PERSPECTIVES: SOLID STATE ORGANIC CHEMISTRY

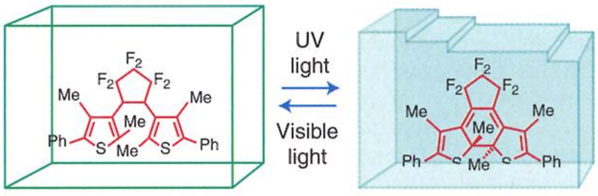
Stepping It Up

John R. Scheffer and Carl Scott

Of the three forms of matter—gases, liquids, and solids—the solid or crystalline state is the least reactive, a circumstance that led the Nobel laureate Leopold Ruzicka to refer to the crystalline state as "a chemical cemetery" (*1*). Not all solids are chemically inert, however, and in recent years, chemists have come to realize that much can be learned from studying the chemical reactions of crystals of organic compounds. On page 1769 of this issue, Irie *et al.* (*2*) report an example of such a reaction that illustrates the potential power of highly controlled solid state reactions in materials science applications and as alternatives to solution reactions in organic synthesis.

Irie *et al.* show that flat, perfectly formed single crystals of the organic compound **1** (see the first figure) turn from colorless to blue when irradiated with 366-nm ultraviolet light and simultaneously develop a series of 1-nm-high steps on the crystal surface, which comes to resemble a microscopic staircase. The compound belongs to a class of organic substances known as photochromic compounds, which undergo a reversible color change when they are exposed to light of the right wavelength (*3*). Such substances are perhaps most familiar as the materials used in photoresponsive eye wear—glasses and ski goggles that darken in bright sunlight and return to normal once the wearer goes indoors (*4*, *5*). In the case of compound **1**, the blue color of the irradiated crystals is permanent and can only be erased by exposing the blue crystals to visible light above 500 nm. During this "bleaching" process, the 1-nm steps also disappear, and the material is restored to its original flat, colorless condition.

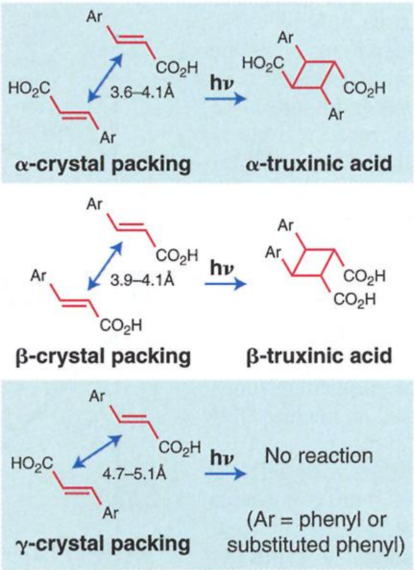
The transformation between colorless, flat and blue, stepped crystals (see the first figure) could be repeated more than 10,000 times without loss of crystal integrity and shape (*2*). This reversibility proves that the surface morphological changes are caused by a fundamental molecular process and are not simply due to local melting or some other trivial factor such as sublimation. Other workers have noted that crystal surfaces become pitted or etched upon photolysis (*6*), but the processes were not reversible.



1 2

Recycling the steps. Compound **1**, 1,2-bis(2,4-dimethyl-5-phenyl-3-thienyl)perfluorocyclopentane can be switched between a colorless, flat crystal and a blue crystal with a stepped surface by irradiation with light of different wavelengths. The crystal remains intact through thousands of cycles.

By examining the x-ray crystal structures of the crystals before and after irradiation, Irie *et al.* show that the steps are formed by a photochemical cyclization reaction of the individual molecules making up the crystal lattice. This reaction shrinks each molecule by a very small amount. The authors estimate that the total shrinkage resulting from reaction of about 600 molecular layers corresponds to a 1-nm step. Photolysis of the stepped crystals with 500-nm light reverses the cyclization; the constituent molecules expand to their original size, thus erasing the steps. As the authors point out, crystals that display reversible light-driven shape changes have potential applications as mechanical microactuators. In addition, photochromic crystals have applications as holographic recording media and other information storage/retrieval devices (*7*).



A classic example. Different crystal forms of trans-cinnamic acid and its derivatives respond differently to irradiation. This led Schmidt to formulate the topochemical postulate.

Photochromism is just one of many topics of investigation in solid state organic chemistry. Topics range from crystal engineering to predictions of crystal packing arrangements and from optical, magnetic, and electronic properties of organic solids to solid state asymmetric synthesis. But one key experimental technique, x-ray crystallography, permeates and informs the entire field. Without detailed knowledge of the shapes and packing arrangements of molecules in crystals, solid state behavior would be virtually impossible to understand.

X-ray structures have only been obtained on a routine basis since modern computing methods emerged in the early 1960s. The father of modern solid state organic chemistry, the late Gerhard M. J. Schmidt of the Weizmann Institute of Science in Israel, was the first to explore the relation between the structure of organic crystals and their chemical behavior systematically. He and his coworkers (*8*) demonstrated that trans-cinnamic acid and many of its derivatives form cyclobutane dimers upon irradiation in the solid state and that the structure of the dimers depends on the packing arrangement of the monomers in the crystal (see the second figure). X-ray crystallography showed that cinnamic acids crystallize in three distinct forms, termed α, β, and γ. In the α form, adjacent molecules are arranged in a parallel, head-to-tail fashion, and irradiation of these crystals produces the centrosymmetric α-truxillic acids. In the β form, adjacent molecules have a head-to-head arrangement, leading to the mirror-symmetric β-truxinic acids upon photolysis. In the γ form, the offset between adjacent molecules is too great for dimerization to occur, and crystals of this type are photochemically inert.

These results led Schmidt to formulate the topochemical postulate, which states that "reaction in the solid state occurs with a minimum amount of atomic or molecular movement" (*9*). Bimolecular reactions are thus expected to take place only between nearest neighbors, and the molecular structure of the product(s) is expected to reflect the geometric relation between these neighbors in the crystal lattice. As a result of these restrictions, solid state reactions are generally more selective than those in solution; fewer products are formed, and greater control is exerted over product structure and stereochemistry.

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On the basis of the topochemical postulate, Schmidt's colleague Cohen formulated the concept of the reaction cavity (*10*, *11*). According to this concept, molecules in crystals can be visualized as existing in rigid, three-dimensional cavities formed by their nearest neighbors. As the central molecule reacts, its geometry changes within the cavity. Reactions that involve minor changes in reactant geometry are topochemically allowed, that is, they proceed without restriction from the cavity walls, whereas reactions with transition state geometries that do not fit within the cavity will be strongly disfavored.

The topochemical postulate and the reaction cavity concept have stood the test of time. Countless scientific studies, including the work of Irie *et al.* (*2*), attest to their validity. The photochromic cyclization reaction of **1** is a unimolecular process that involves very slight geometric changes from reactant to product—so much so that reactant and product can coexist happily in the same crystal lattice, and the reaction is of the relatively rare single crystal–to–single crystal variety (*12*).

Carrying out organic reactions in the crystalline state has one distinct advantage. It eliminates the need to dispose of large volumes of waste solvent once the reaction is complete, a not insignificant consideration in the current age of increased environmental awareness. There will always be a need to carry out organic chemical reactions in the liquid phase, not least because not all organic compounds form solids at convenient temperatures and pressures, but solid state organic chemistry represents a unique and rapidly growing interdisciplinary field with important practical applications in materials science and chemistry (*13*).

References and Notes

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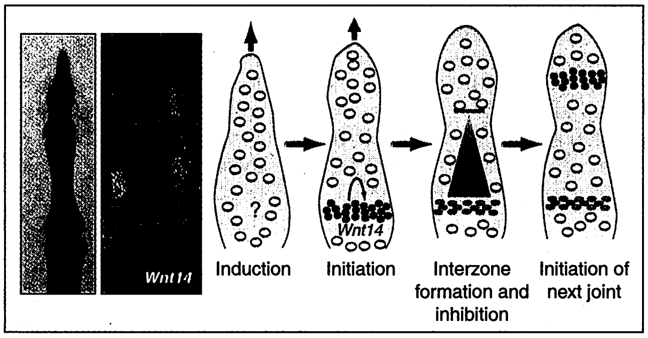
PERSPECTIVES: DEVELOPMENT

The Art of Making a Joint

François Spitz and Denis Duboule

During vertebrate evolution, the successful adaptation of limbs to a variety of ecological niches depended largely on the formation and correct positioning of synovial joints. These articulations between the long bones of our arms and legs enable our limbs to move smoothly—a fact that all of us, sooner or later, come to realize. Diseases of human synovial joints, such as rheumatoid arthritis, restrict movement and are debilitating. To design better therapeutic strategies for treating joints damaged through injury or disease, we need to understand not only how joints are made, but also what determines their exact spacing and reiteration. Several molecules that direct joint development have been identified, including a growth and differentiation factor, Gdf5, that is related to transforming growth factor–β (TGF-β) (*1*). Both mouse Gdf5 and its homolog CDMP1 in humans are mutated in syndromes where the arrangement of bones in the fingers and toes is abnormal (*2*, *3*). With the report by Hartmann and Tabin in a recent issue of *Cell* (*4*), another member can now be added to the meager cadre of proteins that direct joint development. These investigators show that Wnt14, a member of the Wnt family of signaling molecules, is a key player in the formation of synovial joints in the developing limbs of the chick embryo.

During limb development, long bones appear as continuous condensations of mesenchyme composed of prechondrogenic (cartilage precursor) cells. These mesenchyme condensations first form in the proximal region of the future limb, assembling into primordial tissue that will eventually differentiate into the long bones of the arm and leg (humerus and femur, respectively.) As the mesenchyme expands, it starts to branch, forming the bone primordia of the radius and ulna, or tibia and fibula. The distal regions of these bone primordia then branch further, laying down precursor tissue that will form the carpals and tarsals, metacarpals and metatarsals, and finally the phalanges of the fingers and toes (*5*, *6*). Within this continuous branching mesenchyme, the positions of the future joints are demarcated by areas of higher cell density called interzones (see the figure). Cells in the interzone begin to lose the properties of prechondrogenic cells: They become flattened and no longer make the typical extracellular matrix components of cartilage. The interzone becomes arranged into three layers: two areas of higher cell density that will form the articular cartilages of the joint, and a region in between of lower cell density where the cells eventually die, leaving behind the joint



Articulating joint formation. (Far left) A photograph of digit bones in the mouse skeleton illustrates how the articulations of digits rely upon the proper formation and positioning of synovial joints. **(Near left)** A developing embryonic chick limb (stage 33) contains an extending mesenchyme condensation (purple) bounded by two interzone areas (white stripes) that express the signaling molecule Wnt14. Future joints will form at the locations of the white stripes. **(Right)** The three right-hand panels illustrate a possible sequence of events during joint formation in the developing vertebrate embryo. An unknown inductive signal determines the position of the first interzone (question mark). Prechondrogenic cells in the mesenchyme condensation differentiate into interzone cells that produce Wnt14 (blue). This protein activates the expression of downstream genes encoding factors (red) that block the "joint forming" capacity of nearby prechondrogenic cells. The next interzone will form sufficiently far away from the first where the prechondrogenic cells are not affected by the inhibitory factors.

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