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Thermally Induced Organic Reactions in the Solid State

Iain C. Paul* and David Y. Curtin*

Department of Chemistry and Materials Research Laboratory, University of Illinois, Urbana, Illinois 61801

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Almost all organic compounds can be prepared in the crystalline state, and a majority are crystalline under ambient conditions. It is surprising, therefore, that although organic reactions in the solid state have been reported regularly since before the turn of the century,[1] solid-state chemistry has frequently been regarded as a specialty of little interest to the practicing organic chemist.

However, for certain organic compounds which have been of practical value as solids, the importance of behavior unique to the crystalline state has been long appreciated. For example, polymerization in the solid state has been studied at some length.[2a] A striking example of control of the reaction product by incorporation of the reactant in a crystalline matrix is the polymerization of olefins incorporated in crystalline thiourea or urea canal complexes.[2b] The free-radical polymerization[2c] of butadiene in solution gives a polymer with a mixture of about 20% 1,2-butadiene units, 40% cis-1,4 and 40% trans-1,4 units. However, if the butadiene monomer is incorporated into a crystalline urea complex and then polymerization is initiated by ionizing radiation, there is obtained a crystalline, all-trans 1,4 addition product.

In the pharmaceutical industry the rates of solid-state reactions are important because drugs should survive storage for very long times without undergoing chemical change. Moreover, many compounds exist in more than one crystalline form, and the pharmacological effect of a solid compound may vary markedly from one form to another (possibly because of variations in rates of solution).[3] For example, a particular chloramphenicol palmitate suspension was reported to have an unsatisfactory clinical effect. It was discovered that this compound exists in two different crystalline forms. When taken by oral ingestion, blood levels of the antibiotic from one form have been found to be as much as seven times higher than from the other. A number of samples were found to contain the less active crystals.[3]

Polymorphic forms of explosives may have widely differing rates of chemical reaction. Thus the nitramine HMX, a by-product in the production of the explosive RDX, exists in four polymorphic forms varying markedly in reactivity; the less stable forms are responsible for the high shock sensitivity of the material.[3-5]

There are innumerable literature references to reactions in the solid state, many of them not fully investigated. The list includes such diverse examples as resolution of optically active compounds,[6] racemizations,[7] "phase transitions,"[8] proton transfers,[9] Diels–Alder and other electrocyclic reactions,[10] cis–trans isomerizations of olefins,[11] syn–anti isomer-

Iain C. Paul is a native of Glasgow, Scotland, where he received his B.Sc and Ph.D. degrees in chemistry in 1959 and 1962, respectively. After 2 years as a postdoctoral research associate at Harvard University, he joined the faculty in the Department of Chemistry at the University of Illinois. In 1968–1970 he was an Alfred P. Sloan Research Fellow. His research interests are in areas of structural chemistry of compounds of significance to biological and organic chemistry, and also in the solid-state chemistry of organic compounds.

David Y. Curtin received his A.B. degree from Swarthmore College and a Ph.D. in chemistry from the University of Illinois. After 1 year of postdoctoral work at Harvard University and 5 years on the chemistry faculty of Columbia University, he returned to the University of Illinois where he is now Professor of Chemistry. His research interests have covered a range of topics in organic chemistry and have most recently centered in various aspects of the chemistry of organic compounds in the crystalline state.

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(1) (a) For example, the syn and anti isomers of the compound $C_6H_5C(OCH_3){=}NOH$ were reported to be slowly and partially interconverted in the solid state [A. Werner and J. Subak, *Ber.*, **29**, 1153 (1896)]. For reviews of organic solid-state chemistry see (b) H. Morawetz, *Science*, **152**, 705 (1966); (c) Proceedings of the International Symposium of Organic Solid State Chemistry, *Mol. Cryst. Liquid Cryst.*, **9**, 285 (1969).

(2) (a) H. Morawetz, "Physics and Chemistry of the Organic Solid State," Vol. I, D. Fox, M. M. Labes, and A. Weissberger, Ed., Interscience, New York, N. Y., 1963, p 302 ff; (b) J. F. Brown, Jr., and D. M. White, *J. Amer. Chem. Soc.*, **82**, 5671 (1960); D. M. White, *ibid.*, **82**, 5678 (1960); (c) C. S. Marvel, "Introduction to the Organic Chemistry of High Polymers," Wiley, New York, N. Y., 1959, p 68 ff.

(3) J. Haleblian and W. McCrone, *J. Pharm. Sci.*, **58**, 911 (1969).

(4) N. H. Hartshorne and A. Stuart, "Crystals and the Polarizing Microscope," 3rd ed, Edward Arnold, London, 1960, p 498.

(5) W. C. McCrone, "Physics and Chemistry of the Organic Solid State," Vol. II, D. Fox, M. M. Labes, and A. Weissberger, Ed., Interscience, New York, N. Y., 1965, p 725 ff.

(6) R. E. Pincock and K. R. Wilson, *J. Amer. Chem. Soc.*, **93**, 1291 (1971); R. E. Pincock, R. R. Perkins, A. S. Ma, and K. R. Wilson, *Science*, **174**, 1018 (1971).

(7) (a) R. E. Pincock, M.-M. Tong, and K. R. Wilson, *J. Amer. Chem. Soc.*, **93**, 1669 (1971); (b) A. T. Blomquist, R. E. Stahl, Y. C. Meinwald, and B. H. Smith, *J. Org. Chem.*, **26**, 1687 (1961).

(8) W. C. McCrone, "Physics and Chemistry of the Solid State," Vol. II, D. Fox, M. M. Labes, and A. Weissberger, Ed., Interscience, New York N. Y., 1965, Chapter 8.

(9) M. D. Cohen and G. M. J. Schmidt, *J. Chem. Soc.*, 1996 (1964); A. G. Cairns-Smith, *ibid.*, 182 (1961).

(10) J. H. Golden, *J. Chem. Soc.*, 3741 (1961); M. Ehrenberg, *Acta Crystallogr.*, **20**, 177, 182 (1966).

(11) R. S. Atkinson, *Tetrahedron Lett.*, 3937 (1970).

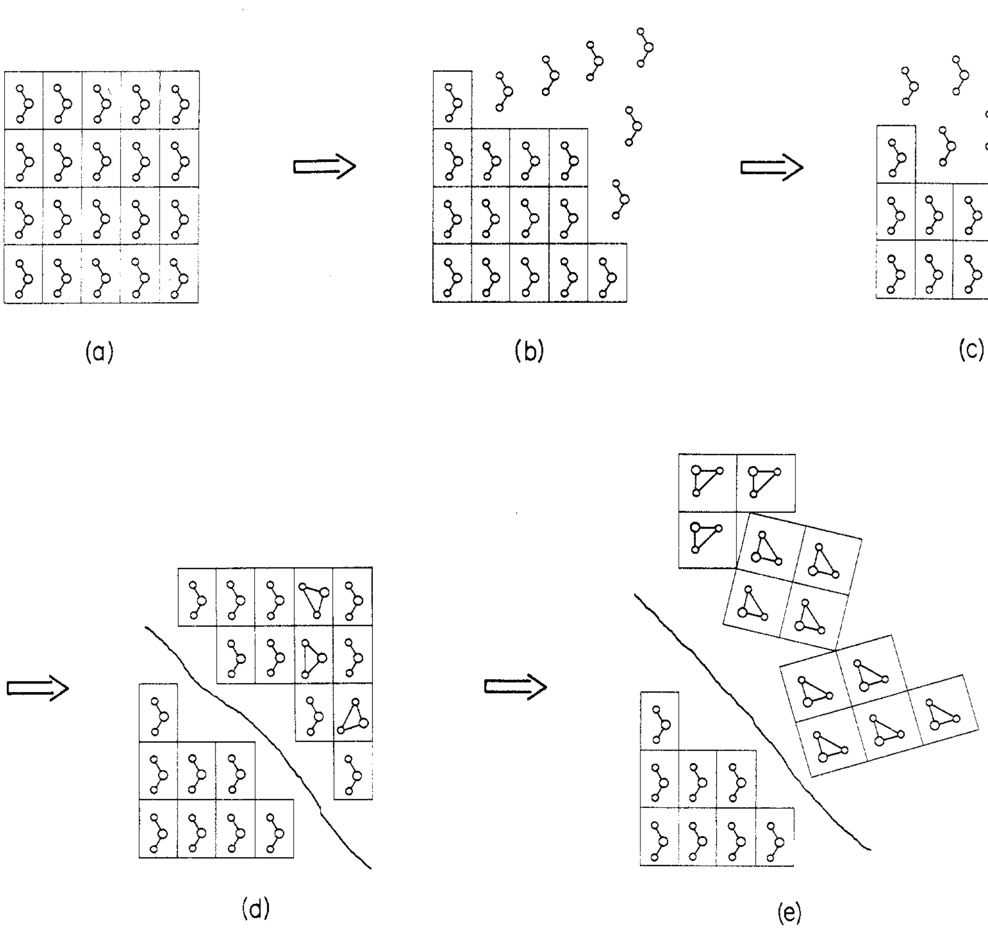

Figure 1. Schematic representation of the stages of reaction in the solid state: (a) unreacted crystal; (b) loosening of molecules at the reaction site; (c) molecular change; (d) solid solution formation; (e) separation or product.

izations of imines and azo compounds,[12] ring-chain interconversions,[13,14] acyl migrations,[15] benzidine rearrangements,[16] Wittig rearrangements,[17.] nucleophilic substitution reactions,[18] azo decomposition reactions,[19] and decomposition of acyl peroxides.[20] As a rough guide, any reaction which occurs in an inert solvent at a reasonable rate at a temperature 60–100° below the melting points of the reactants can probably be made to occur in the solid.

At present, the type of solid-state reaction most valuable for the synthetic organic chemist is the photochemical dimerization of unsaturated compounds. It was reported in 1921 that *trans*-cinnamic acid exists in two different crystalline modifications which give different products on irradiation with sunlight.[21] In 1943 Bernstein and Quimby[21b] proposed that the β form of *trans*-cinnamic acid dimerizes in a head-to-head fashion to give β-truxinic acid because "the phenyl groups lie next to each other in the crystal," whereas the α-crystalline form gives a head-to-tail product, α-truxillic acid, because the phenyl groups are "opposite" in the α-crystal structure.

Two decades later great impetus was given to this field by Cohen and Schmidt with the generalization[22] that in many such photochemical reactions the nature of the product may be explained by the crystal structure of the starting material and that reaction occurs when the potentially reacting carbon atoms are suitably oriented and have contacts of less than 4.1 Å. These principles of topochemistry have found application in biology with studies on thymine and uracil dimerization[23] and in polymerization.[24]

(12) (a) P. P. Peterson, *Amer. Chem. J.*, **46**, 325 (1911); (b) E. Bamberger and O. Schmidt, *Ber.*, **34**, 2001 (1901).

(13) O. Allendorff, *Ber.*, **24**, 2346 (1891); O. Dimroth, *Justus Liebigs Ann. Chem.*, **373**, 336 (1910); O. Dimroth and H. Stahl, *ibid.*, **338**, 154 (1904); B. R. Brown and D. Ll. Hammick, *J. Chem. Soc.*, 1384 (1947).

(14) W. Dilthey, C. Berres, E. Holterhoff, and H. Wübken, *J. Prakt. Chem.*, [2] 114, 179 (1926).

(15) R. Anschütz, H. Aschenberg, H. Kuckertz, F. Krone, K. Riepenkröger, and C. Zerbe, *Justus Liebigs Ann. Chem.*, **442**, 18 (1925); A. J. Gordon, *Tetrahedron*, **23**, 863 (1967).

(16) H. J. Shine and J. C. Trisler, *J. Amer. Chem. Soc.*, **82**, 4054 (1960).

(17) G. Wittig and E. Stahnecker, *Justus Liebigs Ann. Chem.*, **605**, 69 (1957).

(18) R. W. Addor, *J. Org. Chem.*, **29**, 738 (1964).

(19) (a) A. B. Jaffe, K. J. Skinner, and J. M. McBride, *J. Amer. Chem. Soc.*, **94**, 8510 (1972); (b) A. B. Jaffe, D. S. Malament, E. P. Slisz, and J. M. McBride, *ibid.*, **94**, 8515 (1972); (c) K. J. Skinner, R. J. Blaskiewicz, and J. M. McBride, *Israel J. Chem.*, **10**, 457 (1972); (d) N. J. Karch and J. M. McBride, *J. Amer. Chem. Soc.*, **94**, 5092 (1972).

(20) J. Z. Gougoutas, *Israel J. Chem.*, **10**, 395 (1972); *Pure Applied Chem.*, **27**, 305 (1971).

(21) (a) R. Stoermer and E. Laage, *Ber.*, **54**, 77 (1921); (b) see H. I. Bernstein and W. C. Quimby, *J. Amer. Chem. Soc.*, **65**, 1845 (1943), for other historical references.

(22) (a) G. M. J. Schmidt, *J. Chem. Soc.*, 2014 (1964); (b) M. D. Cohen, Z. Ludmer, J. M. Thomas, and J. O. Williams, *Proc. Roy. Soc., Ser. A*, **324**, 459 (1971); (c) M. D. Cohen, A. Elgavi, B. S. Green, Z. Ludmer, and G. M. J. Schmidt, *J. Amer. Chem. Soc.*, **94**, 6776 (1972), and references therein; (d) G. M. J. Schmidt, *Pure Appl. Chem.*, **27**, 647 (1971); (e) G. M. J. Schmidt, "Reactivity of the Photoexcited Organic Molecule," Interscience, New York, N. Y., 1967, p 227; (f) J. O. Williams and J. M. Thomas, *Mol. Cryst. Liquid Cryst.*, **16**, 223 (1972).

(23) J. K. Frank and I. C. Paul, *J. Amer. Chem. Soc.*, **95**, 2324 (1973), and references cited therein.

(24) M. Iguchi, H. Nakanishi, and M. Hasegawa, *J. Polym. Sci., Part A-1*, **6**, 1055 (1968); F. Suzuki, Y. Suzuki, H. Nakanishi, and M. Hasegawa, *J. Polym. Sci., Part A-1*, **7**, 2319 (1969); Y. Sasada, H. Shimanouchi, H. Nakanishi, and M. Hasegawa, *Bull. Chem. Soc. Jap.*, **44**, 1262 (1971).

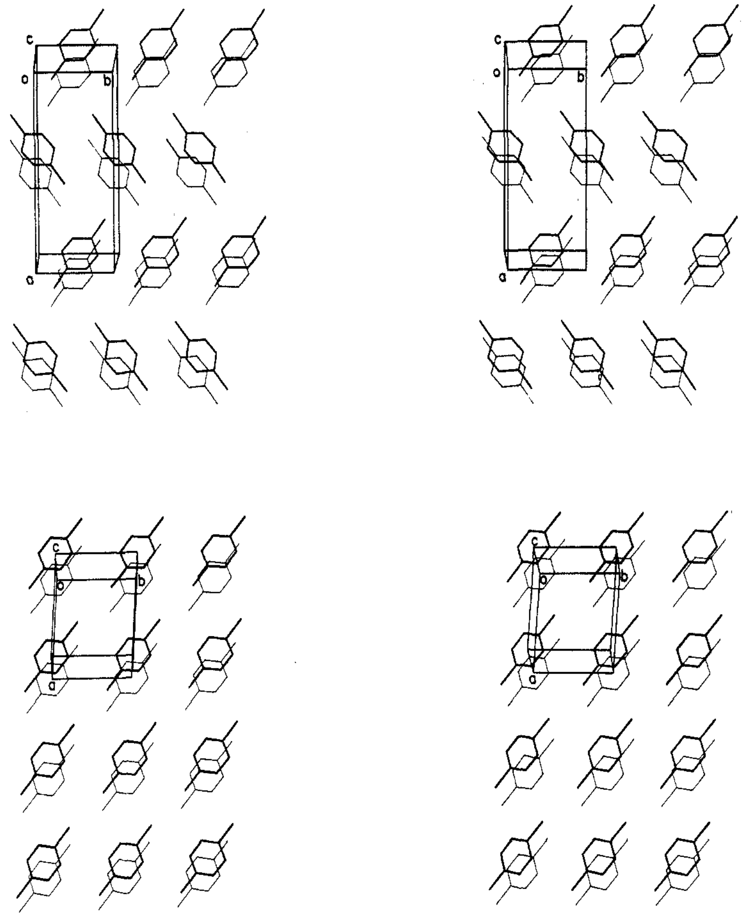

Figure 2. Stereo pair view of the rearrangement of low-temperature-stable (monoclinic) to high-temperature-stable (triclinic) *p*-dichlorobenzene (**1**). The monoclinic structure[30b] is shown in the top pair of drawings, the triclinic[30c] in the bottom pair.

The present Account is, however, devoted primarily to organic reactions which (1) occur in the solid state, (2) are induced thermally, and (3) involve an intramolecular change uncomplicated by the necessity for reagents to diffuse together. For purposes of analysis such processes may conveniently be divided into four stages as shown schematically in Figure 1.

(1) Loosening of Molecules at the Reaction Site. Molecular crystals typically have their constituent molecules tightly packed and have little freedom of motion of the sort needed for reaction.[25] A process involving a significant change in molecular shape must be preceded or accompanied by a loosening (partial unpacking) of the crystal.

(2) Molecular Change. This is the only stage of the reaction which has a counterpart in solution chemistry. It produces early in the reaction molecules of product imbedded in a matrix of starting material.

(3) Solid Solution Formation. Product accumulates as a solid solution in the parent crystal until the "solubility" is exceeded and nucleation induces the crystallization of a separate phase.

(4) Separation of the Product. This process may give product randomly oriented or with a net orientation governed by that of the starting material.

In the following sections each of these stages of reaction is discussed.

Molecular Loosening

Studies of Motion in Molecular Crystals. X-Ray and neutron diffraction techniques[26] and, particularly, nuclear magnetic relaxation[27] have begun to provide information about motions of groups of atoms in crystals at ambient temperature. For example, normal alkanes have been shown to be essentially motionless at low temperatures; as the temperature is gradually increased, rotation of the terminal methyl groups occurs and, at a few degrees below the melting point, rotation of the entire hydrocarbon chain sets in. Thus far, however, such knowledge has not been applicable to studies of reactions of solids. "Plastic crystals,"[28] which are formed by some approximately spherical molecules below their melting points, and "liquid crystals"[29] are two classes of solids that offer particular interest in having much of the molecular freedom of the liquid state.

Nucleation. In the few studies of reactions of single crystals, the observable change has been found to begin at one or more nucleation sites and to spread through the crystal. The seemingly simple reversible change of monoclinic to triclinic *p*-dichlorobenzene (**1**) (Figure 2),[30] involving only reorientation of mole-

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[25] A. I. Kitaigorodskii, "Organic Chemical Crystallography," Consultants Bureau, New York, N. Y., 1955, Chapter 3; *Acta Crystallogr.*, **18**, 585 (1965).

[26] W. C. Hamilton, *Mol. Cryst. Liquid Cryst.*, **9**, 11 (1969).

[27] W. P. Slichter, *Mol. Cryst. Liquid Cryst.*, **9**, 81 (1969).

[28] J. G. Aston, "Physics and Chemistry of the Organic Solid State," Vol. I, D. Fox, M. M. Labes and A. Weissberger, Ed., Interscience, New York, N. Y., 1963, p 543 ff; A. R. Ubbelohde, "Melting and Crystal Structure," Oxford University Press, London, 1965.

[29] Proceedings of the Second International Liquid Crystal Conference, *Mol. Cryst. Liquid Cryst.*, **7**, 8 (1969).

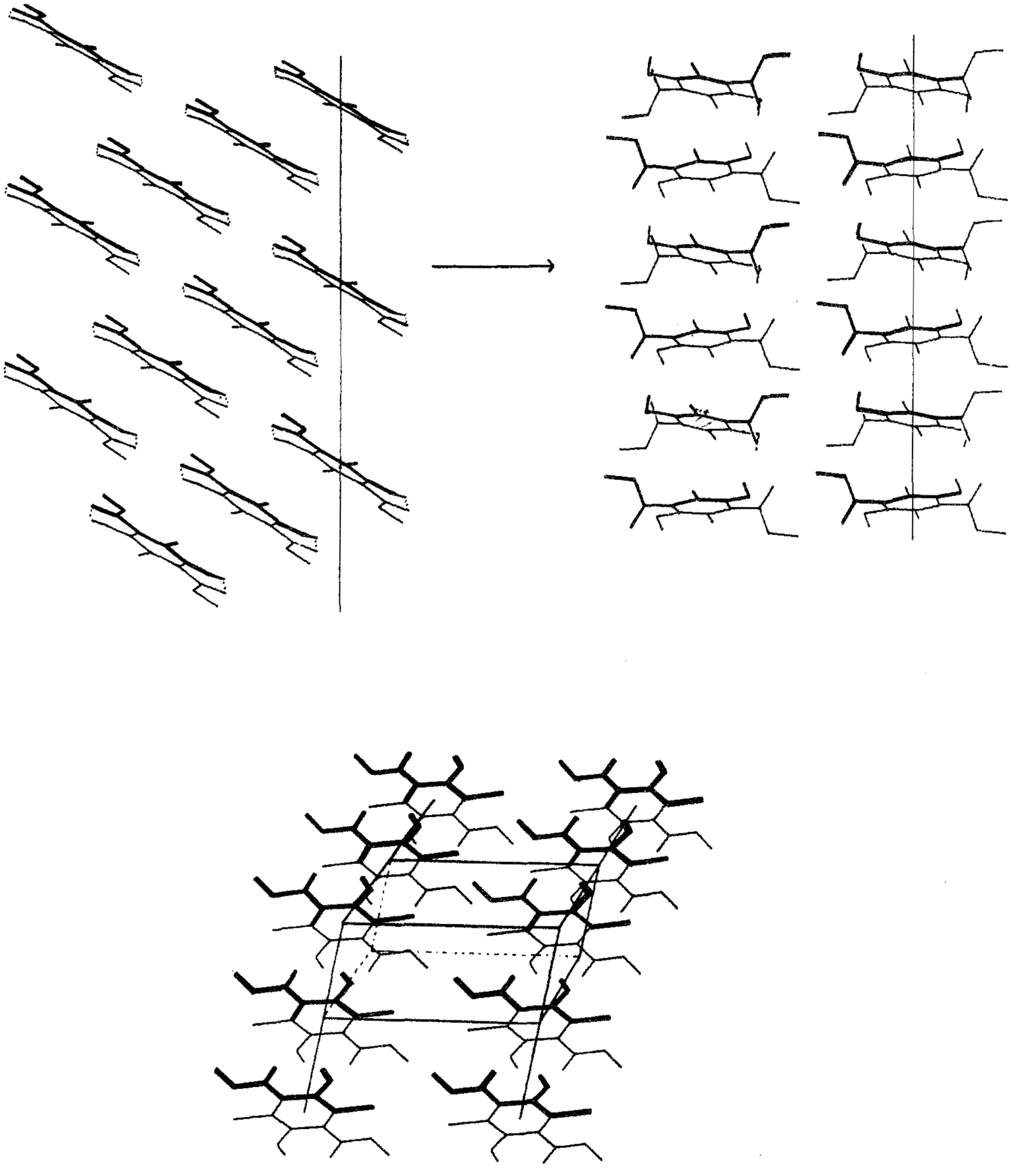
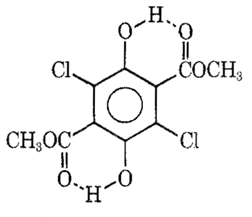


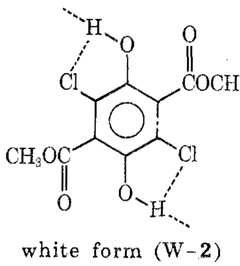
Figure 3. (Upper) Change in the molecular structure in the conversion of the yellow (Y-2) to the white (W-2) dichlorodihydroxyterephthalic ester. The view is down the long morphological crystal axis. Note that every other molecule in the yellow structure must undergo a 180° flip to form the stable form of the white. (Lower) The dichlorodihydroxyterephthalic ester (Y-2) showing it is reasonable that disorientation of one of the vertical layers is not readily transmitted to the next. The long axis (to the right) is the long morphological axis and the top face shown corresponds to the upper surface of the crystal.

cules, does not occur uniformly through the crystal but begins at a nucleation site with a front which can be readily followed with the polarizing microscope.

The spread of a reaction front from a nucleation site throughout the crystal may be highly anisotropic as has been observed[31] in the rearrangement of the yellow form Y-2 of the phenol 2 to the white form W-2. The reaction involves a change in the hydrogen bonds formed by the two protons. There is intramolecular hydrogen bonding to the adjacent carbonyl groups in Y-2, but in W-2 there are bifurcated hydrogen bonds (to the chlorine atoms in the same molecule as well as to carbonyl groups in adjacent molecules). Also, there are substantial changes in molecular shape (the molecules of the yellow form are essentially planar while the ester groups of the white form are nearly perpendicular to the planes of the benzene rings). Moreover, as is shown in Figure 3, every other molecule in a stack in the yellow crystalline form must undergo a rotation about the Cl–Cl intramolecular axis or an equivalent motion to change to the stable packing of the white form (Figure 3).



yellow form (Y-2



white form (W-2)

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[30] (a) A. I. Kitaigorodskii, Yu V. Mnyukh, and Yu G. Asadov, *J. Phys. Chem. Solids*, **26**, 463 (1965); Yu V. Mnyukh, N. N. Petropavlov, and A. I. Kitaigorodskii, *Dokl. Akad. Nauk SSSR*, **166**, 80 (1966); (b) E. Frasson, C. Garbuglio, and S. Bezzi, *Acta Crystallogr.*, **12**, 126 (1959); (c) J. Housty and J. Clastre, *ibid.*, **10**, 695 (1957).

[31] S. R. Byrn, D. Y. Curtin, and I. C. Paul, *J. Amer. Chem. Soc.*, **94**, 890 (1972).

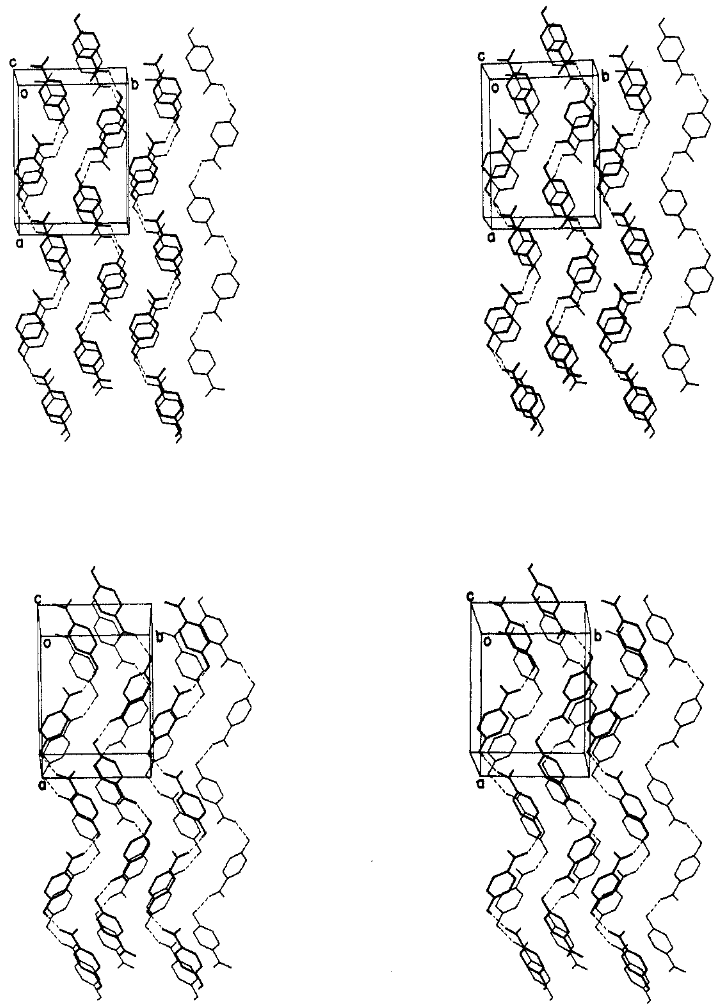

Figure 4. Rearrangement of β- (top pair) to α- (bottom pair) *p*-nitrophenol (**3**).[37] The columns toward the viewer are shown by heavy lines.

Microscopic observation of the rearrangement of single crystals shows that reaction begins at one or more nucleation sites and spreads through the crystal. The spread is highly anisotropic; it is rapid in the plane normal to the long morphological crystal axis and slow in the direction of this axis. Reaction must be rapid through the two-dimensional layers of molecules but slow in moving from one layer to the next, as could be expected in view of the way the layers are separated from each other (Figure 3).

For a mastery of solid-state chemistry it is obviously of prime importance to have an understanding of and an ability to control the nucleation process. When a crystal of the yellow form is heated gradually above 110° both the temperature at which reaction occurs and the region of the crystal where it originates are quite unpredictable.

Nucleation of similar processes has commonly been associated with crystal defects (following section). Changes have been induced by pricking the crystal with a pin[30,32a] or by inoculation with the reaction product.[32a] In the rearrangement of Y-2 these methods failed, as did irradiation with sunlight and spotting with hydrochloric acid or with mineral oil. In short, the induction of the change of the yellow to the white isomer has been impervious to every influence attempted. The white crystalline form could be caused to revert to the yellow isomer by suspension in a saturated solution of the compound at room temperature, a method employed previously in other instances.[32b] Other manifestations of such changes in hydrogen bonding have been discovered in similar compounds[33] and also in the family of morphine alkaloids.[34-36]

A related process is the thermally induced rearrangement of metastable (β) to stable (α) *p*-nitrophenol (**3**)[37] (Figure 4). Single needle-shaped crystals were reported[37] to rearrange with the phase boundary moving approximately perpendicular to the needle [001] axis. The structural change from α- to β-*p*-nitrophenol is subtle and, as shown in Figure 4, involves a twist of rings in adjacent links in the chains.

The observation[37] that rearrangement is slowest in that direction, [001], in which crystal growth was most rapid is consistent with the suggestion[37] that

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[32] (a) N. H. Hartshorne and M. H. Roberts, *J. Chem. Soc.*, 1097 (1951); A. L. Patterson and B. T. Groshens, *Nature (London)*, **173**, 398 (1954); (b) K. Schaum, *Justus Liebigs Ann. Chem.*, **300**, 205 (1898).

[33] A. Hantzsch, *Ber.*, **48**, 797 (1915).

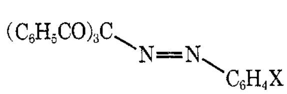
[34] U. Weiss, *J. Org. Chem.*, **22**, 1505 (1957).

[35] We are indebted to Dr. U. Weiss for bringing these samples to our attention.

[36] L. F. Small and E. Meitzner, *J. Amer. Chem. Soc.*, **55**, 4602 (1933).

[37] M. D. Cohen, P. Coppens, and G. M. J. Schmidt, *J. Phys. Chem. Solids*, **25**, 258 (1964); P. Coppens and G. M. J. Schmidt, *Acta Crystallogr.*, **18**, 62, 654 (1965).

extensive unpacking and repacking of the crystal occurs at the reaction front; that is, the crystal face which grows fastest is disrupted slowest. Although it has much less well-defined frontal migration, the formation from *p*-bromophenylazotribenzoylmethane (4, X = Br) of the red enol benzoate 5 and the white hydrazone 6 provides another example of a rearrangement which appears to begin at a number of independent sites in the interior of the crystal and to spread.[38]



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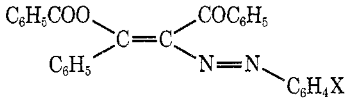

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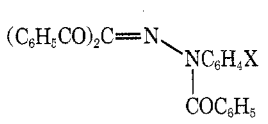

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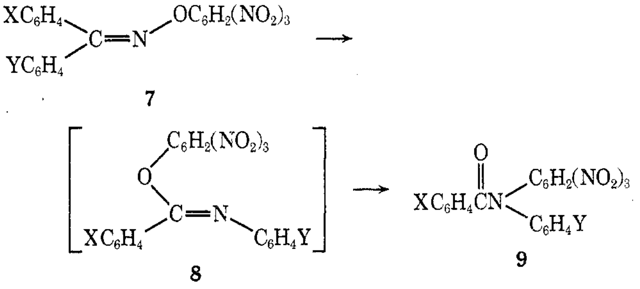
Studies of Crystal Defects. As indicated above, factors leading to nucleation of most solid-state reactions are not well understood. Exceptions are certain photodimerizations, in particular those of anthracene and its 9-cyano derivative,[39] whose dimerizations have been shown to occur initially at sites of emergence of nonbasal dislocations.[22b,40] Crystal defects have not often been directly implicated as sources of nucleation sites in thermally induced reactions, but the interconversion[30,32] of monoclinic and triclinic dichlorobenzene (1) was generally initiated at visible defect sites and could be induced by mechanical stress such as a pinprick. Such studies suggest that defects may play an important role in thermally induced as well as in photochemical reactions.

A further indication of the importance of mechanical stress was found in the study of the Beckmann–Chapman rearrangement of the picryl ether (7, X = Y = H) of benzophenone oxime to the corresponding *N*-picrylbenzamide 9.[41] In the rearrangement of moderately thick crystals a region on the sides of the crystal became yellow as a solid solution of the yellow product 9 accumulated, and the resulting stress caused cracking in the region of the reaction. Development of cracks seemed further to accelerate yellowing, so that in the regions where it had started reaction continued for several hours before it spread to the remainder of the crystal. Similar behavior was shown by the *p*-bromo derivative (7, X = Br, Y = H). It seems possible that the stress induced by reaction led to further nucleation sites.



It is striking that the behavior of benzophenone oxime picryl ether (7) depended on the size and shape of the crystals undergoing reaction; thick crystals but not thin ones showed cracking. In a study[42] of polymorphic transitions of malonic and glutaric acid, very thin crystals behaved more simply than thicker ones; it was presumed that the thinness made possible "emergence at the surface" of a considerable part of the internal stress developed during the change.

In summary, it appears that crystal defects play a substantial role in determining the rates of reactions in the solid state.

The Molecular Change

That stage of a solid-state reaction in which there is a change of covalent bonding (if one is involved) is, of course, the part of the process of most interest to the synthetic chemist.

Utilization of solid-state chemistry to achieve results not possible in solution demands a quantitative understanding of the effects on reaction rates of those features peculiar to the solid state, such as nucleation. The problem of finding rate equations which incorporate the special kinetic features of solid-state reactions has been attacked in studies chiefly of inorganic reactions and explosives. The situation is not encouraging since the behavior of individual crystals (or crystallites) may deviate greatly from the average behavior.[38d] Furthermore, the method of varying the initial concentration of reactants to establish the kinetic order in solution reactions is not possible. Rates[43-46] of a number of intramolecular solid-state reactions are summarized in Table I.

Most of these reactions followed a first-order rate equation (sometimes only after an initial induction period) over a large fraction of the reaction. In spite of the difficulties in interpreting such rates, it is interesting that the range of ratios of $k_{\text{liq}}/k_{\text{solid}}$ is from 1 to 10^2 for reactions of this type. Thus, the difference between the solid and solution rates is smaller than the estimates of 10^3–10^4 or greater made in an earlier review[2a] on the basis of the data available at that time.[48]

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(38) (a) R. T. Puckett, C. E. Pfluger, and D. Y. Curtin, *J. Amer. Chem. Soc.*, 88, 4637 (1966); (b) D. Y. Curtin, S. R. Byrn, and D. B. Pendergrass, Jr., *J. Org. Chem.*, 34, 3345 (1969); (c) J. D. McCullough, Jr., D. Y. Curtin, L. L. Miller, I. C. Paul, and D. B. Pendergrass, Jr., *Mol. Cryst. Liquid Cryst.*, 11, 407 (1970); (d) D. B. Pendergrass, Jr., D. Y. Curtin, and I. C. Paul, *J. Amer. Chem. Soc.*, 94, 8722 (1972); (e) D. B. Pendergrass, Jr., I. C. Paul, and D. Y. Curtin, *ibid.*, 94, 8730 (1972).

(39) D. Donati, G. Guarini and P. Sarti-Fantoni, *Mol. Cryst. Liquid Cryst.*, 17, 187 (1972).

(40) (a) J. M. Thomas and J. O. Williams, *Mol. Cryst. Liquid Cryst.*, 9, 59 (1969); (b) P. Sarti-Fantoni and R. Teroni, *ibid.*, 12, 27 (1970); (c) A. Kawada and M. M. Labes, *ibid.*, 11, 133 (1970), and references cited therein.

(41) (a) J. D. McCullough, Jr., D. Y. Curtin, and I. C. Paul, *J. Amer. Chem. Soc.*, 94, 874 (1972); (b) J. D. McCullough, Jr., I. C. Paul, and D. Y. Curtin, *ibid.*, 94, 883 (1972).

(42) N. I. Musaev and Yu. V. Mnyukh, *Kristallografia*, 15, 555 (1970).

(43) A. Aharoni, H. Ditkovsky, E. H. Frei and A. Tzalmona, *J. Phys. Chem. Solids*, 24, 927 (1963); C. Dehari, Y. Matsunaga, and K. Tani, *Bull. Chem. Soc. Jap.*, 43, 3404 (1970).

(44) M. Tsuda and K. Kuratani, *Bull. Chem. Soc. Jap.*, 37, 1284 (1964).

(45) For a critical analysis of the method see J. M. Thomas and T. A. Clarke, *J. Chem. Soc. A*, 457 (1968).

(46) W. E. Garner, "The Chemistry of the Solid State," Academic Press, New York, N. Y., 1955.

(47) (a) R. E. Pincock, K. R. Wilson, and T. E. Kiovsky, *J. Amer. Chem. Soc.*, 89, 6890 (1967); (b) R. Destro, G. Filippini, C. M. Gramaccioli, and M. Simonetta, *Acta Crystallogr., Sect. B*, 25, 2465 (1969).

Table I
Rates of Solid-State Reactions

Reaction	Temp range, °C	ΔH, kcal/mol	Reaction order assumed	$k_{\text{liq}}/k_{\text{solid}}$	Ref
Racemization of (+)-bicyclo[2.2.1]heptene-*trans*-dicarboxylic acid	131–152	0	1	2–2.5	7
Resolution of α,α'-binaphthyl	135	0		*a*	6
Isomerization of *exo*- and *endo*-norbornenedicarboxylic an-	120	*b*	1	5	47
hydrides	120	*b*	1	1	47
Phenylazotribenzoylmethane (4) to enol benzoate (5) and	75		1	10^2	38
hydrazone (6)	75	−15	1	10^2	38
Monomerization of the anthracene dimer	37–65	−20	1		39
Isomerization of *cis*- to *trans*-azobenzene	36–58		*c*		44
Beckmann–Chapman rearrangement of oxime picrates 7 to picramides 9	60	−80	1	5–14	41, 49

[a] No comparable solution process exists. [b] The equilibrium in the melt contains 54% endo and 46% exo. [c] Followed the Prout-Tomkins equation.[46]

The group of reactions in Table I shows a range from those at the top of the table whose ΔH in solution is 0 to some at the bottom of the table whose ΔH due to the molecular change is quite large. Whether or not these examples give a representative comparison of ratios of rates of solid state to solution reactions, it seems clear that some solid-state reactions are less sluggish than had been believed previously.

The relative rates of formation of the enol benzoate 5 and hyrazone 6 from the rearrangement of the azo triketone 4 differ substantially in the solid state from those in solution. Thus, the ratio 5/6 was 0.5 at 65° in the solid state and 0.95 in dioxane solution at the same temperature. Unfortunately the crystal structure of 4 does not suggest a clear preference for rearrangement to either 5 or 6.

In conclusion, there are in the literature inumerable examples of compounds which were observed to undergo chemical change immediately on melting; in almost none of these cases has the possibility of a solid-state reaction been investigated. It is significant that some reactions in the solid state have been reported to proceed more cleanly and with fewer byproducts than were obtained in solution[50,51]

Solid Solution Formation

The first molecules of product appear as a solid solution of daughter molecules in the parent crystal. Requirements for the accumulation of substantial amounts of one substance in a crystalline matrix of another have only begun to be understood,[25,52,53] and only recently have meaningful experimental data become available.

In Table II is a summary of the "solubilities"—the extents to which molecules of a guest substance can be accommodated in a host crystal without seriously changing the structure—in crystalline naphthalene and in crystalline anthracene. Most striking is the high degree of intolerance which can be shown for the incorporation of guest molecules even when they are similar in size and shape to the molecules making up the host crystal. Thus, the range of thermodynamically stable solid solutions of acridine in anthracene extends from 0 to 12% acridine. (Stable solid solutions of anthracene in crystalline acridine have an even more limited concentration range of 0–2%.) Requirements for the host and guest molecules have been analyzed.[25,52,53] It is significant that *metastable* crystals of anthracene containing as much as 45 mol % of acridine could be grown from the vapor.

The slight tendency for the formation of stable solid solutions even in the relatively favorable examples of Table II suggests that in solid-state reactions the ability of the parent crystal to accommodate product molecules as a stable solid solution will often have been exceeded early in the reaction. The product will either accumulate for a time as metastable solid solution or diffuse out and form its own crystals. Throughout much of the reaction, the medium is no longer the crystal as it existed initially but, instead, as perturbed by solid solution formation and by separation of the product to its own crystalline phase. The structural specificity in the photodimerizations of the cinnamic acids[21,22] is thus particularly striking since the product is produced as randomly oriented microcrystallites.

In examples such as the rearrangement of yellow tribenzoylmethanes (4) to the red enol benzoates 5 discussed earlier, microscopic examination of reacting crystals shows no accumulation of the red product in clear regions of the crystal; instead reaction is followed quickly by separation of product microcrystallites. On the other hand the rearrangements at 60–90° of single crystals of the oxime picryl ethers 7, particularly the anti isomer (7, X = H, Y = Br), give rise to clear regions showing the yellow color of the product; when heating is interrupted separation of the product occurs at room temperature over a period of months. Since the molecular shape of the product 9 as determined by X-ray analysis is quite different from that of the starting molecules of 7, the mol-

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(48) An early example, the "racemization" of the *d*-camphorsulfonate of an optically active biphenyl cation, merits further investigation. It was reported [J. E. Leffler and W. H. Graham, *J. Phys. Chem.*, **63**, 687 (1959)] that the salt remained unchanged in the solid state after 55 days at 100°, and on this basis a maximum possible rate constant was estimated[2a] for comparison with the solution value. However, the salt which would be formed by biphenyl rotation is not the mirror image of the original since it contains a chiral anion; it is possible that the starting salt is the stable species under these conditions so that no reaction would be expected in the solid state.

(49) P. A. S. Smith, "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, Chapter 8.

(50) D. Y. Curtin and C. S. Russell, *J. Amer. Chem. Soc.*, **73**, 5160 (1951).

(51) A. Delle Site, *J. Org. Chem.*, **31**, 3413 (1966).

(52) A. I. Kitaigorodskii and R. M. Myasnikova, *Sov. Phys.-Crystallogr.*, **16**, 1096 (1972).

(53) (a) P. M. Robinson, H. J. Rossell, H. G. Scott, and C. Legge, *Mol. Cryst. Liquid Cryst.*, **11**, 105 (1970); (b) P. M. Robinson and H. G. Scott, *ibid.*, **18**, 143 (1972); (c) M. Radomska, R. Radomski, and K. Pigoń, *ibid.*, **18**, 75 (1972).

Table II
Extent of Solid Solution Formation in Crystalline Naphthalene and Anthracene

Guest substance	Space group (molecules per unit cell of guest substance	Max sol in naphthalene, mol %	Max sol in anthracene, mol %	Ref
Hexachlorobenzene	$P2_1/c$ (2)		0.5	53a
Camphor	$F43m$ (4)	12	3.0	53a
Naphthalene	$P2_1/a$ (2)		2.9	53a
β-Naphthol	Ia (8)	38[a]		53b
Carbazole	$Pnam$ (4)		22	53a
Acridine	$P2_1/n$ (4)		12	53c
Anthracene	$P2_1/a$ (2)	0		53a

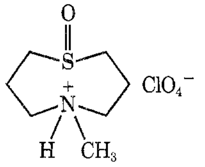
[a] Reported in the older literature as forming a continuous range of solid solutions.

ecules **9** may adopt a new conformation in order to fit into the matrix of starting material. This would be an example of "structural mimicry," a term which has been proposed elsewhere[54] to describe adoption by guest molecules of the shape of the host to form a stable solid solution.

Separation of the Product Phase

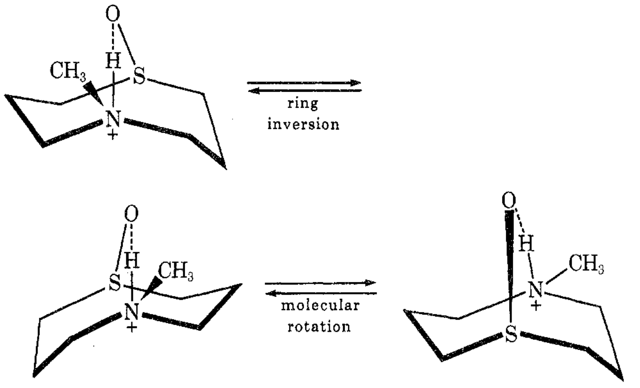
Topotactic Reactions. The final stage of the solid-state reaction consists of the separation of the product molecules from the reaction matrix and assembly of their own crystalline structures. The product often appears as microcrystallites with little or no net orientation relative to the axes of the starting crystal. Such are the rearrangements of the azo triketones (**4** to **5** and **6**), and rearrangements of oxime picryl ethers (**7** to **9**) as well as the rearrangement of β- to α-*p*-nitrophenol (**3**), mentioned earlier. The rearrangement of Y-**2** to W-**2** also resulted in disorder of the product, but powder photographs suggested the presence of some net orientation of the microcrystallites, as was found[55] in the rearrangement of α- to β-resorcinol. Studies of phase transitions which could be carried out as single-crystal–single-crystal transformations, as, for example, that of *p*-dichlorobenzene (**1**), have shown[30,56] that the daughter grows in the mother crystal with an orientation which is random.

On the other hand "topotactic reactions" showing orientation of the product correlated with the reagent crystal have been observed.[20,24,57] An example was discovered during the crystal structure determination of 5-methyl-1-thia-5-azacyclooctane 1-oxide perchlorate (**10**).[58] The crystal at room temperature gave photographs from which the structure was determined to be that designated as "β" in Figure 5. The same crystal at 3° gave photographs which showed the substance had adopted the "α" structure



10

in Figure 5. There was no visible change in the appearance of the crystal, and when returned to room temperature it gave again the photographs of the "β" structure. Study of Figure 5 shows that, for transition to occur, one-half of the cations in each row and each column must undergo a ring inversion and a rotation as shown below.



11

The requirement of nucleation for separation of the product of a solid-state reaction in its own crystalline phase has been observed in the reaction of the *anti*-benzophenone oxime picryl ether (**7**, X = H, Y = Br) at 90° (approximately 20° below the eutectic temperature).[41a] At this temperature the product **9** separated as an orange isotropic glass. This behavior was not observed at lower temperatures, however, where unoriented polycrystallites were formed.

Conclusion

Until this point we have avoided the definition of "solid-state reaction." The criterion most straightforward in its application is based on the use of the eutectic temperature of mixtures of starting material and products as the temperature below which a reaction may be said to occur in the solid state.[6,38b] Some reactions may still be difficult to classify. For example, crystalline cyclodecyl *p*-toluenesulfonate

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(54) L. Sacconi, M. Ciampolini, and G. P. Speroni, *J. Amer. Chem. Soc.*, **87**, 3102 (1965). See also M. D. Cohen, *J. Chem. Soc. B*, 373 (1968).

(55) J. M. Robertson and A. R. Ubbelohde, *Proc. Roy. Soc., Ser. A*, **167**, 136 (1938), and papers cited therein; G. E. Bacon and N. A. Curry, *ibid.*, **235**, 552 (1956).

(56) Yu. V. Mnyukh and N. N. Petropavlov, *J. Phys. Chem. Solids*, **33**, 2079 (1972).

(57) H. Morawetz, S. Z. Jakabhazy, J. B. Lando, and J. Shafer, *Proc. Nat. Acad. Sci. U. S.*, **49**, 789 (1963). See also I. N. Duling and C. C. Price, *J. Amer. Chem. Soc.*, **84**, 578 (1962).

(58) I. C. Paul and K. T. Go, *J. Chem. Soc. B*, 33 (1969).

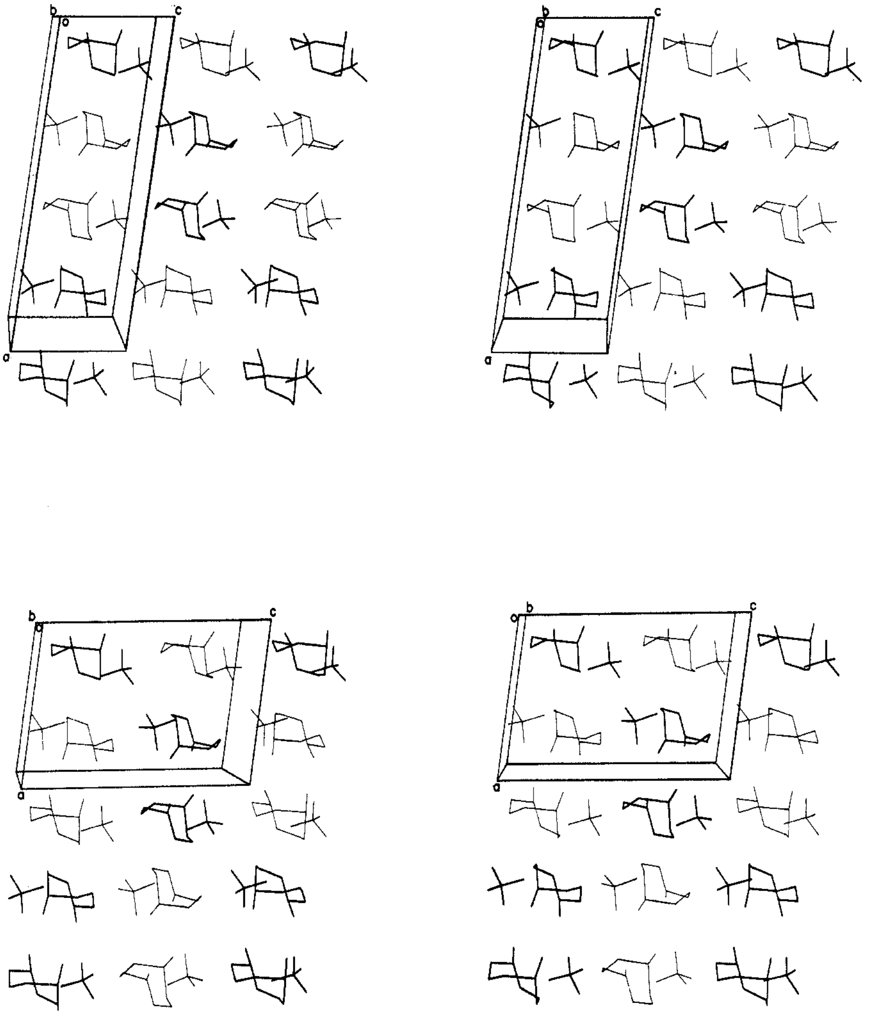

Figure 5. Rearrangement of the β (top pair) (stable at room temperature) to the α (bottom) form (stable at 3°) of 5-methyl-1-thia-5-azacyclooctane 1-oxide perchlorate (**10**).[58] The molecules that do not change in the rearrangement are shown by heavy lines.

(mp 54–55°) decomposes spontaneously at room temperature to give *cis*-cyclodecene (liquid) and *p*-toluenesulfonic acid (crystalline).[59] When the reaction is carried out in acetic acid solution *cis*-cyclodecene is the minor product (20% yield), the major product being the trans isomer (80% yield). The principle[1b] that a reaction is a "solid-state reaction" if it follows a course different from that in solution leads to a different classification of this reaction than would the criterion of eutectic temperature discussed above, as one of the products is liquid.

Although this Account has not dealt with reactions of crystalline solids with gases, many of the topics discussed here are directly applicable to such processes.[1b,60] Interesting anisotropic behavior which has been observed raises the possibility of taking advantage of differing reactivities at different crystal faces.

It is hoped that this brief survey at least hints at the potential of solid-state organic chemistry. The rigidity of the reactant molecule as held in the crystal lattice, the restriction of reactant molecules to specific relative orientations, and the propensity of many substances to form chiral crystals[1b,6] offer exciting possibilities for additions to the repertory of the practicing chemist.

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(59) V. Prelog, W. Küng, and T. Tomljenović, *Helv. Chim. Acta*, **45**, 1352 (1962).

(60) (a) K. Penzien and G. M. J. Schmidt, *Angew. Chem.*, **81**, 628 (1969); (b) R. S. Miller, D. Y. Curtin, and I. C. Paul, *J. Amer. Chem. Soc.*, **93**, 2784 (1971); (c) R. S. Miller, D. Y. Curtin, and I. C. Paul, *ibid.*, **94**, 5117 (1972), and references cited herein.