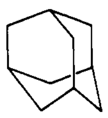
a preliquid behavior. This is likely to happen in crystals of globular or cylindric molecules (Figure 1e), for which it is usual to have a plastic phase near the melting point. Adamantane (6) has been the object of many studies (see, e.g., ref 18, and references therein), though the X-ray diffuse scattering analysis[19] casts doubt on its plastic crystal nature; its derivatives[20,21] and bullvalene (7)[22] are also good candidates to form plastic phases. In crystals of small molecules, such behavior is quite common (see acetylene[23] or CCl$_4$[24]), and *tert*-butyl derivatives also often meet the requirements for the formation of reorientational plastic phases.[25] A somewhat different case is that of succinonitrile, with a complex admixture of trans–gauche isomerization and reorientation of the whole molecule around the CH$_2$–CH$_2$ axis in its plastic phase.[26]



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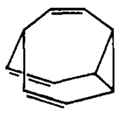

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When some of the translational symmetry of the crystal is also lost and rotation becomes very fast, the liquid crystal state is reached (Figure 1f); 5% of all organic compounds are so transformed near or at their melting points.[27] Reference 27 is an excellent review of the unusual properties of these systems, whose applications in technology are becoming more and more widespread.

Molecular reorientations in crystals can be detected by NMR second-moment measurements; when a change in line width as a function of temperature is detected, a molecular motion is revealed, whose activation parameters can be calculated from Arrhenius-like plots of the spin–lattice relaxation time vs. the reciprocal of *T*. Reference 28 is an example of application of this technique to large aromatic systems, and ref 29, to halogenated aromatics. For adamantane, activation parameters are[30] $\Delta H^{\ddagger} = 5.8$ kcal/mol, $\Delta S^{\ddagger} = 15.5$ cal mol^{-1} deg^{-1}. Table I collects some more examples of measured activation energies.

TABLE I. Experimental Potential Energy Barriers to Rigid-Body In-Plane Reorientations in the Crystal

compound	barrier, kcal/mol
benzene	3.5–4.2[a]
1,2-dichlorotetramethylbenzene	7.7[b]
hexamethylbenzene	6.4–6.7[c]
1,2,3-trichlorotrimethylbenzene	10.2[b]
2-fluoronaphthalene	11[d]
1,5-difluoronaphthalene	13.3[e]
1,8-difluoronaphthalene	11.7[e]
biphenyl	23[e]

[a] Reference 12. [b] Brot, C.; Darmon, I. *J. Chem. Phys.* **1970**, *53*, 2271. [c] Reference 7. [d] Chanh, N. B.; Haget, Y.; Dufourcq, J.; Lemanceau, B. First European Crystallographic Meeting, Bordeaux, The European Committee of Crystallography, 1973. [e] Reference 29.

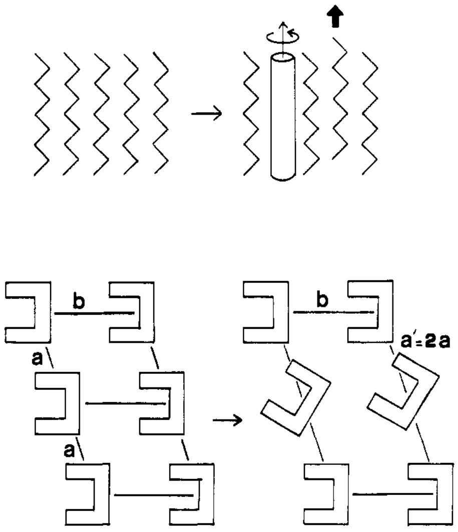


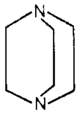
Figure 2. Types of phase transition: (above) order–disorder as in straight-chain alkanes, with rotation and small translational displacements; (below) cell edge doubling due to a soft-mode transition.

C. Phase Transitions

The ability of a substance to crystallize in different crystal forms gives rise to polymorphism. There are reasons to believe that polymorphism is more the rule than the exception in crystals of small molecules (ice is the first example that comes to mind) and in macromolecules (polymorphism and crystal growth are major problems in protein structure determination by X-rays). We shall focus here on medium-size organic molecules, where polymorphism is fairly common, and limits to its occurrence are less restrictive than the experimental difficulties in its detection. Temperature or pressure variations may induce phase transitions, but variable-pressure or -temperature X-ray structure analyses are quite sparse in the literature, even with today's facilities for temperature control in computer-assisted diffractometers. Polymorphism can be intriguing to the organic chemist, since it may not be at first clear whether different crystals are different compounds or just polymorphs of the same compound.

The actual mechanisms of phase transitions in organic crystals are elusive. The ranges of stability of each phase are usually determined from the appearance of anomalies in the heat capacity/temperature curves, but a phase transition can be detected by an abrupt change of optical, electrical, or mechanical properties of the sample. By use of X-ray diffraction, the intensity of Bragg reflections of one phase can be monitored, and the appearance of the reflections of the new phase as it is formed at the transition temperature can be revealed, if the transition is a single-crystal to single-crystal one and the orientation of both phases in the measurement apparatus can be determined. In powder diffractometry, θ angles of diffraction lines can be monitored as a function of *T*. It must be stressed that metastable phases are commonplace, since many phase transitions are quite sluggish.

Many crystals exhibit order–disorder transitions without change in the basic crystallography. Upon heating, some rotational or diffusional motion sets in, as exemplified by the case of *n*-alkanes: in *n*-tritriacontane, rotation of the chain, kink formation, and translational diffusion of sheets of molecules are successively triggered as the temperature increases[31] (Figure 2). Alternatively, simple relationships exist between the cell parameters of different phases, as, for example, in cyclohexane, for which the high-temperature plastic phase is simply related to the low-temperature structure.[32] The same happens in triethylenediamine (**8**).[33,34] Of particular interest is the case of chloranil (**9**), in which the energy of one particular libration mode shows a discontinuity about 90 K,[35] a temperature at which a phase transition takes place such that two lattice parameters are doubled. Such a libration mode is called a soft mode. The symmetry-breaking molecular motion has been identified as a rotation in the molecular plane (see, for a scheme, Figure 2); fluoranil has a different packing structure,[36] and there is no report of soft-mode transition.



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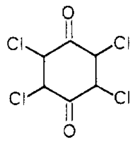

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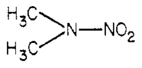
Polyphenyls undergo soft-mode transitions, the involved rotation being around inter-ring bonds.[37] Different from these examples, in that the soft mode is a complex mixture of molecular motions, is the case of *N*,*N*-dimethylnitramine (**10**), for which the crystal structure has been determined at seven different temperatures.[38]



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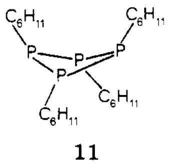
In the majority of cases, the crystallographic relationships between polymorphs are not straightforward (see the scheme in Figure 3). In the case of furan, one phase is rotationally disordered (above 150 K) and another is ordered, but there is no immediate relationship between cell dimensions and space groups.[39] Tetracyclohexylcyclotetraphosphine (**11**) has at room temperature two different tetragonal crystal structures, in which the molecular structure is the same, that are related by rotation of the molecule around one inertial axis with a major change in unit cell edges but not in cell volume.[40,41] *p*-Dichlorobenzene has three different crystalline phases, all of which can exist at 100 K.[42] It is not clear how the structures can interconvert, but it is quite possible that extensive unpacking and repacking takes place at the transition boundary.[43,44] On the other hand, sometimes a phase transition is reversible and a simple mechanism for the dynamics of interconversion can be found; this seems to be the case for *p*-chlorobenzamide, whose low-temperature form has been fully elucidated,[45] while the high-temperature disordered phase has been interpreted by an analysis of the diffuse scattering.[46]



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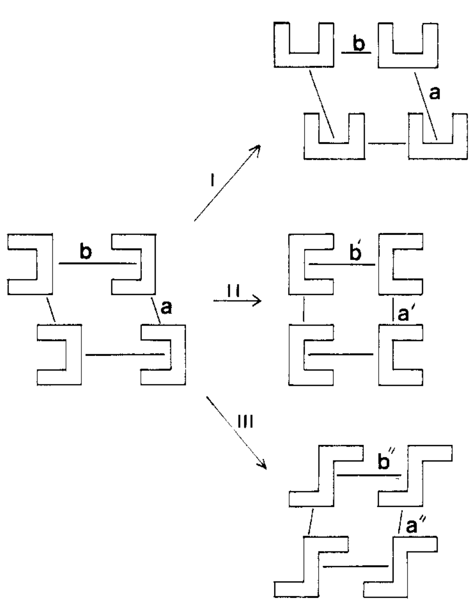

Figure 3. Types of phase transitions: (I) by simple rotation without disruption of the basic lattice geometry and symmetry; (II) complex transition without a simple relationship between the two lattices; (III) phase transition accompanying a conformational change.

The so-called conformational polymorphism is caused by different conformations of the same molecule in different crystal phases (see Figure 3, case III). Torsional isomerism is frequently present, since torsional intramolecular librations are usually soft and deformations can be sensitive to weak intermolecular forces. Iminodiacetic acid (**12**) has three different crystalline forms in which bond angles and distances agree but torsional angles differ.[47] In a large molecule as **13** there are two conformationally distinct crystal phases at room temperature.[48,49]

$$\mathrm{HOOCCH_2NHCH_2COOH}$$

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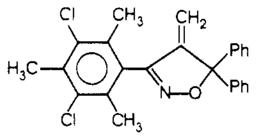

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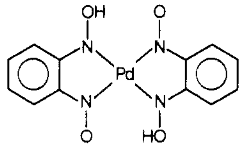

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Charge-transfer dimers and metal complexes with organic ligands form a vast class of compounds with peculiar properties, a field that would deserve separate reviewing. To quote just one example of a peculiar phase transition, we mention the Pd complex **14**, whose crystal structure has been studied down to 19 K by single-crystal X-ray diffraction.[50] The low-temperature phase was shown to be formed by a distortion in the molecular stacking planes that assume a wavelike shape as the periodicity along *a* becomes equal to four of the high-temperature cell edges.

D. Reactions

1. General

The subject of solid-state organic reactivity has been reviewed more or less up to 1975.[51-53] The following discussion will be carried out along the lines laid down in these reviews, to which the reader is referred for many detailed examples; a survey of stimulating developments will then be given.

Solid-state reactions have been reported since the beginning of modern organic chemistry; a major fraction of the reactions that occur in solution 60–100 °C below the melting point of the reactants are said to be likely to occur also in the solid state.[52] In contrast to gas- or liquid-phase reactions, reactants are usually blocked in a fixed orientation and are subject to a highly anisotropic potential in the solid, so that high selectivity is to be expected; the word "topochemistry" has been minted to describe this phenomenon. Unimolecular reactions are usually easier than processes that require an encounter of two or more chemical entities, unless the crystal geometry is such that reacting counterparts are favorably juxtaposed; thus, there are cases in which proper orientation of reacting groups speeds up the reaction in the crystal with respect to solution or the melt. When this is not the case, solid-state reaction rates are slower than solution ones—the month being a more appropriate time unit than the hour. In any case, the kinetics of solid-state reactions is strongly biased by the inhomogeneity of the medium, diffusion and/or mother–daughter separation processes being often the rate-determining steps, so that it is quite unusual to have a simple dependence of reaction rate on reactant concentration.

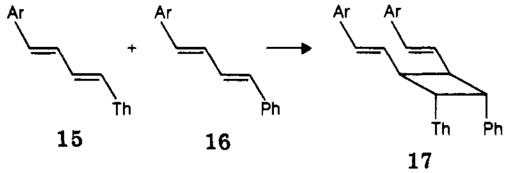
A basic difference between solution and solid-state reactivity is that while the former is crucially dependent on the electronic properties of the reactants, reactivity in crystals depends on a balance between steric packing factors and electronic properties. There are cases of similar behavior of different compounds in isostructural crystals and of different reactivity of the same compound in different crystal phases, only the phase that allows a favorable topochemistry being reactive. Thus, the molecules that surround a reacting site in a crystal provide a sort of extreme "solvent effect". This effect is at work both in thermal and in photochemical solid-state reactions.

Another essential point in the investigation of solid-state reactivity is the relationship between "mother" and "daughter" crystal structures and between both and the transition state. Product molecules can form as a solid solution in the reactant matrix and then crystallize out as separate individual product crystals, or a stable product can be formed at once at the phase boundary (the reaction front). In the latter case, the crystal faces of the mother that are formed more easily (being more tightly packed) when the mother crystallizes are expected to be less apt to reaction propagation if the reaction is such that unpacking of the reactant crystal and repacking into the product must take place. Cases of single-crystal to single-crystal processes without disruption of the lattice are rare, but if a definite crystallographic relationship exists between mother and daughter, the term "topotaxy" applies. At the other extreme, the product can be polycrystalline, amorphous, or even liquid or gaseous; this introduces the possibility of heterogeneous reactions. Examples are known of reactions between crystals and gases, or of reactions in which gaseous products (usually simple two- or triatomic molecules) can diffuse in or escape through channels in the reactant lattice.

A major problem in solid-state reactivity is monitoring the reaction process. This is usually done by spectroscopic or diffraction techniques, though in some cases it is possible to actually observe the movement of reaction fronts in single crystals in a microscope. Another critical point is initiation; reaction is often observed to start at defects or near impurities, which are likely to provide pockets of free space for molecular motion. Sometimes it is possible to induce a reaction in a perfect crystal sample by touching it with a pin.

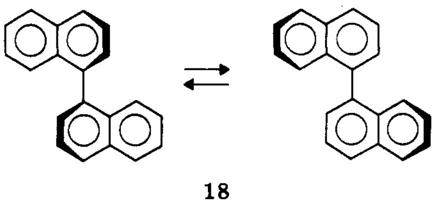
2. Some Examples

A classical case of topotaxy is that of the dimerizations and polymerizations in dienes. Years ago, Schmidt and co-workers[54] discovered a particular topotaxic reaction of substituted butadienes in which mixed crystals of 15 and 16 gave the adduct 17 in an optical synthesis in which the sole chiral element was the space group of the crystal in which the reaction takes place. The requirements for using this kind of photopolymerizations to perform asymmetric syntheses were later analyzed[55a] and exploited systematically by Lahav and co-workers (see, e.g., ref 55b). Such facts must have consequences on our ideas on how asymmetry was first introduced in prebiotic material. In another example of spontaneous generation of optical activity, racemate single crystals of 1,1-binaphthyl (18)



15 16 17

Ar = aryl; Th = thiophene; Ph = phenyl



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were reported to undergo, in the temperature interval 76–145 °C, a solid-solid thermal reaction to give an eutectic mixture of optically active isomers.[56] Just what are the effective molecular and crystal rearrangements was not clear, though rotation about the inter-ring bond is clearly required. Reinvestigation of the reaction[57] revealed the possible participation of a solid–vapor equilibrium.

The topochemical polymerizations of diacetylenes are another class of widely studied solid-state reactions.[58,59] These reactions are of great interest to polymer synthesis and materials science because the polymerization

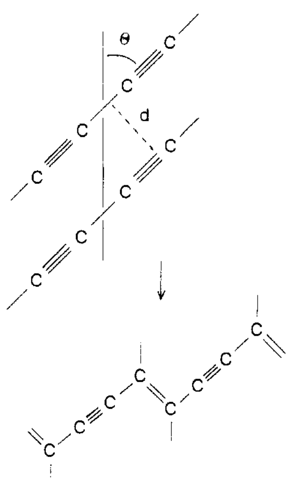

Figure 4. Angle θ and distance d between two adjacent diacetylene chains in crystals that may undergo polymerization. Reaction takes place only if $\theta < 45°$ and $d \approx 3.4$–4.0 Å. See ref 58 and 59.

is a lattice-controlled 1,4 addition in which the polymer has a planar, all-trans configuration. A first example of a theory of solid-state reactivity is represented by the remarkable crystal structure–crystal reactivity relationship shown in Figure 4. Recent energetic studies[60] on the thermal polymerization of **19** gave an activation

$$\mathrm{MeC_6H_4SO_3CH_2C{\equiv}C{-}C{\equiv}CCH_2SO_3C_6H_4Me}$$

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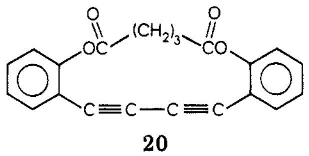
energy of 22.5 kcal/mol. Various derivatives of this sulfonic ester have been systematically investigated for solid-state reactivity (see ref 59 and references therein). The cyclic diacetylene **20** has two crystal phases[61] in one



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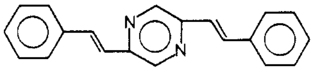
of which the conditions[58] for intermolecular polymerization (see Figure 4) are met while in the other they are not. Polymerization in compounds other than the diacetylenes may be exemplified by the photoreaction in one crystal phase of distyrylpyrazine (**21**)[62] or by the



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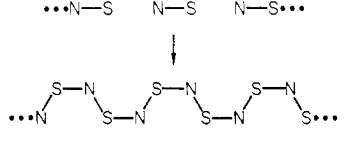
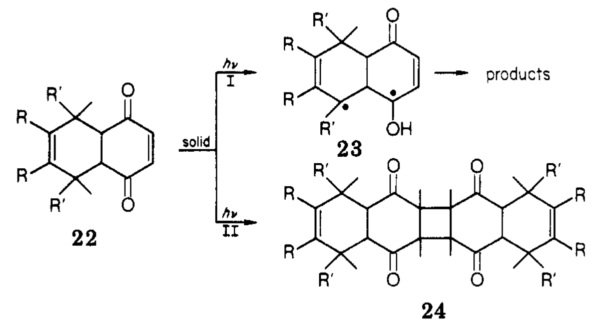
remarkable solid-state process:[63]



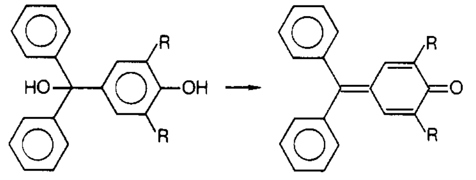
This reaction is thermally induced and has a high degree of topotaxy. The intermediate is a radical species, as demonstrated by the evolution of the intensity of the ESR signal. The resulting polymeric material has some very peculiar conduction properties, in some ways similar to those of a metal, due to electron delocalization (an "organic metal").

A striking example of change in reactivity with change in packing is provided by the system[64] shown in Scheme I. Out of eight different derivatives of **22**, five were found to give reaction I, and three the dimerization II. Correspondingly, two different packing modes were recognized for the reactant crystal; the one that actually undergoes dimerization provides a juxtaposition of the C=C double bonds in two neighboring molecules. Scheffer has recently given an account[65] on this and other examples of structure–reactivity relationships in solid-state photochemical reactions.

SCHEME I



Proper orientation of the reactants in the crystal is the case also for the reaction of the diol **25**, in which a head-to-tail arrangement favors intermolecular dehydration to **26**.[66] **25a** and **25b** are isostructural, but **25b**



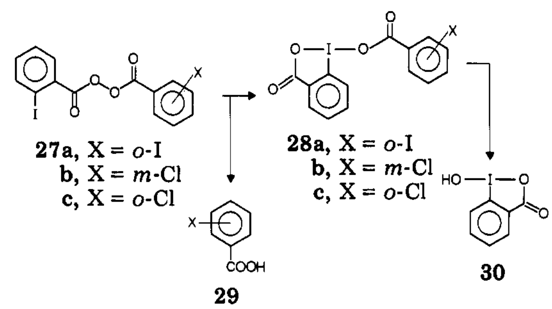
25a, R = CH_3
b, R = Br

26

reacts much faster than the methyl derivative, possibly owing to the increased acidity of the phenolic proton (an intramolecular, lattice-independent factor). The fuchsone **26** has three polymorphs,[67,68] a $P2_1/c$ racemate and a $P2_12_12_1$ chiral phase (that show a closely similar organization of molecular sheets), and a third achiral phase with no immediate correspondence with the other two. Only the $P2_12_12_1$ phase is formed during the solid-state process that was found to obey a formally zero-order kinetic law.

An example of exhaustive study of such packing–reactivity relationships is the work carried out by Gougoutas and co-workers on the solid-state interconversions within the system (see Scheme II). The crystal structures of **27a** and **28a** were first analyzed.[69,70] The product benziodoxolin **28** crystallizes in two polymorphs, only one of which is formed in the solid-state reaction. Interconversion between the two polymorphs and the **27**–**28** reaction require breaking of the peroxide bond and formation of bonds with near-neighbor molecules; the relationships between the orientations of reactant and product crystals were investigated,[71] and possible paths, at a molecular level, for the transformation in the crystal were analyzed. A mechanism based on alternate flipping of molecular moieties was proposed.[72] Further studies[73–75] revealed that the iodobenzoyl peroxides **27** pack in two basic arrangements (as a function of the nature and the position of the substituent X), one of which reacts preferentially to give the benziodoxolines **28** while the other leads to the

SCHEME II



formation, with the intervention of atmospheric moisture, of benzoic acids; for instance

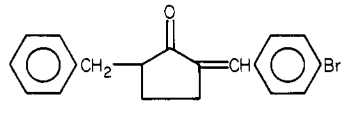
$$\mathbf{27a} \xrightarrow{\text{room temp}} \mathbf{28a}$$

$$\mathbf{27b} \xrightarrow{\text{room temp}} \mathbf{30} + \mathbf{29}\ (X = m\text{-Cl})$$
$$\mathbf{27b} \xrightarrow{60\ ^\circ\text{C}} \mathbf{28b}$$

Another striking example of selectivity was discovered:[76]

$$\mathbf{27c} \xrightarrow{\Delta} \mathbf{28c},\ \text{monoclinic}$$
$$\mathbf{27c} \xrightarrow{h\nu} \mathbf{28c},\ \text{triclinic}$$

In all the above transformations, topotactic relationships were often clear, but sometimes they were obscure. A seemingly perfect topotactic experiment has been reported by Thomas and co-workers:[77] the photodimerization of 2-benzyl-5-p-(bromobenzylidene)-cyclopentanone (31) was followed on a single crystal by taking Weissenberg films before and after reaction. Neither the alignment of the crystal nor the oscillation angles had to be changed to obtain the diffraction pattern from the crystal of the dimer that has the same cell parameters but different diffraction intensities.



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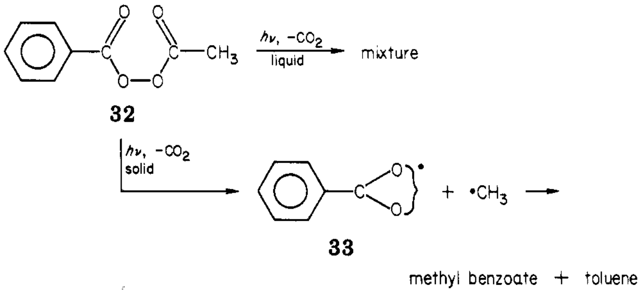
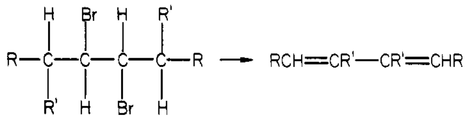
The peculiar kind of reactivity observed in solids has suggested that molecular crystals can be convenient vehicles to perform selective syntheses that mimic enzymatic reactions; this principle was illustrated by the stereospecific hydroxylation of desoxycholic acid.[78] As for selectivity, another good example is the decomposition of crystalline acetyl benzoyl peroxide (32).[79] In this case, deuteration studies ruled out intermolecular processes, and X-ray and ESR studies revealed that not only the reaction products are unique in the solid (while a mixture is obtained in solution), but the methyl radical is capable of discriminating between the two oxygens of the benzoyloxy radical 33. The reasons for this discrimination were only partially found in the analysis of crystal packing, however. More important was found to be the search for an escape path for CO_2. ESR was instrumental in determining the possible motions of the methyl group.



Another example of heterogeneous reaction is the dehydrobromination of dibromobutanes 34 by gaseous ammonia or amines:[80]



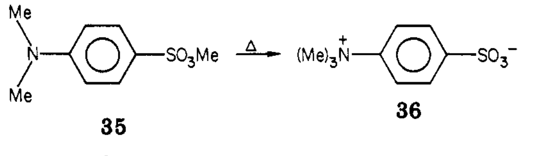
$$\text{RCH}(\text{R}')\text{–CHBr–CH}_2\text{–CBrR}'\text{–R} \longrightarrow \text{RCH=CR}'\text{–CR}'\text{=CHR}$$

34, R = CN, R′ = H

Factors in the solid-state process are (a) diffusion of NH_3 in the crystal that takes place preferentially at defects or near impurities, where the reaction is likely to be initiated, (b) the fact that the less dense the packing, the higher the diffusion rate, the faster the reaction, (c) the possibility that the proton to be extracted by ammonia protrudes out of a layer (which implies preferential reaction at certain faces); and (d) the cohesion energy between layers, since the looser the packing forces between layers, the easier it is for one reacted layer to detach from the crystal to allow further progress of the reaction by contact with an unreacted layer. All these factors were discussed in terms of the crystal structures of various derivatives.

The effect of packing on heterogeneous reactions is further illustrated by the case of the decarboxylation of p-aminosalicylic acid;[81] the crystal structure of this compound is such that molecular layers are approximately perpendicular to the $(10\bar{2})$ face and parallel to the (100) face. Correspondingly, the CO_2 that forms inside the crystal has been observed to escape preferentially from the $(10\bar{2})$ face. In the loss of HCl by p-aminosalicylic acid hydrochloride,[82] the escape of HCl was also found to be dependent on the crystal habit of the sample, and in the reaction between gaseous Cl_2 and solid 2-methylphenol,[83] 6- or 4-chlorinated derivatives were obtained depending on how the crystal samples had been cut.

Thus far, very few direct comparisons of reaction rates in liquid and condensed phases have been presented in the literature. At least one case of specific enhancement of the reaction velocity by proper orientation of the reacting groups in the crystal with respect to either the melt or solution has been described:[84]



Concentrated solutions of 35 were quite unreactive, while solid 35 on standing at room temperature was converted to 36 by 78.8% in 17 days. The crystal structure determination showed that the OCH_3 group in one molecule of 35 points directly toward the $N(CH_3)_2$ group of a neighboring molecule, thus favoring the intermolecular solid-state process.

III. Theoretical Approaches

A. General Remarks

A quantitative theoretical study of the molecular processes in organic crystals requires a model for the crystalline potential field. The potential energy of a crystal made up of discrete entities, in which no essentially ionic bonds are present, can be empirically described by simple functions of intermolecular distance. The types of forces that are at work in such crystals are (i) repulsions between closed shells of electrons (the potential has the form $E = A\exp(-BR)$ or $E = A'R^{-n}$, where A, A', and B are empirical parameters, R is the distance between repelling centers, and n is of the order 9–12); (ii) attractions (of essentially electrostatic nature) between polarization-induced instant dipoles, or London dispersion forces (the potential has the form $E = -CR^{-6}$, C being an empirical parameter); (iii) Coulombic interactions between permanent atomic charges, as resulting from moderate bond polarities, also describable as interactions between time-invariant molecular multipoles calculated from the charge distribution in the molecule; and (iv) hydrogen bonds.

From this list, it appears that molecular crystals may in some cases acquire a partially ionic character. Of course formal charges, as are usually written in organic chemical formulas, have seldom a true meaning in terms of localized electrons in organic molecules.

B. Calculation of Crystal Energies

Potential energy calculations in crystals have the advantage, with respect to liquids or gases, that the position of the molecules does not change on the average with time and can be known from X-rays analyses in full detail. Therefore, a model can be built, comprising a central molecule surrounded by a number of other molecules arranged according to crystal symmetry, and the potential packing energy (PPE) can be calculated for the central molecule by summations of terms i to iv:

$$\mathrm{PPE} = \sum_i \sum_j A\exp(-BR_{ij}) - CR_{ij}^{-6} + \sum_i \sum_j \frac{q_i q_j}{R_{ij}} + E_{\mathrm{HB}} \quad (1)$$

where the index i runs over the atoms of the central molecule and the index j over those of the surrounding ones. If zero potential energy is assumed for the molecule at infinity, PPE is the energy needed to bring one molecule to infinity from the bulk of the crystal. It is to be noted that the centers of repulsion and dispersion forces are usually identified with atomic nuclei. The packing energy, PE

$$\mathrm{PE} = \tfrac{1}{2}\mathrm{PPE} \quad (2)$$

is (neglecting zero-point energy) the energy for the process of bringing a mole of molecules from infinity to contact in the crystal; each molecule thus acquires an energy equal to PPE, but halving is required to avoid counting each contribution twice. This quantity corresponds to the heat of sublimation.

TABLE II. Nonbonded Interaction Parameters for Commonly Occurring Atomic Species[a]

	A	B	C
C···C	71 600	3.68	421
H···H	4 900	4.29	29
O···O	77 700	4.18	259.4
N···N	42 000	3.78	259
Cl···Cl	4 580	2.262	2980
F···F	42 000	4.15	148
S···S	235 000	3.49	2346
C···H	18 600	3.94	118
O···C	75 700	3.91	339.4
O···H	19 500	4.23	88
N···C	55 300	3.73	331.4
N···H	14 400	4.00	91
Cl···C	16 700	2.94	1055
Cl···H	4 560	3.07	322
O···N	57 900	3.97	262.9
S···C	99 400	3.54	847

[a] From ref 86. Energy in kcal/mol, $E = A\exp(-BR) - CR^{-6}$.

The combined effects of forces i and ii are usually designated as "nonbonded interactions". The application of this concept to organic crystals was pioneered by Kitaigorodski (see, for a survey, ref 85). In this line of thought, quantum mechanical arguments are scarce and empirical fitting abundant. The idea that the parameters A, B, and C could be optimized to reproduce observed properties (crystal structures, heats of sublimation, lattice frequencies) began to be exploited. Recently, consistent work in this direction has been carried out, for example by K. Mirsky, who has proposed a pondered list of parameters for commonly occurring atomic species (see Table II).[86] Williams has been working on potentials for hydrocarbons[87] and for chlorine-containing compounds,[88] including also electrostatic contributions, which pose a special problem since the summation 1 includes in principle an infinite number of terms, but must be truncated for practical purposes. In fact, while nonbonded interactions fall off exponentially or with the inverse sixth power of the distance, Coulombic terms fall off as the inverse first power of the distance, so that convergence of the summation series is very slow. Techniques of convergence acceleration have been presented.[89] Where possible, the use of molecular dipoles to represent the charge distribution is computationally convenient.[90] Finally, ad hoc potentials have been proposed for hydrogen bonds.[91,92]

When a rearrangement takes place in the crystal, the associated intermolecular potential energy barrier can be calculated by estimating the variation of PPE along the reaction coordinates. When an intramolecular process accompanies the rearrangement, the total potential energy variation is the sum of the inter- and intramolecular parts. The intramolecular contribution can be estimated by the usual methods (e.g., quantum mechanical ones) that apply in studies of gas-phase conformation and reactivity.

C. Uses of Crystal Potential Energy Calculations

1. *Prediction of Crystal Structures*

PPE calculations enjoyed some popularity among X-ray crystallographers in view of their possible uses in the solution of the phase problem. Direct methods have now taken over, but there still are some cases of unusual or disordered structures in which informations from PPE calculations can be useful. For example, the crystal structure of the zwitterion **36** belongs to space group *Pbca*, but a 50% population of two orientations of the benzene ring has to be postulated to maintain an average symmetry plane[93] (see Figure 5). A simple calculation shows the double-minimum structure of the potential energy profile for phenyl ring rotation (Figure 6); a 35° twist out of the symmetry plane is enough to clear the otherwise impossible H···H contacts in this

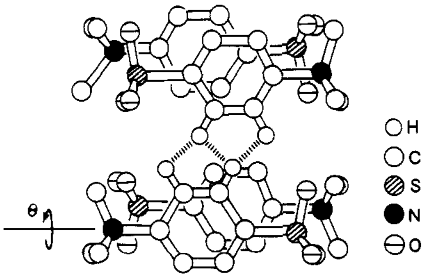


Figure 5. Packing arrangement in the crystal of 36 (from ref 93). The plane of the phenyl rings is a crystallographic mirror plane simulated by 50% occupancy of two orientations of the ring (±35° rotation about the axis shown) needed to clear the short H···H contacts (dashed lines). Angle θ is the abscissa in Figure 6.

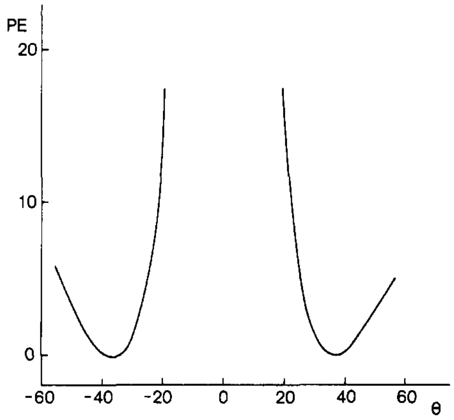


Figure 6. Relative packing energy, PE (kcal/mol) for θ rotation as defined in Figure 5. The two minima correspond to the two orientations 50% populated (found in the crystal by X-ray analysis).

plane. The X-ray picture is thus probably a superposition of diffraction from domains in which the phenyl rings assume each of the two orientations.

The most interesting aspect of the knowledge of reliable crystal potentials is, however, the fact that it opens the way to the calculation of dynamical effects, such as libration, rigid-body rotation, and even, in principle, phase transitions and reactivity. These topics will be briefly considered in the following sections.

2. Small-Amplitude Molecular Motions

These can be classified as either internal or lattice motions. The former are along the normal coordinates of the single molecules; in fact, frequencies are usually similar to those found in the gas phase, but sometimes the influence of the intermolecular potential can produce significant changes. Lattice vibrations can be described as translations and/or librations of the molecules as rigid units (see also section IIA). Rigidity implies little or no coupling between the two kinds of motions; in this case the following treatment (developed by Born and Huang[94] and reformulated by Pawley[95]) applies.

The motion of the molecule in the crystal is described by the six-dimensional vectors:

$$u_i(kl) = U_i(k\mathbf{q}) \exp\{i[\mathbf{q}\mathbf{r}(kl) - \omega(\mathbf{q})t]\} \qquad (3)$$

where $i = 1, 2, ... 6$, $k = 1, 2, ... p$ molecules in the unit cell, $l = 1, 2, ... N$ unit cells in the crystal, and U is the amplitude, $\mathbf{q}$ the wave vector, ω the frequency, and $\mathbf{r}$ the vector from the origin to the center of mass of the molecule. The potential is expanded in a series as a function of the displacement vectors; the first derivatives are identically zero if the molecule is at equilibrium, while derivatives of order >2 are neglected in the harmonic approximation. By double differentiation with respect to time of the displacement vector and use of Newton's equations of motion, the following expression is obtained:

$$m_i\omega^2(\mathbf{q})U_i(\mathbf{q}k) = \sum_{jk'l'} \Phi_{ij}(kl,k'l')U_j(k'\mathbf{q}) \exp[i(\mathbf{q}\cdot\Delta\mathbf{r})] \qquad (4)$$

where the Φ_{ij} are the force constants. All potentials and all potential derivatives are calculated by means of summations over atom–atom terms (eq 1). Solution of the eigenvalue–eigenvector problem implied by eq 4 for each $\mathbf{q}$ value is then carried out. When $\mathbf{q} = 0$, the eigenvalues are the lattice frequencies, which can be measured by IR or Raman spectroscopy. From the eigenvectors, the "dynamical" mean square displacements can be computed,[96] as well as the translational, librational, and correlation tensors; in usual crystallographic work these tensors are obtained from the values of mean square displacements in structure refinement and are used to obtain "corrected" bond distances and bond angles.[3] When $\mathbf{q}$ is different from zero (that is, is allowed to vary along a direction in the first Brillouin zone), phonon dispersion curves are obtained, and from these the density of states, which allows the evaluation of thermodynamic functions for the crystal. This has been accomplished for a number of crystalline hydrocarbons with excellent agreement with experiment.[97] By minimization of the crystal free energy, cell dimensions can be calculated.[98]

3. Large-Amplitude Molecular Motions

The motions so far described occur in ordered, tightly packed crystals, far from the melting point and in presence of potential energy minima shaped as narrow wells, with steep "walls". In different situations, when one or more walls of the potential energy become flatter, the thermal motions become more and more important and views of the molecules, as obtained by means of X-ray diffraction, become progressively blurred as one goes from ordered to disordered crystals (see also section IIB). Disorder can be static, when the molecules assume more or less randomly different orientations at the same lattice site. The potential energy is a many-minima surface, with high barriers between the minima. Dynamical disorder arises from jumps of the molecules through the potential energy barriers that separate those minima, the barriers being lower.

The pairwise potential technique (eq 1) can be applied to the study of dynamical effects involving large displacements. Two models have been built to perform these calculations. In the first one[99] the crystal was built up of rigid motionless molecules surrounding the one that undergoes the rearrangement (usually a rotation about one of the principal axes of inertia). In the second one[90] the surrounding molecules are allowed appropriate librations while the central one rearranges. Of course the cluster of molecules that simulates the crystal must be large enough to allow the calculation of a substantial amount of the barrier and to preclude undue freedom to the librating molecules, due to missing neighbors. The cluster is therefore modeled in two shells, the first including the cooperating molecules

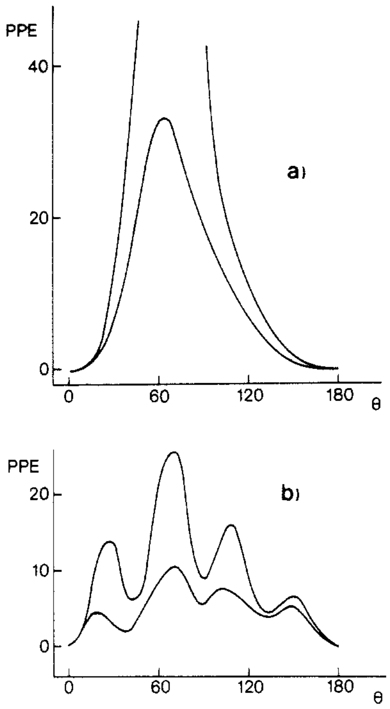


Figure 7. (a) Rotations of 2-fluoronaphthalene in the crystal: relative PPE (kcal/mol) vs. angle of in-plane rotation, *θ* (lower curve) with and (upper curve) without cooperation effects. (b) The same for in-plane rotation in 1,5-difluoronaphthalene. See ref 90 and 99.

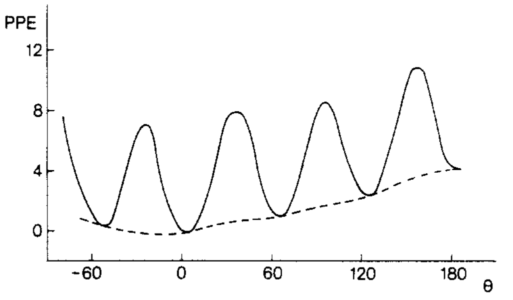


Figure 8. In-plane rotation of the 1,2,3-trichlorotrimethylbenzene molecule in the crystal. The steric energy has a minimum every 60°, but the electrostatic dipole energy (dotted line) is attractive at zero and repulsive at 180° (kcal/mol units). See ref 90.

and the second ensuring that these experience much the same field as the central one. The energy barriers obtained from these calculations agree fairly well with experiment, especially when model II is used. Table III collects some examples of calculated reorientational barriers; besides the quantitative aspects of such calculations, even qualitative indications can be valuable to the X-ray crystallographer, in that they provide information on the number and population of potential energy minima in crystals. Some energy curves for substituted naphthalenes are shown in Figure 7. The effect of the inclusion of dipolar energies is shown in Figure 8.

Other examples of such calculations can be found in ref 12 and 100; the energies involved in molecular translations in crystals have also been considered.[101]

TABLE III. Calculated PPE Barriers to Rigid-Body In-Plane Rotations in the Crystal[a]

compound	barrier, kcal/mol
benzene	3.4
p-dichlorobenzene	29
hexachlorobenzene	7.4
hexamethylbenzene[b]	3.0
1,2,3-trichlorotrimethylbenzene[c]	11
1,2-dichlorotetramethylbenzene[b]	4.9
pyrazine	3.7
chloranil	41
2-fluoronaphthalene[c]	33
1,5-difluoronaphthalene[c]	11
1,8-difluoronaphthalene[c]	22
azulene	40
biphenyl[c]	44
cyclohexane I (plastic)	10

[a] Unless otherwise stated, calculations have been done with the nonbonded parameters of Table II, without inclusion of cooperation effects. [b] From ref 99. [c] From ref 90. The barriers taken from refs 90 and 99 have been doubled in agreement with criticism (Busing, W. R. *J. Phys. Chem. Solids* **1978**, *39*, 691) to the use of 0.5PPE instead of PPE to calculate energy profiles (see also ref 12). Laxity on this point was the result of an essentially qualitative mental attitude in early explorations of the field. See, e.g., the discussion in ref 90 on electrostatic energies, to which an empirical rescaling factor (that happened to be equal to 2) had been applied. See also the discussion in ref 109 on the case in which more than one molecule in the crystal model is allowed to move.

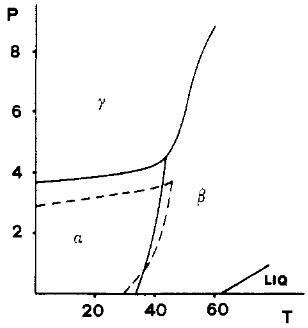


Figure 9. Phase diagram for N_2 (solid line: after Stewart, J. W. *J. Phys. Chem. Solids* **1956**, *1*, 146) and zone where discontinuities were found in calculated unit cell parameters as a function of *T* and *P* (dashed line: after ref 102). *P* in kbars, *T* in K.

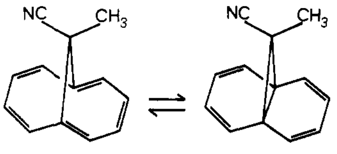
4. Phase Transitions

In principle, phase transitions between ordered structures could be studied by comparison of free energy/temperature curves for the two phases. In some examples a phase diagram can be obtained through the observation of anomalies in the free energy/lattice parameter curves at different temperature or pressure. A calculated phase diagram for solid nitrogen has been obtained in this way[102] (Figure 9) and satisfactorily compared with the experimental one. Another example can be found in the case of anthracene crystals;[103] a new phase had been identified by means of transmission electron microscopy, and a number of possible structures were derived on the basis of packing calculations, but the choice between the various possibilities was based on lattice dynamical computations which showed that only one of the statically determined structures was dynamically stable. PPE calculations have been used to investigate the relative stabilities of barbituric acid derivatives in various crystalline modifications.[104] Similar calculations for solid ethane proved that a previously reported crystallographic X-ray study was incorrect and allowed a new, more stable structure to be proposed.[105] Packing energy evaluation was used to support spectral assignments in the polymorphs system of bromoform[106] and to examine the relative stabilities of the three phases of *p*-dichlorobenzene.[107] Finally, conformational polymorphism has been studied by a mixture of PPE and quantum chemical calculations.[108]

Much more complex is the task of finding a detailed pathway, at a molecular level, for the dynamics of phase transitions. There have been but a few attempts in this direction. In the case of aliphatic chain molecules, phase transitions have been described in terms of the successive onset of rotational jumps, of translational jumps in the chain direction, and of the creation and diffusion of intrachain defects.[31] Intermolecular energy calculations for crystals of *n*-alkanes allowed a semiquantitative discussion of lattice energy variations for molecular motions, defects formation, and inclusion of guest molecules.[109]

5. Reactivity

The use of crystal data in the interpretation of organic reactivity was first proposed by Dunitz and coworkers (see, for recent developments, ref 110 and references therein), in their ingenious attempt to trace reaction pathways by a sequence of snapshots of the reacting group in different packing environments and at different reaction stages. The idea is well exemplified by recent results on system **37**. Crystals of **37** exist at various temperatures in various phases, and the crucial C–C distance varies from 1.622 Å at 173 K to 1.851 Å at room temperature.[111] The crystalline medium offers therefore a good chance to study the reaction progress.



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The calculation of dynamical aspects of reactivity in a solid poses a challenging problem, since a model pathway for the reaction in the crystalline matrix has to be proposed, and, besides packing energies, bond breaking and bond formation energies must be evaluated. Quantum mechanical methods have been used to determine intramolecular energy variations. We have already mentioned (section IID) the isomerization of methyl *p*-(dimethylamino)benzenesulfonate, **35**, as an example of rate enhancement in the solid; the reaction mechanism has been studied following a theoretical approach joining PPE and extended Hückel calculations.[112] The fact that some important hints concerning the possible crystal reactivity can be obtained by PPE calculations is illustrated in Figure 10. It is shown that the "shape" of the potential energy surface surrounding the reacting system can be critical in deciding if a reaction can take place in a crystal. Other examples of the spare literature in this field include calculations on the pyrene excimer[113] and an investigation in which modeling of the elementary step of the chemical transformation of crystals and molecular orbital calculations have been successful in the interpretation of the thermal decomposition, photolysis, and radiolysis of metal azides.[114]

The general problem of obtaining information on solid-state reactivity from theoretical calculations has not yet been tackled in a systematic way. It is a complex one, but the answers could be rewarding to the organic and to the physical chemist. Steps toward a systematic investigation of the packing modes and crystal structures of reactive organic solids are being taken in our laboratory.[115]

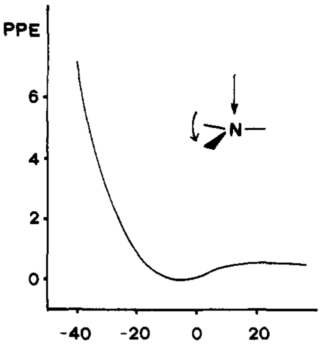

Figure 10. PPE for the pyramidalization of the amino group in the solid-state rearrangement of **35**. The bending motion (bent arrow) that brings the aminomethyl groups against the incoming methyl group is unfavorable (left side of the curve); the opposite motion (toward the correct pyramidalization) has no intermolecular barrier (right side of the curve) (kcal/mol units). See ref 111.

IV. Conclusions

Solid-state reactivity has not enjoyed in the years the popularity of solution reaction studies, and the number of adepts is not large. Solid-state reactions are still regarded as more or less chemical curiosities, and the theoretical calculation of crystal reaction paths is at an early stage of development. The main experimental obstacle is probably the difficulty of spotting reactive crystals; still, there is no doubt that with a deeper understanding of packing effects and of topochemistry such reactions could be planned and exploited in organic chemistry. In this respect, a quick preliminary X-ray study of the crystal structure of reactive compounds of particular interest is recommended, say, in the same spirit as conventional spectroscopic surveys are routinely carried out. Any unusual feature in the crystal packing could thus be detected and possible solid-state processes recognized.

This review is not primarily aimed to the specialist in solid-state chemistry, to which many of the concepts we have illustrated may be quite familiar, but rather to the practicing organic chemist and X-ray crystallographer. To the former, solid-state reactivity as presented here may be a source of new ideas or of unusual views on structure–reactivity relationships. As for X-ray structure analysis, the need is felt for conveying its vast potentialities to some unifying achievements. The study of molecular motions, phase transitions, and reactions in the crystal can be a worthwhile one. So far, the intramolecular data have been privileged; their collection ideally requires perfect ordered crystals. Intermolecular information could probably be given more attention than it is given now, and should not be confined to just a sentence on "contacts below van der Waals radii" at the end of a typical structure report. In this respect, there is much to be learned from unstable and disordered crystals as well.

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