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# Crystallography. Part II

By JOHN A. BILES

## OPTICAL CRYSTALLOGRAPHY

### Optical Indicatrix

The manner in which light is affected by crystals arises from the internal structure. Crystals are placed in one of two classes depending on the effect of the transmission of light in different directions through the crystals. These classes are isotropic and anisotropic. Fletcher (192) introduced the optical indicatrix to explain the effect of light when passing through a nonopaque substance. In relation to this, Wooster (193) has discussed the geometrical properties of a triaxial ellipsoid.

To visualize the optical indicatrix one can consider a point source of light in the center of a crystal. Allow the light to propagate in every direction of the crystal. After an elapse of time, draw wave fronts for all of the waves. The result of all of the wave fronts is either a sphere, spheroid, or ellipsoid (triaxial). The sphere is termed an isoaxial indicatrix; solids producing such a figure are termed isotropic. These solids are also termed isometric. The spheroid, either prolate or oblate, is termed a uniaxial indicatrix; solids producing such a figure are termed anisotropic and belong to the tetragonal and hexagonal systems. The triaxial ellipsoid is termed a biaxial indicatrix; solids producing such a figure are termed anisotropic and belong to the orthorhombic, monoclinic, and triclinic crystal systems.

In order to determine the orientation of the optical indicatrix within the crystal, the crystallographer will examine the interference figures. These figures are defined as telescopic images of convergent light passing through anisotropic crystals between crossed nicols. The theory of formation of interference figures has been proposed by Kamb (194).

### Refractive Index and Molar Refraction

The velocity of the light on passing through the crystal is determined by measuring the refractive index of the section of the crystal viewed. Meaningful refractive indexes are termed principal indexes. The principal indexes are determined by viewing sections which lie in the planes of the indicatrix coordinates. This is done by looking for centered interference figures.

The refractive index depends on the velocity of the light which, in turn, depends upon the atoms, ions, or aggregates present and their position occupied in the lattice. This index is proportional to the polarizability of the molecule. The ease of displacement of positive and negative charges with respect to each other in an electric field is called polarizability. Thus, the refractive index is governed by the kind of atoms present in the molecule and the packing of the molecules, atoms, or ions in the crystalline state. The polarizability is the same in any direction in the crystal for isotropic solids. The polarizability will vary with the direction of propagation of light in anisotropic crystals. The net effect is the polarization of light which is

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quite evident when anisotropic crystals are examined under the microscope between crossed nicols.

It has been shown that the mathematical relationship of the total induced polarization which is caused by the distortion of the electron shells in the molecule is equivalent to the molar refraction (195, 196). Brühl found that conjugated unsaturated groups caused an increase of the molecular refractive and dispersive power (197). This optical exhaltation was quantitative and dependent on the nature and number of unsaturated atomic groups.

Bragg (198) was able to calculate the refractive index values for calcite and aragonite utilizing the specific refractions of the carbonate and calcium ions. This calculation was aided with an X-ray analysis which showed that carbonate ions were flat and the planes of the ions normal to the direction of the least refractive index. Under the influence of an electric field an atom develops a doublet of moment *se*, corresponding to the relative displacement to a distance *s* of elementary charges $\pm e$

$$s = E'e\lambda \qquad \text{(Eq. 3)}$$

where $E'$ = strength of field in neighborhood of atom and $\lambda$ = characteristic constant of atom. This does not depend on the direction of the local field if isotropic.

In each ml. of polarized medium, let there be $N_1$ atoms which form doublets of moments, $e$, $N_2$ forms doublets of moment $s_2e$, etc. It can be shown that

$$(K - 1)\bar{E} = P = (N_1s_1e + N_2s_2e + \ldots) \qquad \text{(Eq. 4)}$$

where $\bar{E}$ = average value of electric density throughout medium, $P$ = total polarization per unit volume, and $K$ = dielectric constant of the medium.

The strength of a doublet is

$$s_1/\lambda_1 \qquad \text{(Eq. 5)}$$

Strength of the doublet is also

$$(\bar{E} + {}^1/_3P)e \qquad \text{(Eq. 6)}$$

Thus

$$K - 1 = \frac{P}{\bar{E}} = \frac{\Sigma Ne^2\lambda}{1 - {}^1/_3 \Sigma Ne^2\lambda} \qquad \text{(Eq. 7)}$$

$$K = n^2 \qquad \text{(Eq. 8)}$$

$$n^2 - 1 = \frac{\Sigma Ne^2\lambda}{1 - {}^1/_3 \Sigma Ne^2\lambda} \qquad \text{(Eq 9)}$$

Or

$$\frac{n^2 - 1}{n^2 + 2} = {}^1/_3 \Sigma Ne^2\lambda \qquad \text{(Eq. 10)}$$

If both sides of Eq. 10 are multiplied by $M/\rho$

$$\frac{M}{\rho} \cdot \frac{n^2 - 1}{n^2 + 2} = a\,({}^1/_3 N_0e^2\lambda_1) + b\,({}^1/_3 N_0e^2\lambda_2) + \ldots \qquad \text{(Eq. 11)}$$

This additive law is obeyed approximately for isotropic material. The law would be exactly obeyed were it not for the fact that all other atoms around any given atom are not arranged at random, since those which form part of the same molecule have a definite relationship to it.

Bragg considered the polarization of the ions in the three directions; he also considered that the polarization in the $y$ and $z$ directions affected the polarization in the $x$ direction. Allowance for these effects yielded an equation for the refraction index, $n$, for any given direction of the electric vector as

$$n^2 - 1 = \frac{(c_1N_1e^2\lambda_1 + c_2N_2e^2\lambda + \ldots)}{1 - {}^1/_3(c_1N_1e^2\lambda_1 + c_2N_2e^2\lambda_2 + \ldots)} \qquad \text{(Eq. 12)}$$

The polarization of the calcium ion in calcite or aragonite is not too important since the ion contributes about 15% of the total refractivity. The value for the calcium ion is given as 1.99. The value for the calcium in calcite and aragonite is determined with the knowledge of the density of the solid. Thus

$$Ne^2\lambda = \frac{3\rho}{M} I_{Ca^{++}} \qquad \text{(Eq. 13)}$$

The value for Eq. 13 is 0.165 for calcite and 0.175 for aragonite. The $I$ value for carbonate was determined utilizing the molecular refractions of $Al_2O_3$, $NO_3^-$, $CO_3^-$, and $SO_3$. The $I_0$ for the three oxygens is between 3.3 and 3.7. When the $I$ value for $CO_3^=$ is substituted into Eq. 13, the value of 0.822 is obtained for calcite and 0.873 for aragonite. The value for $e^2$ may be calculated and then substituted back into Eq. 9. When corrections were made for neighboring interactions, Bragg found that the observed and calculated refractive indexes were similar. These values are reported in Table IV.

TABLE IV.—CALCULATED AND OBSERVED REFRACTIVE INDEX VALUES FOR CALCITE AND ARAGONITE

| Calcite | Calcd. | Observed |
|---|---|---|
| $\epsilon$ | 1.488 | 1.486 |
| $\omega$ | 1.631 | 1.658 |
| Aragonite | | |
| $\alpha$ | 1.538 | 1.530 |
| $\beta$ | 1.694 | 1.681 |
| $\gamma$ | 1.680 | 1.686 |

It is to be noted from the data recorded in Table IV that the calculated value for beta in aragonite is greater than the value for gamma. Those who have a knowledge of the biaxial indicatrix know that this is impossible. It does indicate, however, that at an early date there was developed a quantitative relationship for the calculation of refractive indexes of solids.

Bragg also pointed out that the oxygens surrounding the sulfur in the sulfate ion were uniformly distributed in the three-dimensional pattern. He thus stated that this tetrahedral arrangement of oxygen atoms was the cause of the small difference in the principal refractive indexes. This does point to the use of refractive indexes or molar refractions in prediction of coordination complexes. Dachille and Roy used infrared absorption and molar refractions to check coordination (199). The investigators related primary coordination, atomic number, atomic weight, and ionic charge to absorption wavelengths for the major bands. For $AX_2$ compounds, a $K$ value of 0.168 was obtained where $K$ was found to be

$$K = \frac{(\text{C.N.})(\mu)(A_A + A_X)^{1/3}}{Z_A Z_Z \cdot \lambda^2} = 0.168 \quad \text{(Eq. 14)}$$

where C. N. = coordination number, $Z_A Z_Z$ = valence, $\mu$ = reduced mass term, $A_A + A_X$ = sum of atomic numbers, and $\lambda$ = main absorption wavelength in microns.

Equation 14 was applied to $ABO_4$ type compounds and the $K$ value did not agree for the different compounds studied as well as the value agreed for the $AX_2$ compounds. The molar reactivities supported the conclusions reached using the infrared data.

Batsanov (200) calculated the electronic polarizability of atoms with intermediate bond character. The determination of the effect of the change of bond polarity on the atomic refraction was discussed. The study was quantitated by comparing the ionic and atomic refractivities of the elements. After finding the change in the atomic size with changing ionization and by using the proportionality of refractions to atomic volumes, a law was proposed which governs the change in the electronic polarizabilities of the atoms with a change in the bond polarity. Nutt (201) has reported a correlation and prediction of the optical and thermodynamic properties of saturated liquid hydrocarbons by the group contribution method. Such a relationship can be applied to the solid hydrocarbons which are nonpolar without too much error. Nutt used the Sellmeier-Drude equation for calculations.

The molar refractions of molecules in the solid state have been experimentally determined and compared with the calculated values. When reports were submitted for "Crystallographic Data," molar refraction values were included (202). The molar refractions have been experimentally determined for the antihistamines (203), sulfonamides (204), antitubercular compounds (205), and steroids (206). The experimental values were in close agreement with the calculated values. The reader should recall that Bragg, in calculating the refractive indexes of calcite and aragonite, stated that experimental and calculated molar refractions could be identical were it not for the fact that all other atoms around any given atom are not arranged at random (198). In some cases the experimental molar refraction showed a negative deviation from the calculated value; the deviation was by as much as 14%. Compounds showing such deviation included thiamine hydrochloride (207), $\alpha$-pyridine sulfonic acid (208), cyclotrimethylenetrinitramine (209), cyclotetramethylenetetranitramine (210), and streptidine sulfate monohydrate (211). On the other hand, it was observed that some highly conjugated systems showed a positive deviation from the calculated molar refraction. This deviation occurred with *trans*-azobenzene (212), *trans*-stilbene (213), *trans*-diethylstilbestrol (214), and 1,3,5-tri(*p*-chlorophenyl)benzene (215). The positive deviation was shown also by 4-aminosalicylic acid (216), vanillin (217), 2-mercaptobenzothiazole (218), gliotoxin (219), and 2-naphthoic acid (220). The observed and calculated molar refraction for *l*-naphthoic acid agreed within 1% (221).

Brasseur applied the Lorentz and Lorenz equation to the study of inorganic materials (222). The results obtained were satisfactory for the carbonates of calcium, magnesium, manganese, zinc, ferrous, barium, strontium, and lead.

A comparison between the square of the geometric mean refractive index of crystals and the dielectric constant determined in solvents can be made. Maxwell derived a relationship of the refractive index for light of long wavelength to the dielectric constant (223). This relationship is given by Eq. 8. This relationship is close when the molecules are far apart. A comparison of the dielectric constant calculated from refractive indexes of compounds in the solid state to the dielectric constant of the molecule in solution is shown in Table V. The dielectric constant of acetanilid and D.D.T. was determined using different solvents, and the value changed with each solvent. In addition, D.D.T. was liquefied and the dielectric constant was deter-

TABLE V.—COMPARISON OF THE DIELECTRIC CONSTANTS OF SOME DRUGS OBSERVED BY DIFFERENT METHODS (224–229)

| Compound | $\epsilon$ (from Dioxane) | $n^2$ |
|---|---|---|
| Acetanilid | 3.618 | 2.616 |
| | 2.432[a] | ... |
| Acetylsalicylic acid | 2.2583 | 2.583 |
| Barbital[b] | 2.2556 | 2.373 |
| | ... | 2.322 |
| | ... | 2.338 |
| Cholesterol | 2.2134 | 2.369 |
| D.D.T.[b] | 2.2614 | 2.773 |
| | 2.393[c] | 2.752 |
| | 2.2387[a] | ... |
| | 2.900[d] | ... |
| | 2.381[e] | ... |
| Phenobarbital[b] | 2.2477 | 2.605 |
| | ... | 2.525 |
| | ... | 2.601 |

[a] From benzene. [b] Polymorphic. [c] From carbon tetrachloride. [d] Pure liquid at 104°. [e] Pure liquid at 145°.

mined at different temperatures. The values for two such temperatures are included in the table.

Kleber (230) reported the relation between the dielectric constant and the structure of a crystal. The relation was based on the polarizability of the lattice, the anisotropic nature of the lattice, and the presence of dipoles in the crystal lattice. He related the dielectric constant to the number of structural units on 1 ml. of the lattice and the molar polarizability by

$$\frac{\epsilon - 1}{\epsilon + 2} \cdot \text{v.} = \frac{4\mu}{3} N \left[\alpha \frac{\mu^2}{3kt}\right] \quad \text{(Eq. 15)}$$

Pulou (231) measured the specific inductive capacities for 60 crystals. The dielectric constant of the crystal was measured relative to the characteristic cleavage plane or optic axis. McMahon (232) noted that the dielectric constant of certain organic compounds became higher than normal when solidified in either alternating or undirectional electric fields. In a magnetic field an anisotropic change resulted in an increase in the direction of applied field and decreased perpendicular to the field. Allen (233) related the refractive index to the specific gravity for some crystalline compounds. He stated that the geometric mean of the three principal refractive indexes was proportional to the specific gravity as given by

$$k = \frac{\alpha\beta\gamma}{d} \quad \text{(Eq. 16)}$$

He reported that his equation was good for some polymorphs but not others.

The refractive index has also been used in establishing the conformation of cyclohexane derivatives (234–236). *Cis-trans* pairs of disubstituted cyclohexanes can be differentiated by measuring the refractive index of the melt. The isomer having the higher index of refraction and higher density would be the isomer with the less conformational stability. Kelly (237) proposed that for isomeric cyclohexanes and tetrahydropyran derivatives similarly substituted on corresponding ring carbon atoms, the refractive indexes and densities increase with increasing number of axial substituents.

The refractive index of solids has been used for the identification of mixtures (238), and as a supplement to X-ray analysis of solid solutions to detect any possible heterogeneity (239). The difference between the highest and lowest refractive index values, the birefringence, has been used to predict molecular orientations (240), specific strength of cotton fibers (238), and the nature of montmorillonite complexes (241). In studying the birefringence of aromatic complexes of clays, it was noted that the polarizability of the aromatic molecule would affect the overall polarizability of the complex. When the aromatic nucleus complexed parallel to the silicate sheet, the negative birefringence increased.

### Chemical Microscopy and Optical Crystallographic Properties

The development of chemical microscopy and optical crystallography in the United States was largely the result of the works of Chamot and Mason, Keenan, McCrone, and Witt and Poe. Review articles on chemical microscopy have appeared periodically (242–249). Mason has justified chemical microscopy in the technical organization (250). Hartshorne has discussed the value of optical crystallography in industry (238). During the first and middle part of the first half of the twentieth century there was no standard practice in reporting crystallographic properties. As a result, recommended practices were published (251). Through the efforts of McCrone, optical crystallographic data were published monthly beginning in 1948 (202). This practice ceased in *Analytical Chemistry* with the report of alpha-D-talose (252). Similar reports are now appearing in THIS JOURNAL (253). Winchell has tabulated the optical properties for many compounds (224) and at the peak of the interest in optical crystallographic properties, Kirkpatrick suggested punched cards for the filing of such information (254). McCrone also suggested a punched card system (255).

Keenan and his workers contributed a large amount of data to the literature. Largely through his efforts, data were collected on U.S.P. XII compounds (225). Optical crystallographic

properties were determined for N.F. X compounds (256). Witt and Poe and co-workers contributed to the development of optical crystallographic properties of organic compounds of pharmaceutical interest (203–205,257–260). Plein and Dewey have contributed particularly in the identification of amines (261–264). The optical crystallographic studies of Bryant and Mitchell remain a classic (265–269). Bryant prepared the *p*-bromanilides of acetic acid and propionic acid and found that the acids could be semiquantitated in binary mixtures by determining the optic axial angles using five monochromatic radiations of the mercury arc. With the aid of dispersion of the optic axes and the melting points, the weights of the components could be calculated. Their additional reports emphasized various types of dispersion including crossed axial plane, inclined, horizontal, crossed, and ellispoidal dispersion. In reporting optical crystallographic data of different compounds, McCrone and co-workers had to resort to some imaginative work. Deffner and McCrone (270) reported the problems involved in the determination of the refractive indexes of *p*-dimethylaminobenzaldehyde since the compound was soluble in all of the refractive index oils. McCrone found polymorphism to be prevalent with some of the compounds tested. The relationship between temperature and transition was reported for salicylamide (271). Rose, Van Camp, and Williams have contributed to the literature. Their studies include the Rauwolfia alkaloids (272–276), alkaloids from *Vinca rosea* (277), antibiotics (278, 279), and other compounds of pharmaceutical interest. Shell (280, 281) and Clarke and Krc (282) have contributed also. Shell refined some of his studies by utilizing the universal stage (203, 204). He also stated that the orientation of the biaxial indicatrix in triclinic crystals could be determined only with the use of the universal stage (283).

The work of Prien and Frondel should not go unnoticed by crystallographers. Their original work was important in solving the toxicology of sulfonamide therapy. Through the use of optical crystallographic properties, they were able to prove that acetylsulfathiazole crystallized in the kidney. They also studied the acetyl derivatives of sulfanilamide and sulfapyridine (284–286). These investigators continued their studies with an emphasis on urinary calculi (287–289). Prien reported the structure and comparison of some 6000 human urinary calculi studied by crystallographic techniques. He was able to correlate the optical crystallographic studies with pathogenesis, and found that it was often possible to reconstruct the clinical history by an optical study of the calculus obtained from the patient. In a paper concerning the deposition of solids in the body, Pfeiffer discussed the use of X-ray diffraction, optical crystallography, and infrared absorption spectrophotometry (290). Pfeiffer suggested that the physical chemist could devote greater time to help solve the problem of cholesterol deposition. Stewart made an attempt to examine atherosclerotic and normal tissues and plasma in the fresh state and at temperatures up to 37° with the thought that results might have some bearing on the problem of the integration of certain forms of lipid in tissue. Stewart discussed the significance of the birefringent material observed (291).

Optical crystallographic properties have been used to aid in predicting molecular orientations in the solid state. Studies have been published for purines and pyrimidines (260), and dicarboxylic acids (292, 293). The limitations of the use of optical crystallographic properties in helping to determine molecular orientations has been discussed by Krishnan and Lonsdale and coworkers (294, 295).

**Fusion Methods**

The Kofler group has been responsible for the development of "Thermo-Mikro-Methoden" (296). L. Kofler, holder of the Magister in Pharmacy, Ph.D., and M.D., was a pharmacognosist but had to turn to microscopy because of lack of facilities. His wife, Adelheid, was a mineralogist who received an M.D. (297). McCrone and co-workers have been responsible for the development of fusion methods in the United States (298). McCrone pointed out that both methods were influenced by publications of Otto Lehmann. The two methods were developed apparently independently (298). Reports utilizing Koflers' procedures continue to be published. These include studies of glutamic acid antipodes (299), thermomicromethod studies of polymorphic modifications of organic compounds (300), studies of ergot alkaloids (301), ergothionein (302), binary mixtures of some medicinal agents (303), and ternary mixtures (304). With the Thermo-Mikro-Methoden procedures, the eutectic temperatures of 16 hormones were studied, using benzil, acetanilid, phenacetin, benzanilid, salophen, or dicyandiamid. It was noted that 11 of the 16 hormones were polymorphic and that three were present in commercial products in an unstable modifica-

tion (305). Arceneaux has reported that the polymorphic character of trichlorophenoxyacetic acid and related compounds made it difficult to develop a quantitative microscopic fusion method of analysis for commercial products (306). Arceneaux also presented a study of the microthermal analysis of the binary mixture of 1,2,3,4-tetrachlorobenzene-pentachlorobenzene (307).

The great amount of work that McCrone has done with fusion methods can be appreciated by referring to his text (298). His methods have been applied to pharmaceuticals. These include the sterols (308) and esters of 2,4,6-trinitrobenzoic acid (309). The naphthalene molecular addition compounds of these esters melted incongruently, whereas most of the phenanthrene molecular addition compounds melted congruently. Trinitrofluorenone was found to be capable of forming molecular addition compounds with aromatic hydrocarbons (310). From the study, it was concluded that those substituent groups known to release electrons to the benzene ring either by inductive mechanisms or by a resonance mechanism generally led to a molecular addition compound with the reagent. Bulky groups on the benzene ring prevented complex formation. The study was extended to polynuclear aromatics (311), which included the examination of adlehydes, esters, acids, amides, phenols, and aniline derivatives. The reagent is of more limited applicability to the benzene series than to the polynuclear series. The value of trinitrofluorenone was recognized, but a sub-reagent was also desirable for the identification within a series of compounds. Quinones were investigated as possible sub-reagents. Of nine quinones studied, 2,5-biphenyl-1,4-benzoquinone offered the greatest potential (312).

The use of fusion methods was extended to the identification of high explosives (313). For the identification of these compounds, thymol functioned as the solvent for the solute (explosive) crystallizations. Seven different physical characteristics were noted depending on the solubility of the compounds in thymol. It is interesting that McCrone, in this study, stated that fusion methods ensure that a given compound will always show the same morphological characteristics. West and Granatelli utilized 8-quinolinol in developing a fusion method for the microscopic identification of inorganic ions (314).

The fusion method was used in the determination of 2,2-bis-*p*-chlorophenyl-1,1,1-trichloroethane in technical D.D.T. (315). In a complete study of the problem of the impurity in D.D.T., the investigators applied the Arrhenius rate equation to the rate of crystallization of technical D.D.T. with varying percentages of impurity. When the log rate of crystallization was plotted against the reciprocal of the temperature, straight line plots were obtained. Utilizing methods of fusion techniques, the purity of compounds can be estimated by sublimation procedures (316). Petrucci and Weygandt reported that the impurity content could be determined if about 1% or greater. The same method can be used for removing trace impurities from organic solids.

## CRYSTALLINE PROPERTIES

### Crystallization

Bush reviewed the separation and purification of compounds by crystallization on a small scale (317). Tipson believes that often the best method for separation and purification of organic compounds is by recrystallization (318). He outlined schemes for batchwise, countercurrent fractional recrystallizations, and investigated the distribution of the components in the phases after each recrystallization. He illustrated his theory, scope, and methods with binary and triangular phase diagrams.

Classical multicrystal growths from solution still receives little attention (319). No comprehensive treatment of the batch process has been reported in spite of its wide commercial application. Caldwell reported that crystals of commercially acceptable size could be produced by (*a*) circulation of crystals in the supersaturation zone, (*b*) removal of excess fines, and (*c*) maintaining high magma density (320). He considered these factors in relation to a continuous crystallizer which produces supersaturation by vacuum cooling, rather than by evaporation. The continuous crystallizer, known as the draft tube, which utilizes the above listed factors will produce crystals up to about 16 mesh. Caldwell called attention to the mechanism of crystal formation. He discussed the postulates of Meir, and of Rumford and Bain, concerning nuclei formation. Crystal growth was considered from the viewpoint of bulk diffusion.

Whether crystal growth is bulk diffusion controlled, surface reaction controlled, or interface process controlled has been the subject of study by various workers. Doremus (321) showed that crystal growth rate of ionic salts was controlled by an interface process rather than by bulk diffusion of solute. He proposed an adsorbed layer on the growing crystal, and argued

mation was a fourth-power step. When growth of a constant number of small particles of the same size and concentration was greater than 0.4 m$M$, the precipitation was diffusion controlled and the kinetics was measured according to the following equation

$$k_0 t = \int_0^a a^{-1/3}(1 - a)^{-1}\, da \qquad \text{(Eq. 22)}$$

When the concentration was less than 0.4 m$M$, then the kinetics was expressed by

$$k_R t = \int_0^a a^{-2/3}(1 - a)^{-4}\, da \qquad \text{(Eq. 23)}$$

In the above equations $a$ is represented by the degree of reaction (precipitation). Thus, at low concentrations the crystal growth is increased with the fourth power of the concentration. The changes of the order of 0.4 m$M$ can be observed microscopically. When the initial concentration was less than 0.5 m$M$ the crystals were small prisms. When the initial concentration was between 0.5 and 1.5 m$M$, the crystals were more or less distorted prisms, the corners having grown more than the middle of the faces. When the concentration was greater than 1.5 m$M$, the corners had grown far more than the other parts of the crystals, giving them appearance of stars. Nielsen stated that the stars were to be expected in the case of diffusional control of growth rate since the concentration then is greatest at the corners. Rectangular growth is obtained when the concentration is approximately the same all over the surface and it cannot be so when the consumption of matter is fast compared with diffusion.

Schlichtkrull has studied the nucleation and growth of insulin crystals (339–344). Nuclei were formed by freeze drying a crystalline mixture containing dissolved insulin. Monodisperse insulin crystal suspension with crystal sizes of 5, 25, and 40 $\mu$ were obtained. The rate of nucleation and growth of the crystals as functions of concentration of insulin in crystal mixtures were reported. The rate of growth of pig insulin from a clear solution containing sodium citrate and acetone could be represented by

$$dc/dt = 2.8 \times 10^{-7} \times c\,(95.8 - c)^3 \qquad \text{(Eq. 24)}$$

where $C$ represents the crystalline fraction in per cent of total insulin and is measured in minutes. The linear rate, $R_d$, of deposition of insulin on crystal faces is

$$R_d = 1.63(C_i - 0.080)^2 \text{ u./min. for saline, beef} \qquad \text{(Eq. 25)}$$

$$R_d = 0.38(C_i - 0.066)^3 \text{ u./min. for citrate, pig} \qquad \text{(Eq. 26)}$$

The concentration, $C_i$, of dissolved insulin was expressed in mmoles per L. The shape of the crystals could be related to the species. Using ordinary methods, recrystallized pig insulin precipitated as single, sharp, and perfect rhombohedral bodies. Cattle and sheep insulin crystals were often of a twinned appearance. When urea or a halogenide was present in the mother liquid of all three insulins, perfectly shaped rhombohedral crystals were obtained. A patent was issued to Schlichtkrull for obtaining uniform insulin crystals for injection (345). A relationship between the weight of seeds ($P$), the weight of product desired ($I$), the size of seed crystals ($d_p$), and the size of the product crystals desired ($d_i$) was found to be

$$P = I\left(\frac{d_p{}^3}{d_i{}^3 + d_p{}^3}\right) \qquad \text{(Eq. 27)}$$

Choi and co-workers (346) found that $\beta$-lactose could be determined from its rate of crystallization in a saturated lactose solution abundantly seeded with crystalline $\alpha$-lactose hydrate. In a mixture of $\beta$- and $\alpha$-lactose, the $\alpha$-lactose could then be determined as the difference between the total lactose and the crystallized $\beta$-lactose. The rate of crystallization of $\beta$-lactose was represented by

$$k_2 t = \log \frac{c_0 - s_\infty}{c_t - s_\infty} \qquad \text{(Eq. 28)}$$

where the total initial lactose concentration after seeding was $C_0$, the final solubility $S_\infty$, and the concentration $C_t$, at any given time $t$.

**Crystal Habit**

Crystallographers describe the habit of a crystal as acicular, lamellar, tabular, equant, and columnar (347). The habit of pharmaceutical compounds has been used for purposes of identification. However, this method of identification has definite limitations. It has been stated that "it is virtually impossible to duplicate the crystallization pattern of a single compound on two slides" (348). The angles between any two faces of a crystal will remain the same even if the crystal growth is accelerated or retarded in one direction or another. Should crystal habits be used to identify compounds, the habits from various solvents should be used for differentiation of compounds. The microscopic identification is more reliable the greater the number of crystallizations from various solvents or the greater the number of crystallizations of different derivatives. Identification by this method has been used considerably by chemical toxicologists (349, 350).

In a series of articles Shead discussed the use of profile angles for the identification of compounds.

that fitting a solute unit directly into the crystal lattice from solutions would be difficult. It would be an improbable event for uncharged molecules to collide at a kink in a growth step with just the right orientation to fit into the crystal lattice. For ionic solutes, the difficulties would be even greater because at least two different particles would have to collide simultaneously or alternately in a kink. Furthermore, the ions would have to be desolvated at the same time as they fitted into the lattice. Thus, the concept of an adsorbed layer which permitted desolvation and partial orientation before incorporation into the lattice seemed reasonable.

Bauer (322) considered the general mechanism of crystal growth from a thermodynamic point of view. He stated that the atom layer growth through surface nucleation occurred only for growth on material of the same composition. Growth on a material of different component can occur by original formation of a mono or polymolecular layer without nucleation which then leads to formation of three-dimensional nuclei or through formation of three-dimensional nuclei directly on the foreign substrate. Hoffman (323) called attention to the free energy difference between the rate of nucleation and growth of crystallites in supercooled liquids. The free energy difference was approximated by the expression

$$\Delta F = \Delta H_f \cdot \frac{\Delta T}{T_m} \qquad \text{(Eq. 17)}$$

The equation was derived assuming that $\Delta H$ and $\Delta S$ in the thermodynamic relation

$$\Delta F = \Delta H - T\Delta S \qquad \text{(Eq. 18)}$$

is constant with temperature, and equal to $\Delta H_f$ and $\Delta H_f/T_m$, respectively. In many cases $\Delta H$ and $\Delta S$ depend on temperature. Hoffman derived a simple expression for the thermodynamic driving force in nucleation and growth processes that takes into account the temperature variation of $\Delta H$ and $\Delta S$

$$\Delta F = \left(\Delta H_f \cdot \frac{\Delta T}{T_m}\right)\left(\frac{T}{T_m}\right) \qquad \text{(Eq. 19)}$$

Those interested in the theory of crystal nucleation from vapor, liquid, and solid systems should read Dunning's discussion of the matter as well as the work of Higuchi and O'Konski (324, 325).

Stranski (326), among various workers, developed a classical theory for the growth of crystals. The growth of a crystal depended upon the molecules depositing in layers on a crystal surface. Gibbs (327) stated that a perfect crystal surface could only grow by repeated two-dimensional nucleation of new layers. According to this, a crystal can only grow if the supersaturation amounts to at least 25%. However, Volmer and Schultze succeeded in 1931 in getting iodine crystals to grow further from a 1% supersaturated vapor. This unusually great discrepancy between calculation and experiment was the cause for new investigations. In 1949 Frank succeeded in explaining the discrepancy. He stated that instead of growth occurring by growth in layers, growth occurred in the form of spirals (328, 329). Frank's theory has been tested and positive results have been reported by many investigators. Most recently, Dash and Tweet reviewed the methods of observing dislocations in crystals and discussed the work of Frank and others (330). Studies of growth steps on sucrose crystals (331), paraffin (332), diphenylamine, phenanthrene, and borneol (328) provide interesting reading. The reader should refer also to Buckley's text on "Crystal Growth" (333). Cottrell stated that to understand work-hardening, creep, fatigue, fractures, and recrystallization, one has to study the collective behavior of large, complex assemblies of dislocations, and the theory of this can go forward only when experiments have shown what are the decisive aspects of this behavior in practice (334).

### Kinetics

In a study of the kinetics of barium sulfate precipitate formation, Johnson and O'Rourke said the precipitation process is interpreted as being initially controlled by nucleation reaction and finally controlled by growth reaction (335). They reported that the rate of growth of a single crystal could be represented by

$$da/dt = -k(c_0 - c)^{2/3} \cdot a^q \qquad \text{(Eq. 20)}$$

where $a$ = mean ionic activity of $Ba^{++}$ and $SO_4^{--}$, $b$ = time, and $c_0$ and $c$ = molar concentration of barium sulfate available at $t_0$ and $t$. The kinetic constant and shape factor is incorporated in $k$. The rate of change of the mean ionic activity as well as the surface of the particle is proportional to some power $q$. The growth equation for a constant number of particles becomes

$$da/dt = -k_v^{1/3}(c_0 - c)^{2/3}(a - a_s)^q \qquad \text{(Eq. 21)}$$

Further studies on the kinetics of crystal growth in barium sulfate precipitations were reported (336–338). Nielsen found that the work of Johnson and O'Rourke was valid for precipitations of certain electrolytes. In Nielsen's original work he reported that the rate of growth of barium sulfate was controlled by some sort of chemical reaction in which the crystal for-

Using sublimation procedures, he specified the conditions necessary to obtain thin crystal plates of simple goemetric form suited for measurement of profile angles (351–354). McCrone stated, however, that profile angles are not sufficient for identification except in limited cases (355), and suggested that using profile angles along with fusion, optical-crystallographic and polymorphic studies, and rates of crystal growth would be more conclusive. In a series of articles dealing with "organic chemical microscopy," Dunbar and associates developed tests for organic classes of compounds using specific reagents. They prepared derivatives which could be identified microscopically. They reported methods for the identification of amines (356, 357), carboxylic acids, anhydrides and acid chlorides (358, 359), aldehydes and ketones (360), hydroxy compounds (361), amino acids (362), and cations (363). Van der Wegen reported the microchemical identification of some alkaloids, barbiturates, sulfonamides, and new synthetic drugs. Sixty-nine compounds and 29 reagents were tabulated with 42 drawings of crystal forms (364). Sandri has reported that bromoplatinic acid is more sensitive as a reagent for identification of organic bases than is chloroplatinic acid. Bromobismuthic acid was also studied as a reagent. In addition, Sandri used a special potassium bismuth iodide solution for the microchemical detection and differentiation of β-phenylisopropylamine and N-methylphenylisopropylamine (365–367). Berisso utilized potassium iodobismuthate to characterize and differentiate piperazine and α-methylpiperazine. Mixtures could be detected in any proportion (368). Tenger was able to distinguish derivatives of pyridine used in medicine with a modified Dragendorff reagent (369).

The use of chlortetracycline hydrochloride as a reagent for the qualitative detection or quantitative estimation of common cations or anions has been reported (370). The antibiotic did not show any promise. The characterization of certain cations with isoquinoline has been the subject of some reports (371–373). For a detailed study of the identification of elements in the periodic table, the text of Chamot and Mason should be consulted (374).

A differential method using crystalline habits has been reported for the identification of barbiturates and sedatives (84, 86). Other investigators have reported that solvents may greatly affect the habit of the crystal (375, 376). In a study of crystal habit, Stroitelev reported that a less viscous media favored more coarse and more equidimensional crystals for pregmatities and pneumatolytic, in comparison with magmatic and hydrothermal deposits (377). In a study of the crystal habit of salol, Malkin reported the dependence of the form of crystal growth on the rate of growth (378). Transition to an acicular shape occurred when the rate of growth of a crystal of salol increased. When undercooling was decreased, the rate of growth decreased and the growth of acicular crystals was replaced by growth of crystals of regular shape. The various habits of ice crystals obtained at various temperatures under an atmosphere of oxygen, nitrogen, or air with carbon dioxide have been reported (379–381).

Hartman and Perdok (382) related crystal structure and crystal morphology on an energy basis. They concluded that the morphology of a crystal is governed by chains of strong bonds running through the structure. The effective period of such a chain of strong bonds is called a periodic bond chain vector, a P.B.C. vector. The faces of a crystal are classified as (*a*) F-faces or flat faces, each of which is parallel to at least two P.B.C. vectors, (*b*) S-faces or step faces, each of which is parallel to at least one P.B.C. vector, and (*c*) K-faces or kinked faces which are not parallel to any P.B.C. vector. The faces described are listed in order of decreasing importance. In a later paper Hartman reported on his studies of the equilibrium forms of crystals (383). The F-faces were found to be the most important faces. For nonionic crystals it was found that the equilibrium form may also exhibit S and K faces. Hartman stated mathematically under what conditions S and K faces might exist.

Jackson developed an equation which permits a prediction of which faces of any crystals are smooth or rough and hence a prediction of growth morphology (384). The equation permitting this prediction is

$$\alpha = \frac{L_0}{kT_E} \cdot \frac{n_i}{V} \qquad \text{(Eq. 29)}$$

where

$$\frac{L_0}{kT_E} = \frac{\Delta S}{R} \qquad \text{(Eq. 30)}$$

$L_0/kT_E$ represents the entropy change associated with the crystal transformation divided by the gas constant, and $n_i/V$ is the fraction of the total bonding energy of an atom that can be associated with an atomic layer parallel to the face under consideration. When $\alpha < 2$, faces are rough and initiation of new layers is easy. When $\alpha > 2$, faces are smooth and initiation of new layers is difficult and growth on screw locations is important.

Rules have been established for twinning (385). Hartman (386) derived seven possible twin laws. He applied the periodic bond chain theory of crystal morphology to growth twins. He concluded that when twinnng starts on a face, this face must be an F-face or, less probably, an S-face. He stated that the difference of habit between twins and single individuals can be understood from enhanced growth at the twin boundary. This enhancement takes place only where F-faces or eventually S-faces must meet at a reentrant angle of the twin boundary. The twin plane of contact twins should be an F-face. With penetration twins, a certain F-face or S-face can be indicated that acted originally as a composition plane. Hartman stated that the existence of threefold, fourfold, and sixfold twin axes is to be doubted. The elbow twinning that occurs in calcium carbonate has been diagramed by Bragg (387).

The crystal habit has been used to correlate crystal structure with the thixotropic behavior of aliphatic urethanes (388). Hendrickson and Shulman found that all of the long chain aliphatic urethanes showing thixotropic characteristics had fine needle or cluster of needles type structures. The more pronounced the structure of the cluster of needles, the better the thixotropic properties. Compounds showing no thixotropic properties had rod-like crystal structures. One has to examine the photomicrographs to fully appreciate the relationship between the habit and thixotropy.

Shell (389) has emphasized the role that crystal habit often exerts in the development of stable suspensions. Shell stated that in tableting "the mechanical influence of crystal shape . . . is one factor, but there is another, sometimes dominant one, which results from the anisotropy of cohesion and of hardness which is possessed by organic crystals . . . It is significant that this anistropy bears a fixed relation to the fundamental crystallographic directions. Therefore, as crystal habit varies, the dominant faces may vary in their relation to this anisotropy, and it is the influence of the dominant faces which tends to orient the crystals during a packing or compression process. Thus, major habit variations of an active ingredient can influence greatly the ease or the difficulty of making satisfactory compressed tablets." Shell quantitated the crystal habit of various batches utilizing preferred orientation measurements.

### Crystal Adsorption

Some of the recent work published concerning the modification of crystal habit by the addition of impurities or poisons should provide a real stimulus. The early studies of crystal habit modifications were summarized by Whetstone (390). Whetstone reported that the crystal habit modification by dyes depended on the anionic and cationic substituent groups and the nature of the substitution. Dyes were adsorbed in a majority of conditions when sulfonic acid groups were present. Several sulfonic acid dyes were used in a study of the alteration of crystal habits of ammonium, sodium, and potassium nitrate, as well as ammonium sulfate. The effects of pH and dye presence on the crystal habit of these salts were correlated. In additional publications, Whetstone illustrated the orientation of the dye molecule in relation to the cations and anions on the crystal face where the adsorption occurred. Pleochroism was utilized in determining the face for dye adsorption (391–393). Michaels, Colville, and Tausch studied the effect of cationic and anionic surface-active agents on the growth of adipic acid crystals (394, 395). The effect of cationic and anionic surface-active agents on the growth of adipic acid crystals was studied. X-ray analysis indicated that the linear 6-carbon dicarboxylic molecules are aligned end-to-end in parallel array in the crystal with their long axes parallel to the 010 face so that the 001 face is made up entirely of carboxyl groups, while the 010 and 110 faces contain both carboxylic and hydrocarbon portions of the molecule. Trimethyldodecylammonium chloride (TMDAC) in concentrations of 0.364 mmole was twice as effective in hindering the growth on the 001 face as on the 110 or 010 face. High concentrations of TMDAC caused the formation of very thin plates or flakes. Concentrations of 50 p.p.m. sodium dodecylbenzenesulfonate (SDBS) were three times more effective in reducing growth rates on the 110 and 010 faces than on the 001 face. Higher concentrations of SDBS caused extreme habit modification, the crystals changing from hexagonal plates to long thin rods or needles. Michaels and Tausch reported that the effect of additive depends strongly on the supersaturation level of adipic acid. At low supersaturation, increasing additive concentration results in drastic reduction or cessation of growth on certain faces, while at high supersaturation levels, the additives have relatively little effect on growth, regardless of concentration. Anionic additives significantly accelerated the growth on the 001 face. Additives increased the supersaturation level at which extensive 3-dimensional nucleation occurred, and resulted in better-formed crystals. Michaels and Tausch interpreted their results in terms of 2-dimensional

nucleation and dislocation theories of crystal growth. Mechanisms for growth and habit modification were developed.

Sears reported that lead chloride in a few p.p.m. altered the growth behavior of potassium chloride (396). Sears attributed this alteration to the inhibition of the rate of growth at unit steps and that the rate of two dimensional nucleation was markedly increased by the presence of the impurity. In a second paper Sears stated that the observed alteration of crystal growth by specific soluble impurities was inexplicable by the Frank theory of crystal growth (397). He proposed that the poison was adsorbed at growth steps to give monostep coverage at each step. The growth rate from a step was then controlled by the equilibrium concentration of single unfilled sites in the line of adsorbed atoms. As the concentration of poison increased the number of open sites along a step decreased, and the rate of step motion then decreased. Sears further proposed that if a poison was adsorbed at a step, it reduced the step energy. Thus a growth poison will reduce the critical free energy for two-dimensional nucleation and increase the nucleation rate. Comer presented evidence that cations including stannic, chromium III, and ferric were adsorbed on the surface of primary ammonium phosphate and primary ammonium arsenate (398). The tapering of the crystals in the presence of the foreign cations was explained by the presence of the foreign cation at the intersection of the 100 and 101 plane and the 010 and 011 plane. This inhibited the growth and caused successive layers to deposit at a slight distance in from the intersection of these planes. McCartney and Alexander reported that the rate of nucleation and crystal growth of calcium sulfate dihydrate was most strongly reduced by colloidal materials having regularly ionized carboxyl groups on a chain structure (399). The anionic polymers were most strongly adsorbed on the 111 faces of the crystals.

#### Polymorphism and Lattice Energy

In 1821 Mitscherlich discovered polymorphism with his work on the dimorphism of calcium carbonate. Since that time a considerable amount has been reported in the literature. In 1958 Eitel reviewed the importance of polymorphism in geological problems; his review included 700 references (400). O'Conner's chapter on the polymorphism of fatty acids represents an excellent review of the massive literature on the subject (62). Additional sources concerning polymorphism include Hartshorne and Stuart (401), Kofler and Kofler (296), McCrone (298), and Jelley (192).

The importance of polymorphism has increased in recent years in pharmaceutical research for several reasons. Analytical errors may develop when analytical methods utilizing physical properties change with a change in crystal structure (306). Polymorphs of a drug differ in total solubility in a given solvent (402). The absorption rate can vary with different polymorphs of a given drug (403). Polymorphism can create problems in terms of crystal growth in suspensions (404). Polymorphic forms can create problems involving differences in filterability (405). The thermal stability can vary with different polymorphs of a drug (298). The success of a new product is seldom independent of its physical form (406).

Polymorphism or transitions from one polymorph to another can be detected by various methods. Observation of transitions with temperature can be easily detected using the Kofler melting point block. Dilatometry has been used to study polymorphism of fats and other compounds (407, 408). Cini and co-workers believe that changes in magnetic anisotropy provide a valuable tool in the study of polymorphism (409). Optical crystallography has been a most valuable tool (253), as has X-ray crystallography (410). Electron microscopy has been utilized for such identifications (411). Infrared spectroscopy has been used with success (412). Surface tension measurements have been utilized in determining the transition temperatures (413, 414).

Various methods can be used for the preparation of various polymorphs of a given compound. Pressure has been used (415, 416). This reviewer has not read any articles dealing with the polymorphism of drugs as affected by pressures used in tablet compression. Temperature changes have been widely used for the preparation of polymorphs and phase diagrams for the temperature variable have been discussed (192, 296, 298, 401). Impurities have been known to cause polymorphism (191), as well as mode of crystallization (191). Solvents have been used for the preparation of polymorphs.

Some fundamental studies of polymorphism are lacking. However, von Sydow (191) attempted to study the dipole effect of the solvent on the polymorphic form of fatty acids isolated, and reported that the study was difficult because the rate of crystallization was not controlled. A second way that the solvent could affect the crystallization was related to the vapor pressure

of the solvent. Two polymorphs of chloracetamide have been isolated using solvents (417). The difference between the cell dimensions was found to be only in the value of the obtuse angle in the unit cell. The alpha form was obtained from nonpolar solutions. These crystals were hard to dissolve in benzene or in carbon tetrachloride. Katayama suggested that these molecules become stable in these solutions by making dimers by hydrogen bonds, and the dimers thus formed come into the crystals having the alpha configuration. These crystals are quite soluble in water or ethyl alcohol and the molecules make hydrogen bonds with the solvent molecules. Katayama concluded that "this will be the reason why the crystals obtained from these solutions have a different structure." In a study of the polymorphism of 17-$\beta$ estradiol, Smakula, *et al.*, stated that the ability of molecules of a compound to associate in alternate modes of hydrogen bonding of comparable stability can be expected to be a major cause of polymorphism, thereby causing differences in the solid-state spectra of polymorphic substances (418). W. Higuchi, *et al.*, in a study of the polymorphism of methylprednisolone, reported that the lack of structural information on the methylprednisolone system precluded a single interpretation of the entropy of transition. But they suggested that the entropy difference was a result of greater localization of the functional groups in the side chain in form I resulting either from intermolecular or intramolecular interactions (419).

Because of the similarity in structures, the polymorphism of hydrocortisone terbutylacetate and prednisolone terbutylacetate was studied (420). Four polymorphs of each system were isolated, but the isolation methods were not similar.

The transition rates of some polymorphic systems have been studied. Hartshorne and Thackray have studied the $\alpha$-and $\beta$-sulfur systems (421). The activation energy for the transfer of molecules from the beta to the alpha form corresponded closely to the heat of sublimation of the beta form. Thus the molecules in the transition layer at the interface were energetically equivalent to the molecules in the vapor state. Johansson (422) suggested that should the formation of nuclei be a homogeneous process and that all crystals be of the same size, the probability of transition should be the same for each crystal. The course of the transition could be described as

$$-dN/dt = KN \qquad \text{(Eq. 31)}$$

$$N = N_0 e^{-kt} \qquad \text{(Eq. 32)}$$

where $N$ is the number of nontransformed crystals and $N_0$ is the number of crystals when time is zero. However, when log $N$ was plotted against time, a straight line was not obtained. Thus, the reaction must be heterogeneous and described by

$$N = N_1 e^{-k_1 t} + N_2 e^{-k_2 t} + \ldots \qquad \text{(Eq. 33)}$$

The heat of activation could not be determined for the various nuclei so no conclusions could be made concerning whether or not the number of nuclei was proportional to the surface or the volume of the crystals. Johansson examined the kinetics of the polymorphic transformation since such an investigation might elucidate the influence of a lattice transition on the velocity of reactions in the solid state. In a study of the growth of crystals in the alpha to beta transition in paradichlorobenzene, Bykhovskii, *et al.*, found that the linear growth rate was a function of temperature (423). The temperature dependence of the rate was not in agreement with Hartshorne's supposition that the rate of displacement of the boundary between the phases was determined solely by the difference between the rates of evaporation. Bykhovskii's conclusion was that the material was transferred directly in the solid state as a result of thermal agitation. In the study of the transition rates the results agreed best with the supposition that the alpha to beta, or vice versa, transition in paradichlorobenzene involved a dislocation mechanism in growth.

The rate constant for the reaction of phenylhydrazine with the stable and unstable modification of *o*-methoxybenzaldehyde was determined by Urazovskii (424). Using the metastable form of the aldehyde the rate constant was found to be 4.15 at 3.5°, and persisted at 5, 15, and 25°. The stable form has a much higher rate constant than that of the metastable form. In aqueous dioxane the difference was greater than in aqueous ethanol. The stable form was apparently a hydrogen bonded dimer, whereas the metastable form was chelated by a hydrogen bond. The heat of activation for the stable form was 11,400 cal. per mole and 11,200 cal./mole for the metastable form.

Structural analysis has been valuable in the study of polymorphism. The crystal structure and polymorphism of N-methylacetamide has been reported by Katz and Post (425). The low temperature form changed to the high temperature phase at 10°. Below the transition temperature the unit cell was found to be orthorhombic with 4 molecules per cell. Above the transition temperature, the orthorhombic unit cell contained 2 molecules per unit cell. Along with

this transition there was a reduction in cell size which was brought about by the existence of molecular orientational disorder. The polymorphism of glycine has been studied in detail (183, 184, 426). Three forms, alpha, beta, and gamma, have been isolated. The beta form is unstable. The molecular volume of the three forms was the same within one cubic Å. $\beta$-Glycine consisted of hydrogen bonded molecular layers extending parallel to the 010 plane. The layers have the same configuration of molecules as the alpha form. Single layers in the beta form were connected geometrically by the twofold screw axis and held together by hydrogen bonds extending in the *b* direction. In $\alpha$-glycine the nitrogen atom was buried within the double layer in such a way that very close contact of these two layers occurred. Where molecular layers were discovered in the $\beta$-glycine parallel to the *c* axis, molecular double layers held together by hydrogen bonds were found parallel to the *c* axis in $\alpha$-glycine. $\gamma$-Glycine, which showed a marked piezoelectric property along the *c* axis, was found to have a crystal structure nearly the same as that of $\alpha$-glycine. The bond distances and bond angles were compared with $\gamma$- and $\alpha$-glycine and with $\alpha$- and $\beta$-glycine. The crystal structures of the three forms of the even-numbered fatty acids, *A*, *B*, and *C*, and the four polymorphs of the odd-numbered fatty acids, namely *A'*, *B'*, *C'*, and *D'* are illustrated and discussed by von Sydow (191, 427).

The crystal structures for the polymorphs of acridine have been studied. Acridine was reported to have five distinct polymorphic forms (428). It was found that acridine I was a hydrate. Acridine II and III appeared to have nearly the same free energies at room temperature since neither showed any great tendency to transform to the other and both were produced by the decomposition of I. At higher temperatures II was the stable form. The sizes of the unit cells, lattice energies, and volumes per molecule were almost equal (172–174). A comparison of the packing of anthracene and acridine III was shown. The acridine II consisted of two molecules in the asymmetric unit cell and exhibited significant departure from planarity. This was also evidenced from the lack of fluorescence of the crystal. Birks and Cameron reported that fluorescence in aromatic compounds is associated with planarity (429). The fluorescence was determined by the presence and configuration of the $\pi$ electrons in the molecule. Phillips, *et al.*, reported that the apparent molecular thermal motions in I, II, and III were of the same type but that the translational components of the mean square amplitudes of vibration appeared to be higher in the acridines than in the anthracenes. This result may explain the lower melting point of the acridines than anthracene. Phenazine has been found to be dimorphic (430, 431). Indigo has been found to be dimorphic. The value of $a \cdot \sin \beta$ was found to be the same for the two forms. However, the change of one form to the new form occurred by a slip of about $c/4$ of the molecular plates parallel to the *YOZ* plane (432).

One of the most difficult polymorphic problems to solve was that of cortisone acetate. Several patents have been issued (433–440). The polymorphs of cortisone acetate were detected by infrared spectra (441, 442). Most recently, Callow and Kennard correlated the previous work (443). There is evidence of six crystalline modifications or solvates of cortisone acetate. Five forms of cortisone acetate and methods of their isolation along with photomicrographs were presented by Callow and Kennard. They reported that forms II, III, IV, and V as intact crystals are stable for some time in the presence of water, but when shaken or ground, transformation to form I takes place rapidly. Crystals of form II were apparently unchanged in water after 126 hours, whereas in a shaking machine a change was seen after 20 hours and was complete after 60 hours. If the crystals were ground, transformation could take place in 4 hours, but probably because of caking of suspensions, complete transformation still took about 56 hours. Form IV was found to be a dihydrate which was found to be unstable in water at room temperature. This reviewer, in a study of the polymorphism of cortisone acetate, noted that crystals from aqueous alcohol, presumably form IV, gradually changed to another form when stored at room temperature free from solvent. This change was followed easily by noting the change in the refractive indexes of the crystals.

Polymorphism has been recorded for many steroids and natural and synthetic drugs. It would be impossible to list all of the forms of the various drugs that have been reported in the literature. Though temperature studies have been reported, infrared patterns interpreted, speculations on hydrogen bonding made, little or nothing can be said of the exact molecular orientations. Much work must be done, and perhaps it is up to the X-ray crystallographers to move in.

Polymorphism has been investigated from a thermodynamic point of view. Staveley discussed, in length, the transitions in solids and liquids (444). Hurst obtained a second-order differential equation in the variable $p$ and $T$ which is valid for all phase equilibria of the first and second orders (445). A first-order phase transition is accompanied by the absorption or evolution of latent heat. Second-order transitions differ from first-order transitions in that there is no evolution or absorption of latent heat. Hurst says that a second-order transition is to be regarded as the limiting case of a first-order transition with infinitesimally small $\Delta V$. The heat, entropy, and temperature of transition have been calculated for the forms I and II of methylprednisolone (419). The escaping tendency, or fugacity, for the two polymorphs was determined by solubility studies. It was found that the transition temperature was 118°, that the $\Delta H^{\circ}_{I,II}$ was 1600 cal. per mole, and that the entropy change at the transition point was 4.1 e.u. Exploratory studies involving cloud point determinations indicated that much more energetic crystal forms were probable.

Frederick (404) reported that one of the most important elements of polymorphs is that the different forms of the same drug differ in their solubility properties. Wagner (446) pointed out the significance of differences in dissolution rate *in vivo* of drugs (of different brands of dosage forms of the same drug). The dissolution rate of a compound is proportional to the solubility of the drug in the solvent (447). From these relationships it can be concluded that one polymorphic form may have a greater activity than a second polymorphic form. Higuchi, *et al.* (419), stated that the activity of the more energetic form of methylprednisolone was found to be of the order of 80% greater than that of the more stable form. In an *in vivo* study of the forms I and II of methylprednisolone, Ballard and Nelson (403) found that the mean absorption rate in mg. per hr. per cm.$^2$ was approximately 1.7 times as great with form II than with form I. This study was performed by preparing pellets of the drug for implantation. Rats were used in the investigation. In discussing the physical chemical analysis of percutaneous absorption, Higuchi stated that substances showing lower melting points generally permitted higher concentration in solution and would thus tend to give faster penetrating systems. He stated that it would be difficult to produce rapid absorption of high melting point compounds (448). Higuchi also pointed out that different crystalline modifications may exist having different free energies, thus different thermodynamic activities at room temperature. As to the choice of polymorphs of a given drug, it may be pointed out that in 1952 Dale received a patent for the development of a polymorph of riboflavin which possessed much greater solubility and therefore a more useful form of the vitamin (402).

One can conclude then that the lattice forces are important in terms of the availability of the drug for utilization. Pirsch has contributed to the question of the lattice forces of organic molecules (449). In recognition that the form of the spatial filling of organic molecules is of decisive influence on the magnitude of the molar heat of fusion, Pirsch arranged organic molecules into three large spatial types, according to the magnitude of their molar heat of fusion. These three spatial groups were classified as (*a*) chain molecules, (*b*) disk molecules, and (*c*) spherical molecules.

Organic compounds of the spherical structures show small fusion entropy values and low molar heats of fusion. As a rule, these types of compounds demonstrate no polymorphic changes near the melting point. Closely above the melting point, liquid crystals should persist. The molar heat of fusion is greater for the disk and chain compounds, with the latter showing the highest values. A relationship was presented characterizing the linear dependence of the molar heat of fusion on the position of the melting point

$$\Delta_E H = k(T_e - a) \qquad \text{(Eq. 34)}$$

in which $k$ and $a$ are characteristic constants for each spatial form type. Just as a higher energetic form would be desirable for drug availability *in vivo*, a higher energetic form may not be the most suitable form for drug stability. Higuchi and Guillory determined the stabilities of derivatives of vitamin A (450). The investigators found that the relative rates of degradation of series of similar solid derivatives measured at any temperature were such that the logarithm of the rates was a linear function of the reciprocal of their melting points. Thus a strong lattice offers a stabilizing effect.

An additional consideration in drug availability from the crystalline state would be solvates. Rose, *et al.*, have reported that *trans*-diethylstilbestrol forms solvates when crystallized from chloroform, benzene, ether, 2-propanol, methanol, and acetic acid (214). Rose also reported that erythromycin formed an acetone and chloroform solvate which readily lost solvent

on exposure to air and converted to a powder (279). Gramicidin forms a solvate with acetone which is apparently lost on drying. Different forms were obtained from various solvents (451). Ballard and Nelson (403) reported that anomolous results were obtained when anhydrous tetracycline pellets were implanted *in vivo* (rats). They suggested that the anhydrous tetracycline at body temperature was converted to the trihydrate. Higuchi and Shefter (452) recognized that many drugs exhibit a strong tendency to form discrete hydrate structures, but that much less was known concerning the formation of solvates with organic solvents. These investigators showed that the normal amyl alcohol solvate of fludrocortisone acetate had at least five times the solubility of the nonsolvated species, while there was a twofold increase with the ethyl acetate solvate. The anhydrous forms of caffeine, theophylline, glutethimide, and cholesterol showed a greater dissolution rate than did the corresponding hydrates.

A different approach to drug availability was reported by Sekiguchi and Obi (453). These investigators compared the absorption of sulfathiazole to an eutectic mixture of sulfathiazole. Eutectics with sulfathiazole were prepared using ascorbic acid, acetamide, nicotinamide, nicotinic acid, succinimide, or urea. The urea eutectic was studied *in vivo*. Where sulfathiazole had a melting point of about 200°, the eutectic mixture of 52% sulfathiazole and 48% urea by weight melted at 112°. It was reported that the solubility of sulfathiazole decreased slightly with a continued increase by weight of urea. In a study of the report Nelson (454) stated that the 8-hour cumulative urinary excretion of the eutectic was 50%, while the 8-hour cumulative urinary excretion of the normal sulfathiazole was 39%. In Nelson's studies he reported that using finely powdered sulfathiazole the 8-hour cumulative urinary excretion was 75%.

It is evident that similar studies will follow. A fruitful area should be complexation. Drugs forming clathrates, channel lattice type complexes, as well as the possible complexation of nonpolar aromatics with heterocycles could be investigated. It would be well at this point for the investigator to review the fusion studies of the Kofler group and the McCrone group.

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# *Research Articles*

# Infrared Analysis of Pharmaceuticals III

## Identification and Determination of Adrenocortical Steroids, Barbiturates, and Sulfonamides from Paper Chromatograms

By ALMA L. HAYDEN

**The adrenocortical steroids: cortisone, hydrocortisone, and 17-hydroxy-11-desoxycorticosterone, have been identified and estimated from paper chromatograms in amounts between 50 mcg. and 1.5 mg. Recoveries of 90 to 105% of these steroids were obtained on the basis of infrared spectrophotometric determinations. Analyses were made of commercial tablets which contained (*a*) hydrocortisone and 17-hydroxy-11-desoxycorticosterone, or (*b*) the sodium salts of phenobarbital, butabarbital, and pentobarbital. The results agreed within 3.8% with those published earlier (9), or with the declared amounts. In addition, the identification and estimation of sulfanilamide in a sulfacetamide powder were achieved by these methods.**

PAPER CHROMATOGRAPHY allows the rapid separation of microgram quantities of compounds. However, the coincidence of $R_f$ and mobility values for a standard and a sample does not afford positive identification in all cases. The value of this separation technique is greatly enhanced when it is combined with other identification methods.

In addition to other applications, paper chromatography and infrared spectroscopy have been combined in the investigation of steroids in human placenta (1). Recently, the use of these

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