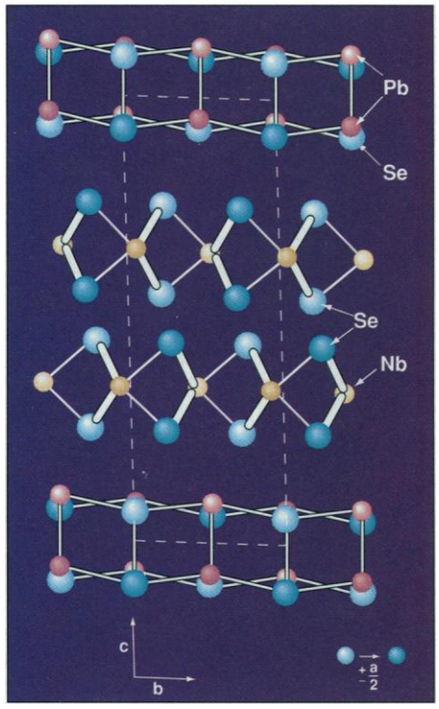
The Emerging Art of Solid-State Synthesis

Bruce Parkinson

Organic chemists have refined the process of producing molecules with specific arrangements of atoms to a high art. The molecules they synthesize, ranging from simple symmetrical cubane structures to complex asymmetric natural products, are a metastable species; that is, they are not the most stable configuration of the constituent atoms. Their synthetic methods take advantage of activation barriers to kinetically trap the atoms in a desired configuration. Because of the intrinsic instability of these molecules, organic chemists are very concerned with the mechanisms of chemical reactions, that is, how the particular arrangement of atoms in the product molecules resulted from the atomic arrangements in the reactant molecules. The products of their efforts represent the vast majority of known chemical compounds containing only three or four of the elements (C, H, O, N).

Solid-state chemists, on the other hand, who routinely work with around 80 of the elements, have been primarily concerned with thermodynamic products, which are the most stable configuration of the atoms at a particular temperature. Solid-state chemists have identified far fewer compounds than the organic chemists despite the vast number of possible combinations of all of these elements. This is partly a result of traditional solid-state synthetic techniques, where the elements to make a particular compound are mixed and heated, often at quite high temperatures and for an extended time, until they find their most stable configurations. As a result of this approach, solid-state chemists have not explored as many metastable compounds, or kinetic products, as have the organic chemists, nor have they been as concerned with the mechanisms of the solid-state reactions.

Solid-state synthesis is changing and a particularly good example of this change is reported on page 1181 of this issue by Johnson and his group from the University of Oregon (*1*). They have been pioneering a method for both the production of metastable solid-state structures and the examination of the mechanisms of solid-state reactions. What they have done is borrow techniques, refined in the semiconductor industry for the production of multilayered films of semiconducting materials, and extend them to the general problem of solid-state synthesis. The key technique is molecular beam epitaxy (MBE), which uses beams of atoms that encounter each other on a suitable substrate and react to form a desired compound. The substrate is usually heated to promote the formation of the crystalline layer, and one can then grow layers of various compositions by changing the atomic identities of the impinging beams. The highest quality semiconductor materials ever produced have been obtained with this and similar techniques (*2*).



Self-assembled solid. Solid-state structure of $(PbSe)_{1.12}(NbSe_2)_2$ showing an edge-on view of the alternating $NbSe_2$ and PbSe layered units [adapted from (*4*)].

The Oregon group uses similar beams of atoms directed at a substrate but at a temperature well below that at which these atoms directly react to form a compound. There is nearly total versatility in the selection of the composition and thickness of the various layers, but only a few of the possible systems have been explored to date. The resulting structure consists of multiple, very thin layers of amorphous elements. One then initiates the reaction of these very thin elemental layers by raising the temperature and promoting the solid-state diffusional interpenetration of the reactants and the nucleation and growth of crystalline phases. The progress of the reaction is followed by x-ray diffraction, which is sensitive to the crystalline compounds present in the thin film, and calorimetry, which gives information about the heats of reaction. Variation of the heating times (annealing) and rates provides a wealth of information about the kinetics (nucleation and growth), products, and thermodynamics of the solid-state reaction. Metastable compounds, or solid-state reaction intermediates, can be seen in many experiments.

The biggest surprise and payoff of the Oregon technique to date is described in this issue: A superlattice—repeating units of distinct, well-defined phases—was spontaneously assembled by careful control of the composition, thickness, and annealing parameters (*1*). Alternate layers of Nb, Se, and Ti were deposited and heated, resulting in a superlattice in which three nearly pure layers of the layered material $NbSe_2$ were alternated with three nearly pure layers of $TiSe_2$, which also has a layered structure. Higher temperatures produced further intermixing and the more thermodynamically favorable solid solution of niobium and titanium diselenide. Changing the composition and thickness of the initial layers results in superlattices with different numbers of $NbSe_2$ and $TiSe_2$ layers in the alternating structure.

In principle, these superlattice structures could be built up one layer at a time by a variation of MBE called van der Waals epitaxy, as has been demonstrated by several groups (*3*). However, mechanistic and thermodynamic information about the crystallization of the new phases would not be available. These superlattice structures are also reminiscent of some interesting bulk compounds synthesized in several laboratories, primarily those of Rouxel (*4*) and Weigers (*5*). One example of these bulk compounds consists of two layers of $NbSe_2$ layered structures alternated with one layer of layered structure PbSe, resulting in a final stoichiometry of $(PbSe)_{1.12}(NbSe_2)_2$ (see figure). In a sense, these solid-state materials are reminiscent of self-assembled structures, which are being intensely studied by other chemists (*6*). Self-assembly means that complex structures spontaneously form from simple components. Folded protein structures, micelles and vesicles, and some types of molecular monolayers are all examples of self-assembly.

Now, solid-state chemists have taken the first steps into the realm of self-assembly. In

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the future, unique properties of these self-assembled systems may be identified. In the case of the $NbSe_2/TiSe_2$ superlattices, the superconductivity of the system may be revealing. Bulk $NbSe_2$ superconducts below about 7 K, whereas $TiSe_2$ is not known to superconduct. Preliminary results have shown superconductivity in some of these superlattice structures (*7*). Tailoring of optical and magnetic properties will also be possible with this approach, which could yield an unlimited number of new compounds.

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Unraveling Immune Privilege

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Immune privilege, first described more than a century ago, protects tissue grafted to certain sites—the eye, testis, and brain, for example—from rejection. At first, immunologists accepted (and were satisfied with) Medawar's original explanation for this phenomenon (*1*). Medawar's view was that immune privilege was actually "immune ignorance"; privileged sites were isolated behind blood-tissue barriers and lacked lymphatic drainage. Antigenic material, trapped inside these sites, remained invisible to the immune system. As it turns out, nothing could be further from the truth.

In the 1970s, it became clear that foreign tissues in privileged sites could eventually evoke antigen-specific systemic immunity (*2*) and that certain privileged sites (such as the testis) had extensive efferent lymphatic pathways (*3*). Immune ignorance was no longer a valid explanation of privilege. Rather, the systemic immune apparatus can recognize antigens in privileged sites and cooperates to create and sustain a graft-friendly environment. As part of this renaissance, a report in this issue by Griffith *et al.* (*4*) shows that the constitutive expression of Fas ligand (FasL) on parenchymal cells within a well-studied privileged site—the anterior chamber of the eye—contributes to its privilege. In a recent issue of *Nature*, another group reported a similar finding for Sertoli cells of the testis (*5*).

These two papers illustrate two distinct aspects of immune privilege: privileged sites and privileged tissues. Immune-privileged sites are regions of the body where grafts of foreign tissue survive for extended periods (even indefinitely), compared to conventional (nonprivileged) sites. Griffith *et al.* (*4*) show how FasL may help to maintain the integrity of immune-privileged sites such as the eye. They report that Fas^+ lymphoma cells are triggered to undergo apoptosis when exposed in vitro to explants of cornea and iris–ciliary body from eyes of normal mice, but not from eyes of *gld* mice (which do not express FasL). FasL expression in the anterior chamber equips the site to delete by apoptosis Fas^+ T cells that enter the site, and lack of FasL expression may interfere with immune privilege.

By contrast, immune-privileged tissues resist immune rejection when grafted into conventional (nonprivileged) sites. In the experiment by Bellgrau *et al.*, testis cells grafted from C57BL/6 mice into a nonprivileged site (renal capsule) of BALB/c mice could survive indefinitely, whereas similar grafts prepared from *gld* C57BL/6 mice were rejected. Survival of grafts from normal mice correlated with constitutive expression of FasL on Sertoli cells, and the authors concluded that FasL expression triggers apoptosis in Fas^+, antigen-activated T cells of the recipient that engage the testis graft. Thus, constitutive expression of FasL may be crucial for the maintenance of both immune-privileged sites and immune-privileged tissues.

Immune-privileged sites and tissues
Anterior chamber of the eye
Cornea
Retina
Brain
Hair follicles
Cartilages
Liver
Adrenal cortex
Pregnant uterus
Placenta
Ovary
Testis
Prostate
Tumors
Hamster cheekpouch

Multiple features enable privileged sites to accept foreign grafts: blood-tissue barriers (in the eye and brain); absence of efferent lymphatics (eye); direct drainage of tissue fluid into the blood (eye and brain); integrity of the spleen (eye) (*6*); establishment of a potent immunosuppressive microenvironment containing growth factors [transforming growth factor–β (TGF-β) in the eye, brain, placenta, and testis] (*7*); neuropeptides [α-melanocyte–stimulating hormone, vasoactive intestinal peptide, and calcitonin gene–related peptide (CGRP) in the eye] (*8*); soluble and membrane-bound inhibitors of complement activation and fixation (anterior chamber of the eye) (*9*, *10*); and now FasL expression on cells of the ocular anterior segment (*4*).

Privileged tissues are characterized by other features: intratissue structural barriers, such as extensive tight junctions among parenchymal cells (Sertoli cells and retinal pigment epithelium); elaborate surface expression of hyaluronic acid (placenta and trabecular meshwork of the eye); reduced or absent expression of class I and II major histocompatibility complex molecules (brain, eye, and placenta); expression of class Ib molecules (placenta); release of soluble class I molecules (liver) (*11*); secretion of immunosuppressive cytokines (TGF-β in the cornea) (*12*) and corticosteroids (gonads); and now constitutive expression of FasL on parenchymal cells (testis) (*5*).

The biologic meaning of immune privilege extends well beyond experiments with tissue grafts. Antigenic materials placed in privileged sites, such as the anterior chamber of the eye, evoke a remarkable state of deviant systemic immunity in which the usual mediators of immunogenic inflammation (delayed hypersensitivity T cells and complement-fixing antibodies) are curtailed, while others (cytotoxic T cells and noncomplement-fixing immunoglobulin G antibodies) are enhanced (*13–15*). Termed anterior chamber–associated immune deviation (ACAID), this stereotypic systemic response to ocular antigens is dictated by features of the eye itself. After injection of antigen into the eye, intraocular dendritic cells pick up antigen locally and migrate via the blood to the splenic white pulp where antigen-specific regulatory and effector T cells (chiefly class I–restricted $CD8^+$) are activated. ACAID emphasizes that privilege is actively acquired and maintained, and that the immune system itself must participate.

A recent report in *Science* by Tafuri *et al.* (*16*) makes these points quite dramatically. Transgenic CBA female mice with anti-K^b

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