plexes ($M\equiv CR$) with alkynes to produce metallacyclobutadienes. Schrock's group has made a series of stable rhenium alkylidyne compounds related to **47** that illustrate the complexities of the mechanism of alkyne metathesis (Scheme 16) (*39*). When the alkoxide and alkylidyne ligands have small substituents, an irreversible reaction with alkynes produces stable metallacycles **48** with an apical alkoxy ligand; no alkyne metathesis is seen. Complex **47** having large alkoxy and alkylidyne substituents was unusual in that it effectively catalyzed metathesis of alkynes with bulky substituents. Both alkylidyne complexes similar to **47** and an isomeric metallacycle with an apical imido ligand were observed during catalysis.

Schrock and co-workers have proposed that for complexes with relatively small substituents on the alkoxy and alkylidyne ligands, electronically preferred attack of the alkyne occurs on the C/N/O face of the pseudotetrahedral complex to produce the stable metallacycle **48** and no catalysis is seen (*39*). However, for bulky catalysts and alkynes, the alkyne attacks the less hindered C/O/O face of the pseudotetrahedral catalyst **47** to give the reactive metallacycle **49**. Isomerization of **49** to the related metallacycle **49′**, which also has an apical imido group, proceeds through intermediate **G** by two Berry pseudorotations. A new alkyne is then eliminated from **49′** by the microscopic reverse of the initial addition. Occasionally, alkyne addition to the C/N/O face of **47** occurs to produce the stable metallacycle **48** and catalysis ceases. This explanation requires that metallacycle **48** be much more thermodynamically stable than **49** and that conversion of **49** to **48**, which could occur by a Berry pseudorotation about an oxygen pivot, be very slow.

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Turning Down the Heat: Design and Mechanism in Solid-State Synthesis

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Solid-state compounds have historically been prepared through high-temperature solid-solid reactions. New mechanistic understanding of these reactions suggests possible routes to metastable compositions and structures as well as to thermodynamically stable, low-temperature phases that decompose at higher temperatures. Intermediate-temperature synthetic techniques, including flux and hydrothermal methods, as well as low-temperature intercalation and coordination reactions, have recently been developed and have been used to prepare unprecedented materials with interesting electronic, optical, and catalytic properties. The trend in modern solid-state synthesis resembles increasingly the approach used in small-molecule chemistry, in the sense that attention to reaction mechanism and the use of molecular building blocks result in an ability to prepare new materials of designed structure.

The birth and development of useful technologies often hinge on the availability of solid-state materials with appropriate physical and chemical properties. Forty years ago, the preparation of pure semiconductors as single crystals led to a complete transformation of the electronics industry. Today, new high-temperature ceramic superconductors, nonlinear optical solids and thin films, supermagnetic alloys, and "nanophase" catalytic materials also promise to initiate sweeping changes in relevant technologies, including communications, computing, transportation, and chemical manufacturing, to name the most obvious.

Although many of these key solid-state materials have been discovered the old-fashioned way (by accident), rational synthesis is now playing an increasingly important role. The interplay between structural chemistry, physical measurement, and theory is today sufficiently refined that it is often possible to predict a priori the structure and

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composition of compounds that are expected to have a certain desirable property. The problem simply lies in how to make them. For example, one family of thallium cuprate superconductors may be represented by $Tl_2Ba_2Ca_nCu_{n+1}O_x$, where $n + 1$ is the number of contiguous copper oxide planes between thallium–barium oxide layers. As $n + 1$ increases from 1 to 2 to 3, the superconducting transition temperature T_c goes from approximately 80 to 110 to 125 K (*1*). Several theories point to the importance of interplane coupling in the superconductivity of these materials (*2*), and one might reasonably ask whether the highest T_c values should be anticipated for the compound with $n = \infty$, if only it could be made. Unfortunately, attempts to prepare pure phases of this stoichiometry in the desired structure have to date been unsuccessful.

The problem with trying to make such materials is that the products of solid-state reactions today are predictable only in a very limited sense. Thus, although it is often possible to calculate properties on the basis of known or theoretical structures (*3*), predicting the most stable structure for a given composition of matter is still more of an art than a science. Through a massive inventory of known compounds and reactions, a framework of structural families and heuristic composition-structure relations has emerged; nevertheless, even seemingly innocent isomorphous substitutions in known compounds can lead to unexpected materials.

A good case to illustrate the latter point was the initial preparation of the 1-2-3 superconductor, $YBa_2Cu_3O_{7-\delta}$, in 1987. After the discovery by Bednorz and Müller (*4*) of superconductivity in $La_{2-x}Sr_xCuO_4$, which adopts the relatively simple K_2NiF_4 structure (see below), it was observed that T_c could be increased slightly by the application of pressure. Chu and co-workers (*5*) reasoned that substitution of a smaller trivalent element for lanthanum, such as yttrium, might have the same effect as increasing the pressure and therefore attempted to synthesize a Y-Ba-Cu-O compound in the same stoichiometry. To their surprise, they found the first compound with superconductivity above the boiling point of liquid nitrogen, but only in a small fraction of the sample, and no phase with the K_2NiF_4 structure at all. Subsequent experiments in many laboratories revealed that the stoichiometry of the new superconducting phase was quite different from that of the La-Sr-Cu-O compound (*6*) and in fact represented an entirely new structure.

Although this is a spectacular example, it is not unusual in the sense that completely new structures are found all the time from relatively simple combinations of elements in solid-state reactions. The solid-state chemist is guided much more by intuition than by the kind of definitive principles that would be used in planning an organic synthesis. This synthetic style is often difficult to justify in grant proposals; nevertheless, it ensures a considerable measure of excitement and joy of discovery for those who prospect in solid-state phase fields.

Mechanisms of Solid-State Reactions

Molecular chemists are usually more comfortable with notions of stepwise transformations and kinetic control in synthesis than they are with thermodynamic considerations. The fact that organic reactions proceed at reasonable rates under mild conditions allows for the design of intricate, multistep synthetic pathways in which the true thermodynamic minimum for a particular combination of elements is usually irrelevant. Kinetic control over product distributions implies that the reaction mechanism may be learned, and thus chemical reactivity may be classified according to structure, that is, according to the functional groups present in a molecule.

On the other hand, traditional solid-state synthetic techniques produce thermodynamically stable products, usually by solid-solid reactions at temperatures in the neighborhood of 1000°C. There is no doubt that there will always remain many important and useful high-temperature, solid-state reactions and processes, for example, the manufacture of dense AlN ceramics and SiC heating elements. Still, in these reactions the mechanism is generally not considered, and there is little control over the formation of metastable intermediates. The rate-limiting step is diffusion of atoms or ions through reactant, intermediate, and product crystalline phases. Often, the activation energy for diffusion is a substantial fraction of the individual bond strengths in the product and significantly exceeds the activation barrier for converting metastable phases into the most stable one. Even thermodynamically stable compounds can be inaccessible by this route. Because solid-state diffusion is slow, there is often no kinetic access to compounds that are stable at low temperature but decompose at higher temperatures.

Mechanistic solid-state chemistry, and the design of interesting metastable phases, may therefore be considered only at temperatures significantly lower than those of "brute force" solid-solid reactions. This idea is now only beginning to be explored, at suitably low temperature, for reactions in which diffusion is normally rate-limiting. Johnson and co-workers have recently described a new strategy for studying such reactions (*7*). Reactions are made to proceed at observable rates by drastic shortening of the length scale over which solid-state diffusion must occur. That is, the reactants are vapor-deposited as nanometer-thick layers on top of each other in a repeating sequence that ultimately yields a thick enough "lasagna" so that both x-ray diffraction and thermal measurements can be carried out as the reaction proceeds. Not surprisingly, intermediates that are inaccessible by high-temperature techniques are detected under these controlled conditions. Among the most common intermediates, when the layers consist of two different elements such as nickel and zirconium, or iron and silicon, are "glassy" alloys. Although the crystalline reaction products are more stable than the amorphous material, a kinetic nucleation barrier prevents their formation at low temperatures.

The ability to form amorphous metals in this way is interesting because some of these alloys are superior to crystalline materials as ferromagnets. More importantly, it opens the door to a detailed mechanistic study of solid-solid reactions. Although the technique is quite new, it has already been used to identify kinetic "dead ends"—intermediate phases through which diffusion is extremely slow. For example, in the synthesis of the cluster compound $LaMo_6Se_8$ from the elements, a variety of refractory solids ($MoSe_2$, Mo_6Se_8, and La_2Se_3) can be identified in the course of the reaction. The formation of these crystalline intermediates is quite rapid, but their conversion to the ultimate product requires 2 weeks at 1200°C in bulk samples (*8*). Thin-film diffusion also offers one possible route to new materials that are unstable at high temperature and to interesting metastable arrangements of atoms.

Lessons from Molecular Synthesis

Procedures for the synthesis of organic compounds differ from the solid-solid reaction route outlined above in two important respects. First, diffusion limitations are removed because the molecular reactants are dispersed in a suitable medium, such as a solvent, so that they are always intimately mixed. Second, the reactions proceed by transformation of only part of the molecule (the functional groups) at a time, leaving intact the bonding relations between most of the atoms. We discuss below how both of these concepts are now taking root in the rational design and synthesis of new solids. Intimate mixing of reactants can be accomplished by using molecular precursors that can react either in the vapor or in the solution phase or by dissolving refractory reactants either in a molten metal or salt (the flux method) or in a molecular solvent (the hydrothermal method). A somewhat

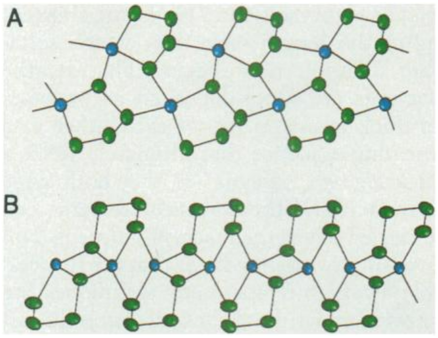

Fig. 1. Ball-and-stick representations of the Cu (blue) and S (green) atom networks in (**A**) α-$KCuS_4$ and (**B**) β-$KCuS_4$ (*13*). Note that S_4^{2-} anions are present in both structures and that in (A) both terminal and internal sulfur atoms are bound to Cu^I whereas in (B) only terminal S–Cu bonds are formed.

more elegant approach to mixing of reactants, "la chimie douce" (the latter word translating both as "gentle" and "sweet"), involves making a single-phase solid precursor of the appropriate stoichiometry and converting it thermally to product, all at relatively low temperature. In all of these techniques, particularly the last one, we find an increasing trend toward retention of structural elements of the reactants in the final product phase. Especially at low reaction temperatures, the solid-state analog of organic functional group chemistry is now emerging.

Flux and Hydrothermal Syntheses—Hot But Not Too Hot

Many precursors to inorganic materials, such as metals, binary metal oxides, network solids such as silicates, and most nonmetallic elements, are quite insoluble in ordinary solvents. Unlike molecular solids, which are held together by weak noncovalent forces, these "extended" solids contain no molecules per se but consist of an infinite lattice of atoms held together by strong ionic or covalent bonds. Solubilization of the network usually requires highly polarizing media at elevated temperatures. In the flux method, this medium is a molten salt, usually in the temperature range from 200° to 600°C. In the hydrothermal (or more generally, solvothermal) method a polar solvent is used, often containing a "mineralizer," that is, a soluble inorganic salt. The temperature regime of the hydrothermal method is lower than that of the flux method, and in fact interesting examples of hydrothermal crystallization at room temperature and even at ice temperature have recently been found (9). More typically these reactions are carried out in closed vessels above the normal boiling point of the solvent, at temperatures up to about 400°C. At these intermediate temperatures, thermodynamic considerations favor more complex structures of lower enthalpy, lower entropy, and lower symmetry. Many interesting metastable structures can also be formed and trapped kinetically. An additional advantage of this particular temperature regime is that it is still sufficiently high to be conducive to the growth of single crystals, or at least well-ordered polycrystalline samples, that are amenable to characterization by diffraction methods.

New and better materials from flux reactions. In flux reactions the distinction between "solvent" and "solute" is often lost, in the sense that the flux may supply atoms or structural building units that end up in the final crystalline product. In addition, the chemical properties of the flux, such as its acidity and redox potential, have a controlling influence on the nature of the products. These parameters allow considerable latitude for fine-tuning the outcome of flux reactions.

One class of compounds that illustrates these ideas is the alkali transition metal polychalcogenides. Chalcogens (sulfur, selenium, and tellurium) have a rich chemistry both in molecular compounds (*10*) and in the solid state (*11*) because of their ability to catenate (the S_8 allotrope of sulfur being one familiar example) and to bind to multiple metal centers. Polychalcogenides (materials containing chalcogen-chalcogen bonds) are interesting as low-dimensional photoconductors, semiconductors, and metals. Polychalcogenide solids cannot be formed at high temperature, either in solid-solid or vapor transport reactions, because catenated anions tend to decompose endothermically to simpler species (*12*):

$$Q_x^{2-} \leftrightarrow Q_{x-n}^{2-} + nQ \ (Q = S, Se, Te) \qquad (1)$$

The flux from which these compounds are grown contains variable amounts of strongly basic alkali chalcogenide (M_2Q) as well as oxidant (Q) so that the basicity, oxidizing power, and temperature of the reaction medium are all controllable parameters. A remarkable example of the complexity of these solvent systems is the phase relation between the $KCuS_4$ polymorphs prepared by Kanatzidis and co-workers (*13*). The structures of the α- and β-forms of this material are compared in Fig. 1. Although both are one-dimensional and contain S_4^{2-} groups, they differ substantially in Cu^I-anion connectivity. Both compounds were isolated in quantitative yield from identical flux compositions, the difference being that the α-form is made at 210°C and the β-form at 250°C. The transformation between the two forms is not reversible, except in the molten flux. Also, the Q_{x-n}^{2-} products of flux reactions carried out at higher temperature (*14*) (CuS and KCu_4S_3) do not transform to either $KCuS_4$ polymorph upon slow cooling through the relevant temperature regime. This example provides some evidence for the existence of "precursor" catenated species in the molten flux that are incorporated into the solid that is ultimately isolated and that are not readily interconvertible under intermediate temperature conditions.

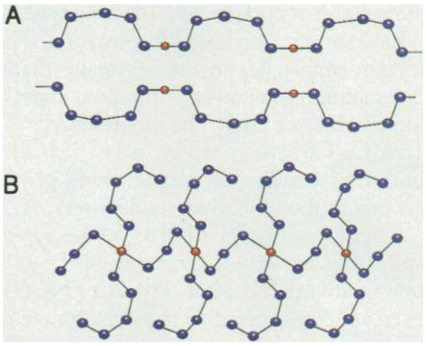

Fig. 2. Ball-and-stick diagrams of the one-dimensional Au (red) and Se (blue) atom networks in (**A**) $KAuSe_5$ and (**B**) K_3AuSe_{13} (*15*). In (A) the Au^I (d^{10}) centers have a linear coordination and are linked by bridging Se_5^{2-} ligands. In (B) the chains consist of both terminally bound Se_5^{2-} ligands and bridging Se_3^{2-} groups surrounding square planar Au^{III} (d^8) atoms.

Small changes in the oxidizing power of the flux can be quite important in transition-metal polychalcogenide reaction systems. Both $KAuSe_5$ and K_3AuSe_{13} (Fig. 2) are one-dimensional chain structures isolated from polyselenide melts at 250°C (*15*). The Au^I compound $KAuSe_5$ forms from an ever-so-slightly less oxidizing (K_2Se/Se = 0.9/4) flux than the Au^{III} compound K_3AuSe_{13} (K_2Se/Se = 1/4). In the former compound, the anion is Se_5^{2-}, whereas in the latter both terminal Se_5^{2-} and bridging Se_3^{2-} groups are present. Longer polychalcogenide anions are more oxidizing, and the choice of a five-membered chain versus a mixture of five- and three-membered chains obviously represents a subtle interplay between oxidation potentials, covalent bond strengths, and crystal packing forces. When this variability is combined with the multiplicity of oxidation states and coordination geometries available to late- and posttransition metal ions, it is no wonder that the whole family of crystalline polychalcogenides produced by flux methods within the last few years presents an almost bewildering array of new low-dimensional structure types (*12*).

For the growth of oxide crystals, chalcogenide melts are unsuitable and hydroxide fluxes are an obvious choice. The most commonly used are NaOH and KOH. These are relatively low-melting salts, the eutectic temperature being 175°C. Normal-

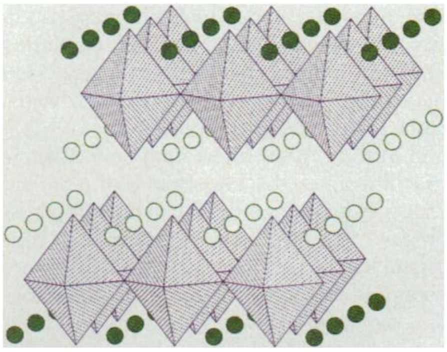

Fig. 3. Polyhedral packing diagram of $La_{1.78}K_{0.22}CuO_4$, after Stoll *et al.* (*19*). The blue elongated octahedra represent corner-sharing CuO_6 units. Solid green circles are sites containing only lanthanum atoms, whereas open circles indicate sites where there is partial substitution of lanthanum by potassium.

ly, one thinks of these as very basic compounds, but this is only because aqueous solutions are our conventional reference point. In molten hydroxides, there is an acid-base equilibrium:

$$2\ OH^- \leftrightarrow \underset{\text{acid}}{H_2O} + \underset{\text{base}}{O^{2-}} \qquad (2)$$

that is analogous to the familiar autoprotolysis of water:

$$2\ H_2O \leftrightarrow \underset{\text{acid}}{H_3O^+} + \underset{\text{base}}{OH^-} \qquad (3)$$

In hydroxide fluxes, the strongest acid that can exist is H_2O, the conjugate acid of the solvent. Addition of this "acid" to the medium solubilizes the basic oxides through the equilibrium:

$$MO_{(s)} + H_2O_{(solution)} \leftrightarrow M^{2+}{}_{(solution)} + 2\ OH^- \qquad (4)$$

Therefore "acidic" (wet) fluxes dissolve metal oxides, whereas "neutral" fluxes precipitate them.

Two recent examples in the synthesis of high-T_c oxide superconductors illustrate the utility of hydroxide flux growth in the preparation of oxide materials with unusual structures or superior physical properties. Substitution of alkali metals for polyvalent cations has the effect of hole doping the CuO_2 sheets and transforms semiconducting phases such as $BaBiO_3$ and La_2CuO_4 into *p*-type superconductors $Ba_{1-x}K_xBiO_3$ (*16*) and $La_{2-x}M_xCuO_4$, where M = Na, K (*17*). Difficulties arise in attempting to dope these oxides with alkali metal ions through solid-solid reactions because of the volatility of alkali metal oxides under ceramic processing conditions. A few reports of incompletely characterized samples of $La_{2-x}K_xCuO_4$ exist from the reaction of CuO, La_2O_3, and KO_2 in sealed gold tubes at 800°C (*18*). Recently, however, Stoll *et al.* have shown that single crystals of the pure sodium- and potassium-doped compounds can be made from NaOH and KOH fluxes, respectively (*19*). These compounds adopt the structure of the Zürich oxide $La_{2-x}(Ba,Sr)_xCuO_4$ (*4*), that is, the K_2NiF_4 structure, with the important distinction that in the potassium analog the alkali metal ions order in the structure, as shown in Fig. 3. The K_2NiF_4 structure may be regarded as an intergrowth of perovskite ABX_3 and rocksalt AX structures. It shares two features with all high-T_c superconductor structures, namely (i) CuO_2 planes lying in the perovskite-like block and (ii) an intergrown "charge reservoir" layer that serves to dope the sheets with holes or electrons (*20*). The ability to juxtapose, in an intermediate-temperature synthesis, an ordered array of monovalent cations with the superconducting sheets augurs well for future "designed" superconductor structures.

Undoubtedly the most thoroughly studied cuprate superconductor is the 1-2-3 phase, $YBa_2Cu_3O_{7-\delta}$. The initial euphoria created by this 92 K superconducting ceramic has been damped by problems associated with its mechanical and chemical properties. Above 400°C, orthorhombic $YBa_2Cu_3O_{7-\delta}$ begins to lose oxygen and undergoes a structural phase transition to a tetragonal, nonsuperconducting phase $YBa_2Cu_3O_{6.5}$ (*21*). Therefore, the usual synthesis of the compound entails the formation of the oxygen-deficient phase at high temperature, followed by a low-temperature reoxygenation step to produce the superconducting stoichiometry. The accompanying tetragonal-to-orthorhombic phase transition creates twin planes that limit the amount of current the superconducting phase can carry (*22*) and degrade its mechanical integrity (*23*). Consequently, critical currents (J_c) for bulk samples of $YBa_2Cu_3O_{7-\delta}$ are typically two to three orders of magnitude lower than those of conventional materials used in superconducting magnets (*24*). By using a NaOH-KOH flux, a barium-deficient 1-2-3 superconductor $EuBa_{2-x}$-Cu_3O_7 can be directly precipitated below the structural phase-transition temperature (*25*). The material, which is superconducting below 75 K, is fully stoichiometric in oxygen and has a greatly reduced density of twin planes.

Hydrothermal reactions: Following nature's example. The next logical step in controlling the outcome of solid-state syntheses, as the temperature is lowered further still, is modular design—that is, assembling prebuilt units of desired geometry or composition into a larger unit. Hydrothermal chemistry is the major geological mode of formation of a variety of minerals that appear to have this property; that is, mineral structures can be decomposed (at least conceptually) into common building blocks. A particularly interesting class of such minerals is the zeolite family, the members of which are microporous, metastable aluminosilicates. Zeolite structures can be grouped according to so-called secondary building units, such as hexagonal or square prisms composed of $(\text{–Si,Al–O–})_n$ rings (n = 4, 5, 6, and so on). Although these units were once thought to be involved in the growth mechanism of aluminosilicates, it has become clear that even smaller species lead to the formation of zeolite crystals. Other prebuilt units may also redissolve and form completely different structures depending on the specific reaction conditions. More promising methods for preserving the structure of molecular aggregates during the assembly of crystalline solids are described below.

Despite a lack of direct routes to planned structures through molecular building blocks, scrutiny of natural structures provides clues as to composition and hydrothermal reaction conditions for the design of solids with specific structural features. An elegant example is the recent synthesis by Davis and co-workers (*26*) of a zincosilicate molecular sieve containing three-membered rings. This synthesis was prompted by a correlation between the minimum framework density and the smallest ring size within natural, synthetic, and hypothetical molecular sieve structures (*27*). The correlation suggests that highly porous frameworks, which are desirable for catalytic applications, can be expected for structures containing three-membered rings. Davis *et al.* noted the existence of these rings in the beryllosilicate minerals lovdarite, phenakite, and euclase, as well as in the zincosilicates clinohedrite and willemite. Avoiding highly toxic beryllium compounds, they chose the zincosilicate system and were able to prepare a new molecular sieve material, VPI-7, the framework of which is topologically related to lovdarite. The preparation of VPI-7 provides the first synthetic foothold on silicates containing three-membered rings and opens the door to molecular sieves with very low framework density.

Although evidence is sketchy for structural preassembly in hydrothermal reactions, the existence of templating effects is quite well established. Organic and inorganic templates (typically alkylammonium cations, amines, and alkali metal cations) have been used to direct the structure of the microporous solids. The templating mechanism is not completely understood, as one template can lead to different structures, and one structure may often be obtained with different template molecules. Charge-compensating and space-filling effects are thought to contribute to the process. In order to gain access to the structural microporosity, the

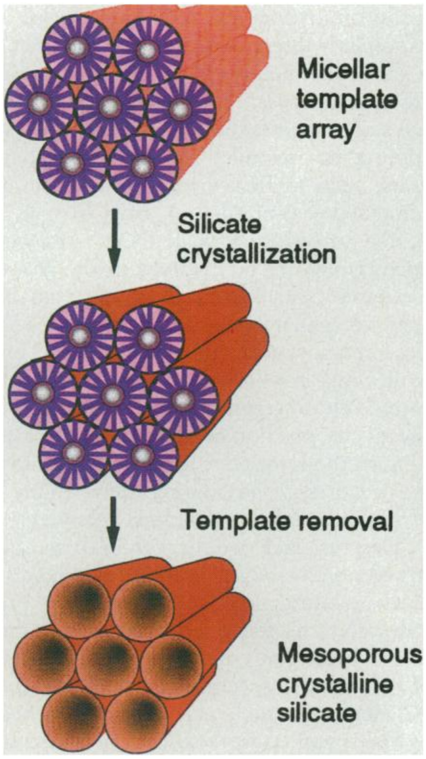

Fig. 4. Schematic diagram of the templating mechanism proposed for mesoporous molecular sieves (*28*). The surfactant molecules are thought to form cigar-shaped micelles with the polar head groups pointing outward, and these micelles organize into a hexagonal array. The aluminosilicate framework crystallizes in the polar interstices of the liquid crystalline template. Templating molecules are then removed by calcination, leaving hollow tubes of the molecular sieve.

template must be removed, usually by calcination. However, this becomes a problem if the framework collapses during removal of the template. Certain structures require the presence of space-filling molecules and collapse as soon as the template is removed, regardless of conditions. In other instances the collapse may be due to the high temperature required for template calcination. Therefore, a new and as yet unexplored strategy may be the design of template materials containing photolyzable bonds that allow for decomposition through irradiation, followed by removal of template fragments through the micropore network.

By using a cationic template with a very long hydrophobic tail, Kresge *et al.* recently synthesized a new class of mesoporous molecular sieves with adjustable channel diameters in the range 16 to 100 Å (*28*). The large, variable pore sizes make these materials extremely interesting as potential size- and shape-selective heterogeneous catalysts for high molecular weight organic compounds. They are also of considerable fundamental interest as hosts for semiconductor quantum dots, conductive polymer filaments, molecular photodiodes, and other nanometer-scale optical and electronic "devices" that have been studied in microporous solids of more limited channel dimensions (*29–31*). These mesoporous sieves are templated with cubic or hexagonal micellar assemblies of cetyltrimethylammonium hydroxide and 1,3,5-trimethylbenzene in conjunction with a relatively pedestrian precursor gel—water, sodium aluminate, silica, and tetramethylammonium silicate—at reaction temperatures between 50° and 175°C. An interesting new templating mechanism (Fig. 4) has been suggested for the formation of these materials, in which the anionic aluminosilicate precursors occupy the aqueous region between surfactant cylinders in order to balance the cationic hydrophilic surfaces of the latter. The long-chain surfactants are then encapsulated during silicate crystallization. The key to forming an ordered channel structure in this way appears to be the formation of a liquid crystalline template phase that is stable under the conditions of hydrothermal silicate crystallization. Removal of the template by calcination yields stable mesoporous sieves with very high internal surface area (in excess of 1000 m^2/g).

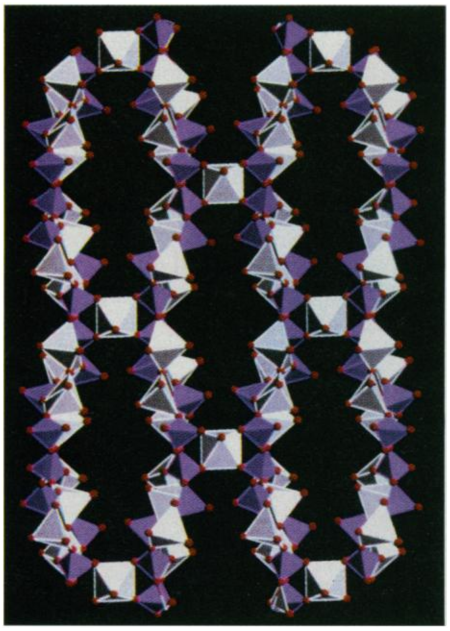

Fig. 5. Structure of the octahedral-tetrahedral vanadium phosphate molecular sieve $(H_3NCH_2CH_2NH_3)_2(H_3NCH_2CH_2NH_2)[V^{III}(H_2O)_2(V^{IV}O)_8(OH)_4(HPO_4)_4(PO_4)_4]\cdot 2H_2O$ (*33*), showing the large elliptical channels formed by the framework atoms. The organic template is omitted for clarity. [Adapted from (*33*)]

Molecular sieve science has focused heavily on tetrahedral species, such as silicon- and aluminum-containing tetrahedra, as connectors in framework structures. This traditional barrier may be broken if metal ions are used that prefer higher coordination numbers, under hydrothermal conditions in the presence of suitable templating reagents. Although many such materials have been discovered in the last few years, particularly among the phosphates of Mo^{IV} and Mo^{V} (*32*), an interesting new example that illustrates the importance of template effects is found among the vanadium phosphates. The structure shown in Fig. 5 is assembled from corner-sharing V^{IV} square pyramids and HPO_4^{2-} and PO_4^{3-} tetrahedra, connected by V^{III} octahedra (*33*). Vanadium, oxygen, and phosphorus atoms are joined into large amphiphilic rings with holes of 6.2 to 7.2 Å diameter, as well as large elliptical channels with a major axis length of 18.4 Å. In these channels, hydrogen bonding interactions exist between the polar $-NH_3^+$ ends of the organic amine template, the water of crystallization, and the polar P–OH and $V(H_2O)_2$ portions of the framework. The less polar carbon backbone of the organic cations fills the void volume and associates with nonpolar framework V–O groups. The formation of large voids filled with hydrophobic groups in this structure suggests an interesting templating mechanism, wherein phase segregation into hydrophilic and hydrophobic nanometer-scale domains precedes crystallization.

Toward the Future: Solid-State Synthesis in a Round-Bottom Flask

Solid-state reactions that take place at low temperatures offer the advantage that either inorganic or organic structural elements can be preserved in the transformation from reactant to product. In this way, new structure types, most of which are metastable, can be arrived at by rational means through a series of mechanistically well understood steps. One class of such reactions involves replacement or removal of ions from materials prepared at high temperature, through solution-phase ion exchange or electrochemical oxidation-reduction of the host framework. Subsequent low-temperature processing (usually to drive off water or other small molecules) completes the reaction. An example of this approach is the preparation of two new allotropes of TiO_2, which at high temperature crystallizes in the rutile structure. By exchanging the layered compound $K_2Ti_4O_9$ with aqueous acid, $H_2Ti_4O_9 \cdot H_2O$ is formed (*34*). Gentle heating eliminates water to give lamellar TiO_2 in which the bond connectivity of the original $K_2Ti_4O_9$ phase is preserved. A tunnel-structure TiO_2 can likewise be prepared by electrochemical oxidation of the hollandite phase KTi_4O_8, which, like $K_2Ti_4O_9$, is made by high-temperature, solid-solid reaction of K_2CO_3 and TiO_2 (*35*).

Low-temperature, topochemical insertion of ions, atoms, and molecules into host

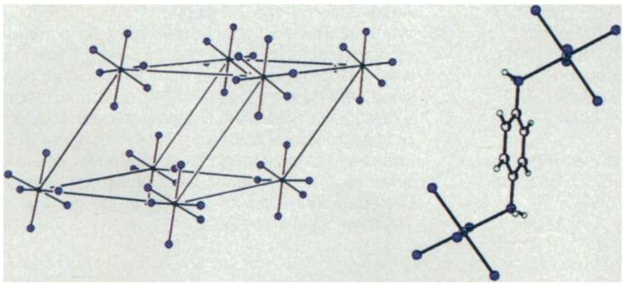

Fig. 6. Schematic ORTEP diagram indicating the connectivity of the Cd(1,4-phenylenediamine)$_6$ octahedra that form a distorted cube of perovskite connectivity in Cd(1,4,-phenylenediamine)$_3$-$(NO_3)_2$ (*42*). The diagram on the right shows the zigzag joining of two cadmium atoms by the bridging ligands, which for clarity are replaced by a solid line in the diagram on the left. The two nitrate anions (omitted) are located inside the box.

solids that are typically prepared at high temperature are called intercalation reactions. Although these reactions have been the subject of several recent topical and comprehensive reviews (*36*), we mention one interesting example, again in the area of high-temperature superconductivity. Unlike most cuprate superconductors, the bismuth-containing materials $Bi_2Sr_2Ca_nCu_{n+1}O_x$ have two contiguous Bi–O sheets that are held together by very weak interlayer bonds. These sheets can separate to admit guest species such as I_2 (*37*). Although the reaction causes significant expansion of the structure along the layering axis, remarkably T_c is only slightly affected. This result indicates that, although electronic coupling within a $Ca_nCu_{n+1}O_{2n+1}$ block in the parent superconductor is important, coupling between blocks is quite weak. Therefore, superconductivity in these materials may be regarded as largely two-dimensional.

Molecular minerals. At room temperature, solids can be assembled from molecular precursors without fear of their decomposition, and metastable connections between building blocks can be expected to survive. The question is, what kind of subunits and connections will be most versatile and reliable in this kind of "Lego" solid-state synthesis? Attempts at using ceramic precursors, such as siloxane cubes $[Si_8O_{12}](OCH_3)_8$ and related polyhedra (*38*), have failed to yield crystalline materials at room temperature, probably because of the irreversibility of Si–O–Si bond formation; that is, the connecting links between building blocks are as strong as intrablock bonds, so attempts to anneal structures into a crystalline form result in decomposition of the metastable building units. Nevertheless, interesting oligomeric analogs of aluminosilicates have been made at room temperature from the condensation of structurally well defined building blocks (*39*), and it is possible that this approach will lead to infinite three-dimensional frameworks in the future.

A very interesting new strategy is to use coordinate covalent bonds as links between molecular units containing stronger covalent C–C and C–N bonds. This approach has the advantage that several coordination geometries (octahedral, tetrahedral, square planar, and others) are available for the connecting metal ions, and generally bond formation to them is reversible, allowing for crystallization through "ripening" of amorphous solid or solution precursors. Robson and co-workers have explored this idea using cations such as Cd^{2+} and Cu^+, which normally prefer octahedral and tetrahedral coordination, in combination with nitrogen-bearing bridging ligands such as linear CN^-, square planar tetra(*N*-pyridyl)porphyrin, triangular $C(CN)_3{}^-$, and tetrahedral $C(C_6H_5CN)_4$ (*40*). In related work, Fischer and co-workers have prepared open frameworks from octahedral $M^{III}(CN)_6$ (M = Fe, Co) building blocks, which coordinate linearly through their nitrogen atoms to Me_3Sn^{IV} trigonal bipyramidal linkers (*41*).

The synthesis of these coordination polymers simply requires combination of the appropriate metal salt and ligand in a polar organic solvent at room temperature or slightly above. In some cases, the frameworks that result are topologically related to known inorganic solids. For example, the combination of a tetrahedral connector and a tetrahedral ligand gives rise to a zincblende (ZnS) structure, whereas an octahedral connector combined with a triangular ligand results in a rutile (TiO_2) topology. Because the ligands used are much larger than simple S^{2-} or O^{2-} ions, the framework is microporous and can contain large counterions, solvent molecules, or even a second metal-ligand framework. In many cases, coordination nets for which no mineral analog is known result.

Two interesting structural families that can be approached by this technique include perovskite, ABX_3, and silica, AX_2. Apart from their relevance to high-T_c superconductivity, perovskites are of practical interest as ferroelectrics. Among the silica polymorphs, quartz is a useful piezoelectric material; zeolites and related molecular sieves, all of which, like the silica polymorphs, are based structurally on corner-sharing SiO_4 tetrahedra, are also interesting for a variety of applications. "Expanded," topological relatives of these oxide structures can be synthesized if a bidentate ligand is substituted in place of the usually two-coordinate oxygen, which should be linear in the case of perovskites and bent in the case of silica structures (*42*). The structure of a perovskite-like solid composed of octahedral Cd^{2+} connectors and 1,4-phenylenediamine bridging ligands is shown in Fig. 6. Compounds with AX_2 stoichiometry, which appear to have silica-like framework connectivity, have also been synthesized from tetrahedral Cu^+ and the bent bridging ligand 1,3-dicyanobenzene.

Concluding Remarks

In decades past, new solid-state syntheses were often undertaken simply for the sake of preparing materials with new structures and compositions. Today, there is an increasing need for structures "made to order," designed to display a specific set of physical properties. The tools of the trade have evolved considerably away from high-temperature solid-solid reactions, partly in response to this demand and partly because molecular concepts and synthetic strategies have begun to invade the thinking of solid-state chemists. The technologically and conceptually important compounds discussed in this article—superconductors, polychalcogenides, mesoporous and nontetrahedral molecular sieves, and coordination solids—have all been prepared within the past 5 years, largely owing to this new awareness. These recent success stories suggest that continued work on mechanisms and low-temperature reactions in the solid state will lead to further rapid development of synthetic techniques and important new materials.

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Phosphorodithioate DNA as a Potential Therapeutic Drug

W. S. Marshall* and M. H. Caruthers†

This article summarizes methods for the synthesis of phosphorodithioate-linked deoxyoligonucleotides and details an analysis of one of the distinctive properties of phosphorodithioate DNA oligomers, their ability to strongly inhibit human immunodeficiency virus type–1 reverse transcriptase (HIV-1 RT). Mechanistic studies indicate that oligomers of this type interfere with enzyme function by binding tightly to the active site for primer-template, which results in low or subnanomolar inhibitory constants. Although many of these studies have used deoxyoligocytidine analogs, a rationally designed approach has led to the discovery of a very active phosphorodithioate deoxyoligonucleotide inhibitor. This type of inhibitor, which binds strongly to the primer-template active site of HIV-1 RT, provides another type of potential therapeutic agent against HIV-1.

The classical approach for discovering new drugs, such as 3′-α-azido-2′,3′-dideoxythymidine (AZT) for treating the debilitating consequences of acquired immunodeficiency syndrome (AIDS), involves the use of massive screening programs (*1*). A number often quoted is that on average 10,000 compounds must be tested in order to identify one new, biologically active substance. These are formidable statistics that have led many researchers to focus on more rational drug design strategies. The most successful have been those based upon understanding the biology, genetics, and biochemistry associated with a particular disease state. As a result of these efforts, many small organic molecules have been identified that inhibit cholesterol biosynthesis (*2*), nucleotide metabolism (*3*), and other disease-associated biological systems. Additionally, by using recombinant DNA technologies in association with a thorough understanding of the appropriate biology, proteins such as erythropoietin (*4*), granulocyte–colony-stimulating factor (*5*), insulin (*6*), and human growth hormone (*7*) have been shown to be effective for several therapeutic applications.

Primarily because of inherent disadvantages in these approaches such as the cost and uncertainties associated with massive screening programs and the instability of proteins, new drug design strategies have been explored. Two of these are based on the assumption that new drugs will interact with important binding sites on proteins or active sites of enzymes and thereby block the development of a specific disease state. For example, perhaps a molecule can be designed that binds within the deep clefts found on the surface of rhino- and picornoviruses and inhibits interactions of these viruses with host cells (*8*). These two strategies differ in how new drugs are identified. One uses the three-dimensional structure of a target protein in combination with computer modeling to identify potential drug candidates (*9*). The other, which does not require knowledge of tertiary structure, is based upon the vast information content of amino acid or nucleotide (nt) sequences. Libraries of completely random peptides or oligonucleotides are prepared from the monomers and then, through various selection protocols, highly specific, biologically active molecules are identified as potential drug candidates (*10–12*). Although these strategies appear very promising, success is still limited to the laboratory as clinical and even animal studies remain to be done.

An alternative new approach is to use the information content of the nucleic acids and knowledge of their interactions with

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