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Reactions of Organic Crystals with Gases

Gas-solid reactions offer unique possibilities in organic chemistry.

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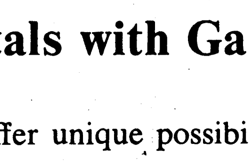
Although reactions of gases with solids are very well known, for example, the corrosion of metals (*1*); the organic chemist only too often regards the solid state as one which provides nearly complete invulnerability to attack by gaseous reagents. Any practicing organic chemist has encountered examples of substances which, in solution or the melt, were attacked by oxygen or water vapor in the air, but were "stable" when converted into a purified crystalline state. A typical example is the hydroquinone (**1**) which has been reported to be stable in air as a crystalline solid but in acetic acid is readily oxidized by air to the quinone (**2**) (*2*). A particularly striking example of the practical advantage which has been taken of the relative unreactivity of solids is the "molecular packaging" of unsaturated fatty acids, thus protecting them from oxidation, by incorporating them in the channels of urea crystals in the form of urea inclusion compounds (*3*). Notwithstanding the impression which might be obtained from such examples, reactions believed to occur between molecular crystals and gases have been reported for more than a century (*4, 5*). As an example of such a reaction, a picture of a single crystal of 2-naphthol reacting with ammonia is shown in Fig. 1. Curiously, certain reactions (*6*) of great practical value, those of graphite, the ultimate polynuclear aromatic hydrocarbon, with gaseous oxygen, water, or hydrogen, as well as the interesting intercalation reactions of graphite with potassium metal vapor or bromine vapor, have been almost totally ignored by the organic chemist.



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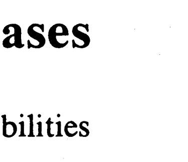

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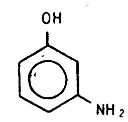
The most straightforward reason for interest in reactions between gases and solids is simply that the trouble or expense of providing and removing a solvent is avoided. For example, the reaction of 3-aminophenol (**3**) with carbon dioxide has been shown to give the carboxylic acid (**4**) in 90 percent yield by grinding the reactant (**3**) with solid potassium carbonate in an atmosphere of carbon dioxide at 175°C in a ball mill "with sufficient iron balls to keep the reactants as a freely flowing powder" (*7*). Other workers have used a rotary evaporator as a reaction vessel capable of tumbling large amounts of crystals in an atmosphere of a reacting gas (*8*), or a more elegant fluidized bed technique which has been used (*9*) for a gas-solid version of the E2 conversion of solid alkyl halides to olefins. Another method for preparative scale oxygenation has involved absorbing the substrate on microcrystalline cellulose or silica gel (*10*). These examples illustrate amply the possibility of carrying out gas-solid reactions on a synthetic scale without difficulty.



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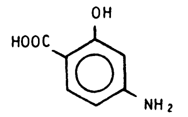

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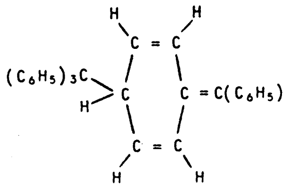
Although the advantages of dispensing with solvent would justify more general use of solid-gas reactions, the well-known fact that molecular crystals have far less structural complexity than the corresponding substances in solution (for example, their constituent molecules are almost always conformationally homogeneous) suggests that solid-gas reactions may eventually provide reaction specificity not found in solution.

Observations on a number of gas-solid reactions. A most striking characteristic of previously reported solid-gas reactions is the great sensitivity of reactivity to what would seem to be minor changes in molecular structure. A few examples merit discussion. The dimer (**5**) of triphenylmethyl radical (**6**) exists as a colorless crystalline solid which in solution rapidly dissociates to **6**. Solutions of the equilibrium mixture of **5** and **6** react rapidly with oxygen to give the peroxide (**7**).



5

$(C_6H_5)_3C\cdot$

6

$(C_6H_5)_3COOC(C_6H_5)_3$

7

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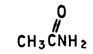
Crystals of **5** also have been reported to form the peroxide to a limited extent when exposed to air, but as a coating of peroxide forms on the crystal surfaces it protects the interior of the crystal from oxidation (*11*). In a study (*12*) of the effect of the structure of the crystalline matrix on the reactivity of triphenylmethyl radical with oxygen, the radical was introduced into such matrices composed of a series of triphenylmethyl derivatives by its formation from some of the matrix molecules by γ- or ultraviolet irradiation or by use of a Tesla coil. Oxygen was found to penetrate a matrix of triphenylacetic acid rapidly to react with the interior triphenylmethyl radicals, whereas triphenylmethyl chloride was penetrated slowly. A more extended series of comparisons gave the order

$$(C_6H_5)_3CCOOH > (C_6H_5)_3CBr > (C_6H_5)_3CCl > (C_6H_5)_3CCOO^-Na^+ > (C_6H_5)_3CCOO^-Ag^+$$

Unfortunately only the crystal structure of triphenylmethyl bromide is known (*13*), so that no correlation of ease of reaction with crystal structure can be attempted.

Studies (*14*) of the reactivity of oxygen toward radicals produced in a number of crystalline amides showed great differences in reactivity, depending on the crystal structure. For example, radicals in the interior of crystalline acetamide (**8**) or the diamide (**9**) were not attacked by oxygen under conditions that led to rapid reaction of radicals in crystalline propionamide (**10**).

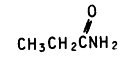


$CH_3\overset{\overset{O}{\|}}{C}NH_2$

8

$NH_2COCH_2CH_2CONH_2$

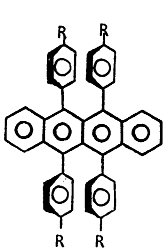
9



$CH_3CH_2\overset{\overset{O}{\|}}{C}NH_2$

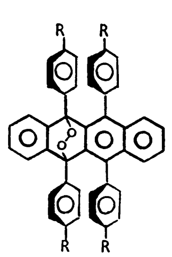
10

A further example of the dramatic effect on rate of a solid-gas reaction by a seemingly small structural change has been provided by the demonstration that deep red crystals of tetramethylrubrene (**11**) undergo ready oxidation to a colorless transannular peroxide (**12**) when illuminated in the presence of oxygen gas, whereas crystals of the parent hydrocarbon (**13**) are not oxidized at a significant rate even in an atmosphere of undiluted oxygen (*15*).



11 R = CH_3

13 R = H



12 R = CH_3

Microscopic examination has shown that oxidation occurs at the crystal surface, and the difference in reactivity of **11** and **13** was attributed to differences in permeability of the two crys-

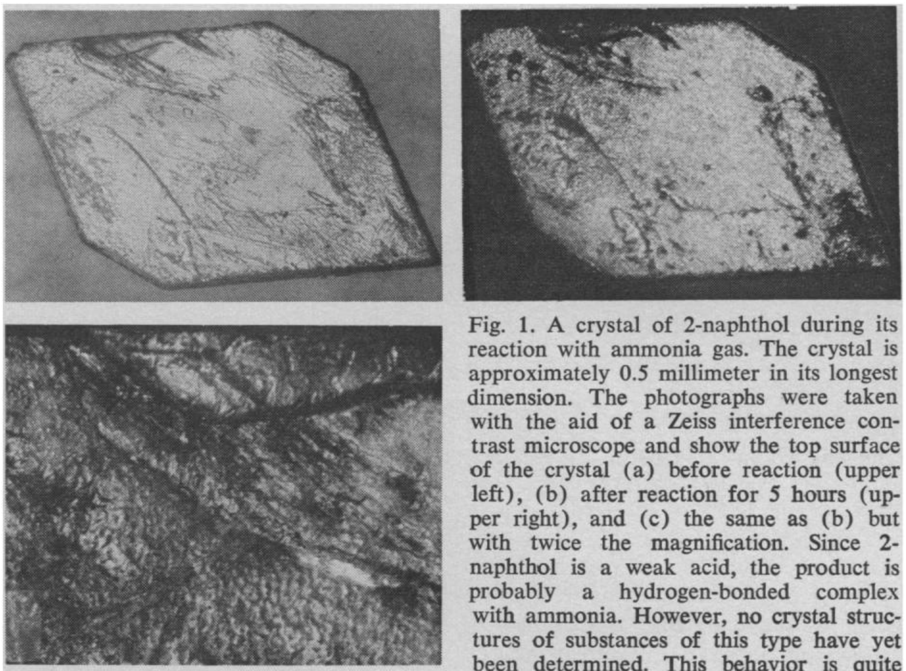


Fig. 1. A crystal of 2-naphthol during its reaction with ammonia gas. The crystal is approximately 0.5 millimeter in its longest dimension. The photographs were taken with the aid of a Zeiss interference contrast microscope and show the top surface of the crystal (a) before reaction (upper left), (b) after reaction for 5 hours (upper right), and (c) the same as (b) but with twice the magnification. Since 2-naphthol is a weak acid, the product is probably a hydrogen-bonded complex with ammonia. However, no crystal structures of substances of this type have yet been determined. This behavior is quite different from that of other compounds, such as the carboxylic acids discussed in this article, and is not yet well understood. Crystal defects or other factors may be of importance in this reaction. [Photograph by Dr. John Engelmann]

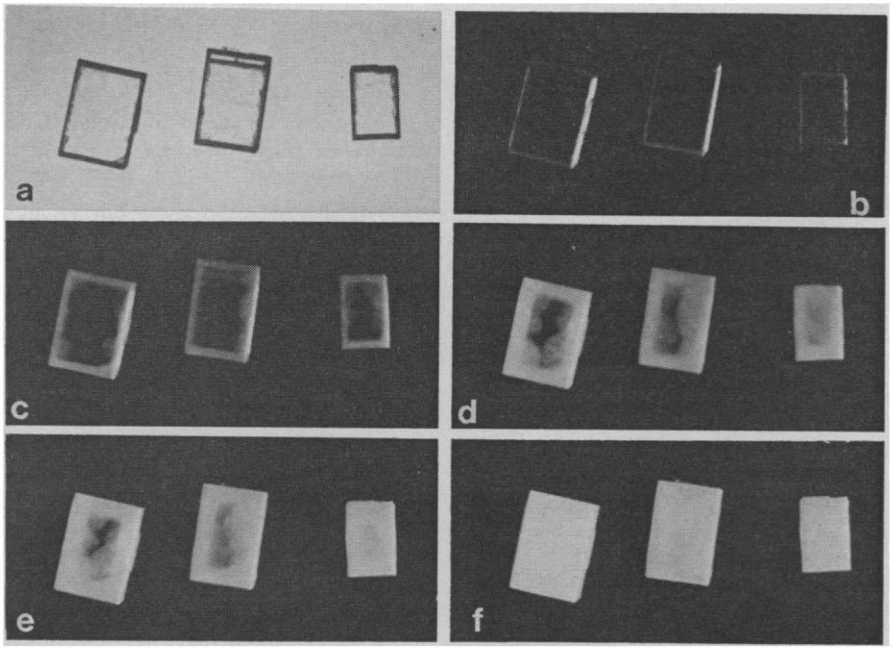
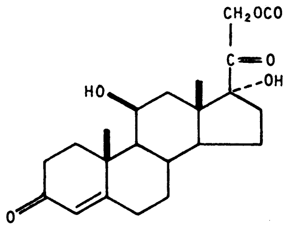
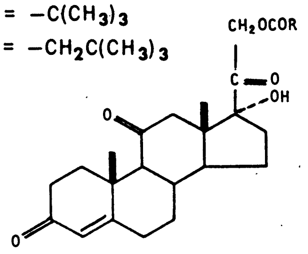


Fig. 2. A series of photographs of crystals of *p*-bromobenzoic acid undergoing reaction with ammonia. The crystals are plates with the (100) face in the plane of the picture. The top left-hand picture is viewed with regular transmitted light, while the other pictures are taken through crossed polarizing filters and with the crystals at an extinction position. Thus, the white, opaque regions correspond to regions of formation of microcrystalline product. Times are (a) 0 minute, (b) 0 minute, (c) 30 minutes, (d) 150 minutes, (e) 245 minutes, and (f) 19 hours.

tals. Once again, the crystal structures of the participants in these reactions are still unknown. A second group of examples is illustrated by the report (*16*) that, although the pivalate ester (**14**) of hydrocortisone was completely resistant to oxidation on storage for 15 to 17 years, the *t*-butylacetate ester (**15**), with a single additional methylene group, was oxidized to the ketone (**16**) to the extent of 40 percent after 1 to 2 years of storage and 80 percent after 15 years. It has been proposed that those compounds related to **14** and **15**, which undergo oxidation in the solid state, are distinctive in that they incorporate solvent in nonstoichiometric amounts when they crystallize.



14 R = $-C(CH_3)_3$
15 R = $-CH_2C(CH_3)_3$



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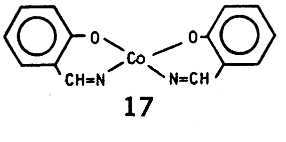
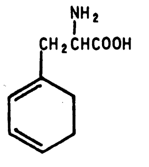
More striking still are substances that exist in two different crystalline forms, one of which is reactive toward oxygen while the other is not. The first family of such compounds is exemplified by the structure **17**, which was found to exist in different crystalline forms, one of which is inert toward oxygen and the other of which absorbs oxygen and releases it on heating. These compounds have a fascinating history, much of which has been reviewed (*17*).



17

A further example is the dihydrophenylalanine (**18**), which as the solid racemate was stable to oxidation. The single enantiomer *S*-**18**, however, showed puzzling behavior since samples were stable in the crystalline state but others were oxidized on exposure to air to *S*-phenylalanine (**19**) (*18*). Further investigation showed that *S*-**18** could be made to crystallize either in a solvent-free crystalline form that is stable or in a solid form containing water of crystallization; it is this solid form which undergoes the air oxidation that had been observed.



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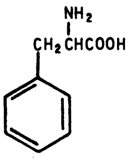

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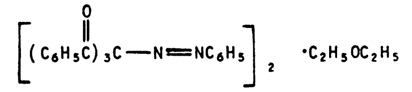
Throughout discussions in the descriptions of such examples, there is the view that the subtle effects of the structural changes noted are due to a change in the permeability of the substrate toward the reacting gas. It will have been noted also that more than once reactivity has been associated with crystallization of the substrate with solvent incorporated in the reactive form. It has naturally enough been suggested that reactivity toward the gaseous reagent might result from the diffusion of the incorporated solvent out of the crystal in such a way that channels remaining could provide access to the reactant gas. This may well be, but, unfortunately, there is little detailed structural information about such reactants, particularly concerning the mechanism of loss of solvent and structure of the solid remaining after the solvent has been lost. It might be noted that in another connection we studied (*19*) the loss of diethyl ether from single crystals of the hemietherate (**20**).



$$\left[(C_6H_5\overset{\overset{O}{\|}}{C})_3C-N{=}NC_6H_5\right]_2 \cdot C_2H_5OC_2H_5$$

20

The ether was observed to be lost initially from one or more sites at a crystal surface leaving behind crystal disorder which could be observed microscopically as a "reaction front" which swept slowly through the crystal. The hope was not realized that after the exodus of the ether there might remain a new crystalline form of the parent molecule (**21**) with cavities distributed throughout the crystal; instead

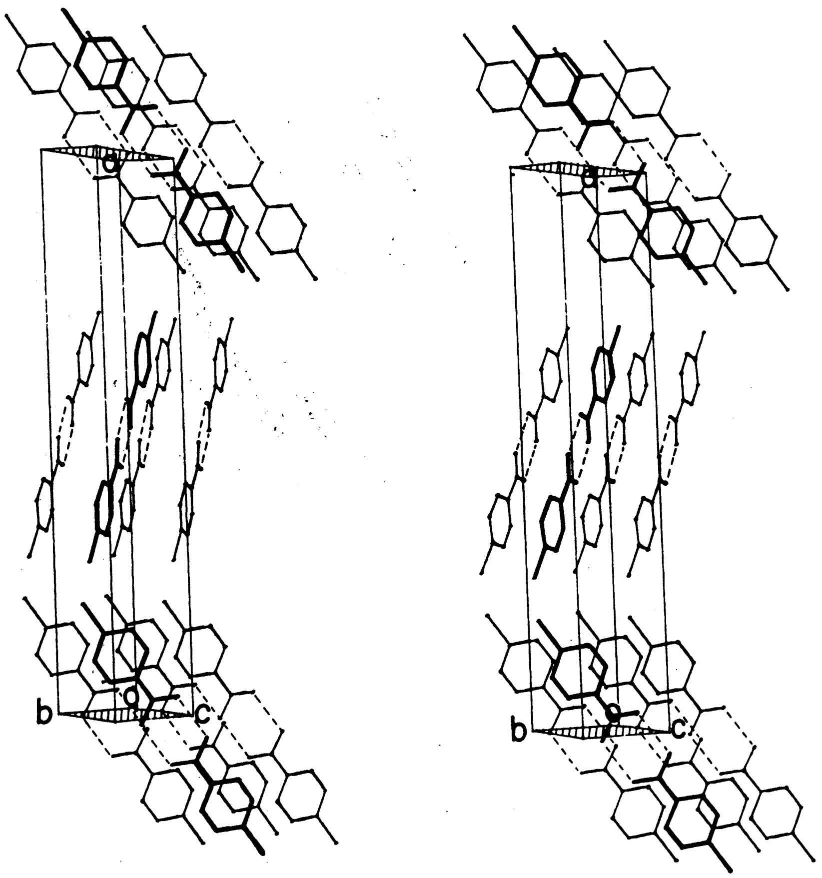


Fig. 3. A stereoscopic view of the molecular arrangement in the crystal of *p*-bromobenzoic acid. The molecules form hydrogen-bonded dimers. The (100) face that corresponds to the large developed face of the plate (Fig. 2) is normal to the *a*-axis (that is, parallel to the horizontal face shaded in the drawing). The photograph is best viewed with the aid of a stereoscopic viewer.

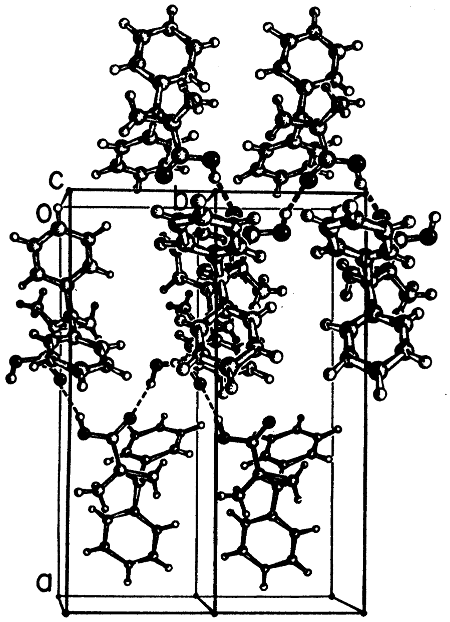
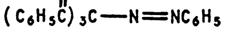


Fig. 4. Drawing of the molecular arrangement of the cyclopropane-carboxylic acid derivative (**25**). The linear chains of hydrogen bonds run horizontally so that attack by ammonia occurs readily in the direction of the *b*-axis. The carboxylic acid groups (oxygen atoms are shown in black) are effectively protected from attack in other directions by bulky hydrocarbon groups.

there was obtained an aggregate of microcrystallites of **21** which gave the same x-ray powder photograph as a finely ground sample of **21** that had been crystallized without the incorporation of ether in the first place.


$(C_6H_5\overset{O}{\overset{\|}{C}})_3C{-}N{=}NC_6H_5$

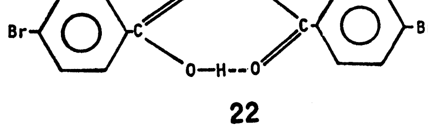
21

The effect of crystal structure has been examined more quantitatively (*20*) in studies of the addition of bromine vapor to the β- and γ-polymorphic modifications of certain meta-substituted cinnamic acids. Polymorphic forms were found to differ both in the instantaneous rates and in the manner in which they changed with time. Further, the introduction of small amounts of impurities such as the photo dimer or saturated analog produced an increase in reaction rate.

Anisotropic reaction of crystalline benzoic acid and its relatives with ammonia gas. Insight into the relation between reactivity toward a gas and crystal structure was provided by the discovery (*21–26*) that benzoic acid and a number of related compounds as powders or even as single crystals with external dimensions up to a millimeter or more react with ammonia vapor to form the 1 : 1 ammonium salt quantitatively; microscopic observation of single crystals during reaction revealed that certain crystal faces were attacked preferentially, and the resulting reaction front traveled more rapidly through the crystal in certain directions which could be correlated with the internal structure of the crystal (*21–26*). These reactions were particularly interesting because (i) they proceed rapidly to completion without side reactions; (ii) the starting materials and products are sufficiently high melting so that the incursion of a liquid phase is unlikely; and (iii) a wealth of information about crystal structures of these acids had accumulated. As an example of this behavior, crystals of *p*-bromobenzoic acid are shown undergoing reaction with ammonia (Figs. 2 and 3).

In Fig. 2 it can be seen that, as reaction occurs, formation of the ammonium salt produces disorientation of the crystal which is readily visible with the aid of a microscope. The use of an x-ray powder camera confirms that these disoriented crystals are microcrystallites of the ammonium salt with no net orientation relative to the axes of the original crystal and with average dimensions of the order of 100 to 10,000 Å (*27*), visible because they scatter light passing through the crystal. It is seen further that the ammonia attacks uniformly around the periphery of the crystal in preference to the top face, and that the advance of the front occurs at approximately the same rate from the sides of the crystal (other than the top and bottom).

In Fig. 3 is shown the internal structure (*28*) of a *p*-bromobenzoic acid crystal such as those in Fig. 2. A combination of x-ray crystal data and measurements with an optical goniometer of interfacial angles of crystals (*29*) permits the orientation of the internal structure of the crystal to be determined with respect to the crystal faces viewed by the observer. It will be noted in Fig. 3 that the crystal is made up not of *p*-bromobenzoic acid molecules but rather of hydrogen-bonded dimers (**22**). If an idealized top surface is imagined to be a perfect plane, it will be seen that it is composed of a layer of *p*-bromophenyl groups which the ammonia molecules must penetrate in order to reach the carboxylic acid functional groups with which they can react. Furthermore, should the presence of defects in the surface permit the *p*-bromophenyl layer to be breached, another such layer is encountered below, and, in fact, a similar barrier is repeated over and over again.



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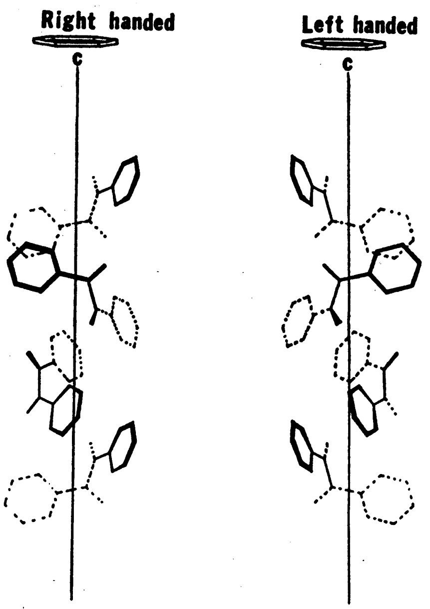
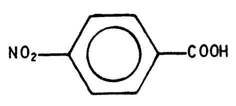


Fig. 5. Views of the arrangement of benzil (**33**) molecules in right- and left-handed spirals. The space group of these crystals is $P3_121$ or its enantiomorph.

It is reasonable, then, that attack by ammonia in a direction normal to the top face should be unfavorable. On the other hand, at any of the side faces of the crystal are exposed hydrogen-bonded carboxyl units available for reaction; and once reaction occurs, with resulting local disorientation of the acid molecules as they are converted to molecules of ammonium salt, a passageway is provided by the rows of carboxyl groups leading into the interior of the crystal and permitting ammonia molecules to pass readily from one carboxyl group to the next. Consequently, the reaction front moves relatively rapidly in directions parallel to the plane of the top crystal face. It will be noted that there is not a significant difference in Fig. 2 in the rates at which frontal advance occurs from the four side faces of the crystals, in spite of the differences in spacing and orientation of the carboxyl groups along the alternative paths.

The nature of the crystal packing and the description of the reaction of single crystals with ammonia gas found with *p*-bromobenzoic acid occurs with a number of other aromatic acids (*24–26*). We have given the name "ditropic" to the limiting case of a reaction in which the front advances at the same rate along two of the major crystal directions (*30*). Most reactions of acids with ammonia thus far studied are ditropic (*24, 25*), but two acids, *p*-nitrobenzoic (**23**) (*25*) and acenaphthylene-1-carboxylic acid (**24**) (*26*) have one zone axis along which reaction is appreciably faster than the second, and with attack in the direction of the third zone axis being relatively quite slow. In these cases the reaction rate was indistinguishable along the two opposing directions of the zone axes. These differences can seemingly be rationalized in terms of the crystal structures of the acids, but further work in this area is desirable.



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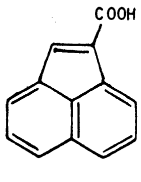

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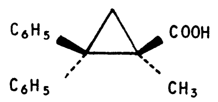
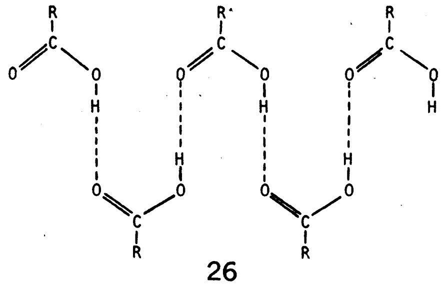


R(+)-25

The optically active cyclopropane carboxylic acid (**25**) was studied because it exemplifies a second and much less common packing arrangement of a carboxylic acid (*30*). In this case the carboxyl groups are joined in infinite single-stranded chains, the O–H of one acid molecule being hydrogen-bonded to the O=C group of the next (**26**).



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The chains are parallel to the direction of the long axis of the crystal. The reaction with ammonia gas begins at the end faces of the crystal and proceeds along the hydrogen-bonded chains. It is thus an example of a "unitropic" reaction. Bulky hydrocarbon regions

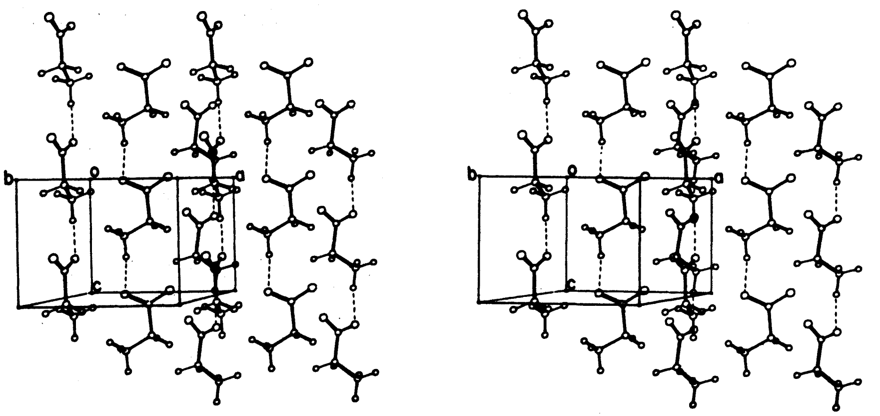


Fig. 6. The crystal structure of γ-glycine (**38**), space group $P3_2$. The polar crystal axis is the vertical *c*-axis.

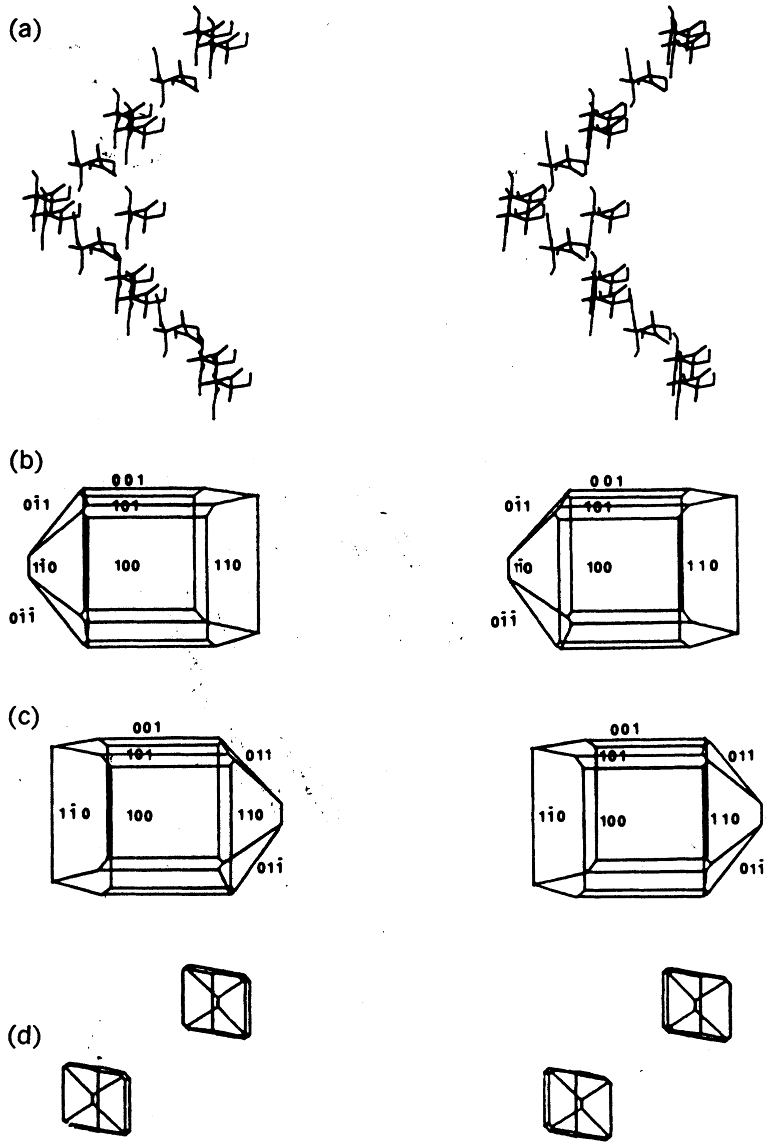
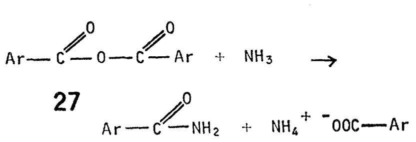


Fig. 7. (a) A stereo pair drawing of a part of the crystal structure of *R*-(−)-tartaric acid. Molecules are selected to show the characteristic (0$\bar{1}$1) and 0$\bar{1}\bar{1}$) faces which can be seen in the drawing of the crystal in (b). (b) A stereo pair drawing of a crystal of *R*-(−)-tartaric acid in the same axial orientation as (a), showing the faces which enabled Pasteur to distinguish *R*-(−) from *S*-(+) crystals. (c) A stereo pair drawing of *S*-(+)-tartaric acid. (d) A stereo pair drawing of *R*-(−)- and *S*-(+)-tartaric acid turned 90° around the *c*-axis to look along the *b*-axis. The angle between (001) and (100) (required for distinction between the *R* and *S* crystals) is shown more clearly in this drawing.

prevent propagation of reaction in other directions of the crystal (Fig. 4).

In the reaction of the cyclopropane acid **25** and also in the earlier study of acenaphthylene-1-carboxylic acid (*26*), tongues of reaction were observed to precede the reaction front, a result which suggests that crystal defects may be important in such gas-solid reactions. The importance of defects was stressed by Adler in his discussion of the reaction of oxygen with free radicals cited previously (*14*).

Reaction of ammonia gas with crystalline anhydrides. Since the reaction of ammonia with acids could be expected to be essentially instantaneous in solution, it was of interest to see whether the anisotropy observed with such highly favorable reactions could be found with reactions that proceed at a much slower rate in solution. The carboxylic acid anhydrides provided an excellent transition to other classes of reactants since they react moderately readily with ammonia in solution or in the solid state to give the amide and ammonium salt as shown below, and since they have a layered packing rather similar to the acid dimer structures, such as that shown in Fig. 3. Indeed, crystalline *p*-chlorobenzoic anhydride (**27a**) was found (*22, 25*) to undergo a ditropic reaction with ammonia rather like the reaction shown in Fig. 2. In addition, the potential utility of such reactions has been demonstrated with the finding (*25*) that the bicyclic anhydride (**30**) reacts smoothly in the crystalline state to give the expected amide-ammonium salt (**31**); although it had been previously observed (*31*), since in solution the anhydride (**30**) underwent a retro Diels-Alder reaction to give **32** and phthalic anhydride so readily, that hydrolysis was unsuccessful.



$$\mathrm{Ar{-}\overset{O}{\overset{\|}{C}}{-}O{-}\overset{O}{\overset{\|}{C}}{-}Ar + NH_3 \longrightarrow}$$

27

$$\mathrm{Ar{-}\overset{O}{\overset{\|}{C}}{-}NH_2 + NH_4^+\ {}^-OOC{-}Ar}$$

28 29

(a) Ar=p$-$Cl$-C_6H_4$
(b) Ar=p$-$Br$-C_6H_4$

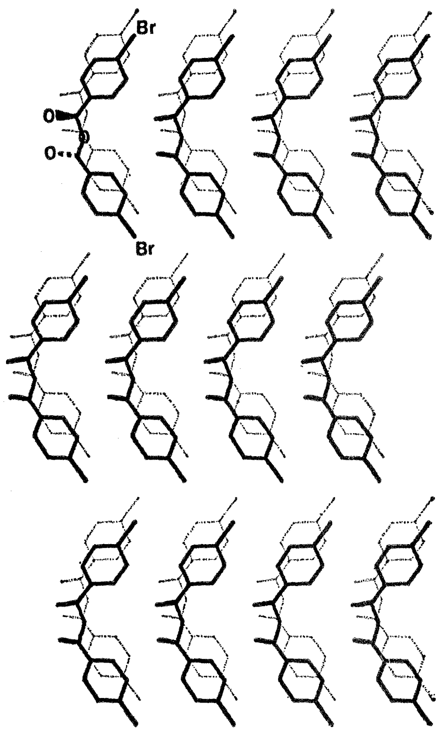
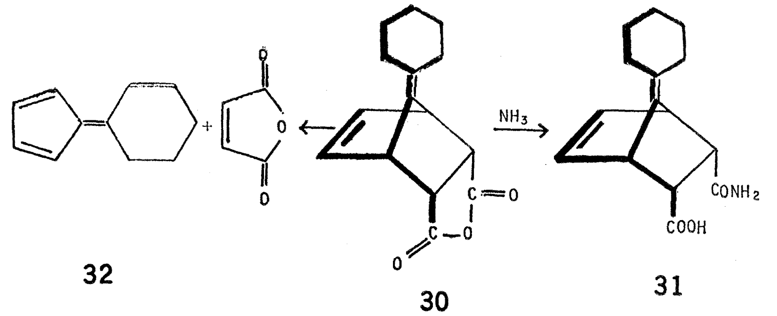


Fig. 8. Drawing of the packing of *p*-bromobenzoic anhydride (**27b**), showing the carbonyl groups all pointing approximately in one direction along the polar axis.

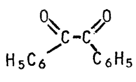
Reaction of crystalline phenols with ammonia gas. Among the earliest studies of solid-gas reactions were several investigations of the reactions of phenols (*5, 32*). The point of particular interest at that time was that by working without solvent even those phenols (see Fig. 1, for example) which were too weakly basic to form ammonium salts to an appreciable extent in aqueous solution were converted to solid 1 : 1 ammonia complexes, and in a number of cases even more ammonia was taken up to give complexes which often lost excess ammonia on standing under ambient conditions. Even today crystal structures of these ammonia complexes have not been determined, but it is now known that many phenols have a layered crystal structure rather similar to the structures of those carboxylic acids which form linear hydrogen-bonded chains (*33*). A preliminary investigation (*34*) has indicated that these compounds, like the carboxylic acids, can undergo anisotropic reaction in a way which can be related to the crystal structures of the reactants.



32 30 31

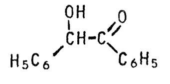
Reactions of chiral crystals. The great selectivity of the crystallization process has long been recognized (*35*) as providing a means of separating certain enantiomers by "spontaneous resolution" under favorable conditions. The completion of a resolution by this means requires that (+) and (−) crystals be distinguished and mechanically separated. The reaction of (+) and (−) crystals with the vapor of an optically active amine has been shown (*36*) to provide a simple method of assigning chirality to individual crystals, and, thus, to provide a potentially much more practical separation method.

Of much potential interest is the fact that many substances which in solution are rapidly equilibrating mixtures of enantiomers (and are thus regarded by the organic chemist as optically inactive) can undergo spontaneous resolution on crystallization, as can readily be recognized from determination of the space group by x-ray methods (*37*). The possible use of such chiral crystals as reactants which might undergo the introduction of a new asymmetric center with "asymmetric induction" was recognized by Morawetz (*38*). The substance benzil (**33**) is remarkable since it crystallizes in large, chiral, hexagonal-shaped uniaxial plates with the optic axis normal to the major face and with the impressive rotation α_D 25° per millimeter (*39*). With a polarizing microscope equipped with a monochromatic light source it is thus a simple matter to separate and identify (+)-rotating and (−)-rotating crystals. The crystal structure (*40*) is shown in Fig. 5. It is seen that the molecules pack in a spiral structure arranged in such a way that attack from one of the sides at any of the carbonyl groups should give a product with one chirality from a right-handed crystal and with the opposite



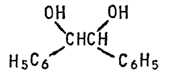
$\mathrm{C_6H_5{-}CO{-}CO{-}C_6H_5}$

33



$\mathrm{C_6H_5{-}CH(OH){-}CO{-}C_6H_5}$

34



$\mathrm{C_6H_5{-}CH(OH){-}CH(OH){-}C_6H_5}$

35

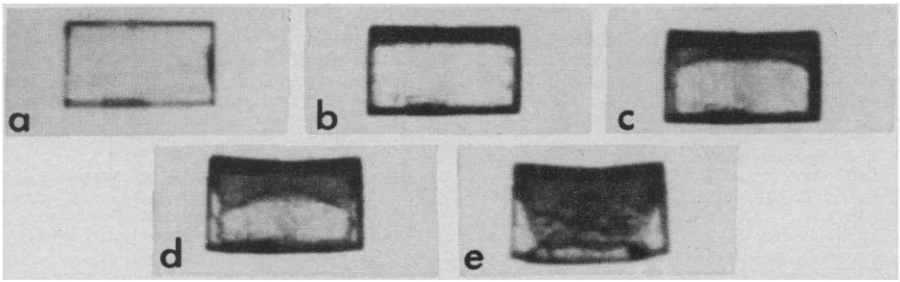
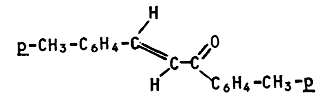


Fig. 9. A series of photographs of a crystal of *p*-bromobenzoic anhydride reacting with ammonia gas. The polar axis runs vertically in the plane of the paper. There is clear differentiation of the progress of the reaction in the two directions of the polar axis. Times are (a) 0 hour, (b) 4 hours, (c) 7 hours, (d) 13 hours, and (e) 25 hours.

chirality from a left-handed one. Unfortunately, attempts to cause crystalline benzil to react with diborane gas to give benzoin (**34**) or hydrobenzoin (**35**) with the introduction of stable asymmetric centers have been unsuccessful (*41*). There remains the major challenge of finding a suitable gaseous reagent to take advantage of the unusual properties of the benzil crystal.

The most impressive success in obtaining asymmetric induction in a gas-solid reaction has been obtained by Penzien and Schmidt (*42*), who found that bromine vapor reacts with crushed chiral single crystals of 4,4′-dimethylchalcone (**36**) to give the dibromide (**37**). The detailed mechanism of the



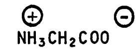
36

p-CH_3-$C_6H_4CHBrCHBrCOC_6H_4$-CH_3-p

37

reaction should be of considerable interest. Bromine is known to have an affinity both for oxygen atoms and for pi-aromatic systems, as has been shown by the rather large number of crystalline complexes it forms (*43*). There could thus be intermediate complexes in the chalcone-bromine reaction.

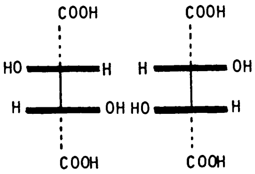
Polar crystals. Another aspect of crystal dissymmetry which has no counterpart in solution and which can be expected to attract much more of the organic chemist's attention in the future is manifested by those substances which have one or more polar directions in the crystal. An example is the γ-form of the amino acid glycine (**38**) whose crystal structure (*44*) is



$\overset{\oplus}{N}H_3CH_2CO\overset{\ominus}{O}$ **38**

shown in Fig. 6. The striking feature of this structure is that along the polar axis (which runs vertically in the plane of the page) all glycine molecules are oriented alike, with the carboxylate anion up and the ammonium group down. In a structure of this type an ideal crystal would have a substantial dipole moment. Polar crystals whose permanent dipole can be reversed by an electric field are called ferroelectrics and some members of this class of compounds, primarily organic and inorganic salts, have been investigated extensively (*45*). Of particular interest are their electrooptic properties (*45, 46*).

To be of the greatest possible chemical interest as a polar solid, a substance must (i) crystallize in a polar space group (*47*), (ii) have molecules with a high degree of structural differentiation along at least one molecular axis, and (iii) have this molecular axis oriented approximately parallel to the polar direction of the crystal (*48*). That the presence of a polar axis can have important chemical consequences seems often to have gone unrecognized. The development of hemihedral faces in the crystallization of such compounds as tartaric acid and its salts (*49*) is possible only for crystals with polar directions. It has been pointed out further (*50*) that with sufficient knowledge of factors determining rates of crystal growth, it will be possible to deduce the absolute configurations from the crystal morphology and x-ray structure. In Fig. 7 is shown a crystal of *R*-(−)-tartaric acid (**39**) together with stereo pair drawings of edges of the critical faces. Since the absolute configuration of *R*-(−)-tartaric acid is known, it can be concluded that the (011) and (01$\bar{1}$) faces have grown themselves into extinction whereas the (0$\bar{1}$1) and (0$\bar{1}\bar{1}$) faces have a lower relative growth rate and therefore survive; conversely, if the information about the relative rates of growth of such surfaces had been known, the absolute configuration could have been deduced.



R(-)-39 S(+)-39

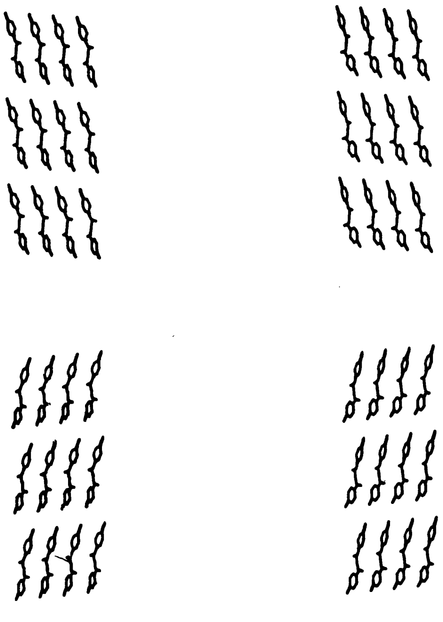


Fig. 10. Stereoscopic views of the packing of *p*-bromobenzoic anhydride looking along the directions of the +*b* and −*b* axes (the polar axis).

The demonstration that crystalline-substituted benzoic anhydrides react with ammonia gas anisotropically has provided the first example of a polar unitropic reaction. Thus, *p*-bromobenzoic anhydride (**27b**), space group *C*2 with two molecules per unit cell (*51*), unlike the other acids and anhydrides studied (*21–26*), has a polar axis with the carbonyl groups aligned along it in such a way that in a perfect single crystal they all point in the same general direction (Fig. 8). The reaction of a single crystal has been found to give a product "crystal" consisting of *p*-bromobenzamide (**28b**) and ammonium *p*-bromobenzoate (**29b**). It will be seen (Fig. 9) that reaction begins at only one end of the polar axis and moves along it in a single direction. Inspection of idealized drawings of faces at the two ends of the polar axis (Fig. 10) shows a clear preference for attack in that direction designated in the original x-ray structure elucidation (*52*) as the negative direction along the *b*-axis of the crystal, provided that it is assumed that the dominant factor is access of the ammonia molecules to the carbonyl groups. Confirmation of this prediction, which must be regarded as tentative, is a challenge as yet unmet. In any case, the ability of ammonia gas to distinguish between the positive and negative directions of the same crystal underscores the extreme sensitivity of solid-gas reactions to small variations in crystal structure.

Conclusion. Although reactions of molecular crystals are much more widespread than has been generally appreciated (*53*), the great sensitivity of their rates to seemingly trivial changes in molecular structure clearly provides a major stumbling block to the general utilization of such processes. A key to understanding the effects of structural changes has been provided by the demonstration of anisotropy of such reactions discussed in this article. It is recognized, however, that many factors in addition to those aspects of the crystal structure utilized in the discussion above may play a part in determining reactivity of crystalline solids with gases. The recent ready availability of crystal structure data for molecular crystals should lead to a more rapid development of the principles governing the packing of such crystals and their reactivity. The resulting control of such reactions should not only provide the means of causing them when they are desired, as, for example, for synthesis, but also the means of preventing them when they are to be avoided, as in the stabilization of pharmaceuticals. Finally, it appears that we have only just begun to exploit the potential reaction specificity and the exciting possibilities resulting from the unique symmetry properties of the crystalline state.

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