On the border between chemistry and biology, information can flow in both directions. Information from chemistry into biology helps us understand how biological systems work and also furnishes many of the tools needed to explore and understand biology generally. However, there is another aspect in which information from biology flows into chemistry. This inspires new chemistry based on the principles used by Nature, a field that I have named “biomimetic chemistry” (1–4). It mirrors an activity that humans have pursued for a long time: inventing new things inspired by what Nature does.

For example, when humans were trying to decide how to fly, they examined the flying organisms, birds and insects, and realized that wings were a major and fundamental idea. However, when early inventors tried to make the wings flap the way they do in birds and insects, they discovered that there were better ways to furnish the power. People took the principle of flight using wings, but not the details of how biology actually used them. As Philip Ball has stated, a jumbo jet is not just a scaled-up pigeon (5). In biomimetic chemistry, we also take inspiration, but not blueprints, from natural chemistry.

As a child, I became interested in chemistry with my first chemistry set. I was excited by the magic that occurred when iron filings were added to a blue copper sulfate solution: the iron became coated with copper, and the solution lost its color. I wanted to know more about this wonderful field and was fortunate that Max Tishler, the head of medicinal chemistry at Merck in Rahway, NJ, where I lived, was a patient of my physician father. Max gave me a college textbook on organic chemistry, by Conant and Blatt, when I was in seventh grade, and I was hooked.

I loved the two facets of chemistry. On the one hand, it tries to understand the physical world, as do other sciences. However, it also creates new substances and new reactions. The synthesis of new compounds and new organized systems is a special creative aspect of chemistry, and it contrasts with such fields as astronomy and geology where there is no synthetic component. (I sometimes suggest to students that they establish the field of synthetic astronomy, a virgin area.)

In high school, I set up a lab in my basement and tried to synthesize the silicon analog of benzene to see if it was also stabilized by aromaticity. I was not successful (it was made many years later by others), but my attempts did land me a position as a finalist in the Westinghouse contest. In my trip to Washington to meet with the President, I also met many other young budding scientists, some of whom are my friends to this day.

At Harvard, I plunged directly into the organic chemistry course, and by my fourth year, I had taken most of the graduate courses. Thus, I went off to the medical science program at Harvard (it was the first year, and all the faculty were involved) to see what scientific path I wanted to pursue. I learned biochemistry from Jack Richards and Eric Ball and physiology and even some pathology from leaders in the field, and I earned a master’s degree in medical science.

However, I concluded that chemistry was still my true interest, so I went back to the chemistry department and completed my Ph.D. with Bob Woodward while keeping an eye on biology. After a 1-year postdoctoral study with Alex Todd, I came to Columbia University as an instructor.
I pursued a program in both theoretically interesting chemistry (we made the simplest aromatic system and established the phenomenon of antiaromaticity) and biologically relevant chemistry. I am now a member of both the chemistry and biology departments, co-director of the Columbia Nanocenter, and one of eleven University Professors. In 1991, I won the National Medal of Science, 4 years after Max Tishler, my earliest mentor. I will focus this account on our work in biomimetic chemistry.

In our first studies, I was concerned about understanding how the coenzyme thiamine diphosphate could catalyze reactions such as that in pyruvate decarboxylase, a process for which very unusual catalysis would be needed. Many chemists had speculated on possible ways in which thiamine diphosphate might catalyze such a reaction; indeed, we made a false start with one such speculation before we discovered that the thiazolium ring had a hitherto unsuspected chemistry (6, 7). The proton on carbon 2 of the thiazolium ring can be fairly readily removed to generate a zwitterion that is the catalytic species derived from thiamine diphosphate (Fig. 1). We showed that this was the species that catalyzed model reactions for the enzymatic process, in what was the likely process by which thiamine diphosphate operated biologically. Many others have since confirmed this idea.

We then explored the new chemistry that this interesting species implied. We showed that we could understand the stability of this species in terms of a second resonance form, a carbene, and that many other heterocyclic cationic systems could also form a related species (8).

In the 50 years since that time, many others have used such zwitterion/carbene species to catalyze chemical reactions and also to serve as ligands for metal ions in important catalytic processes. For example, such a species is the preferred ligand in the metathesis catalyst that was part of the work winning Robert Grubbs a recent Nobel Prize in chemistry. Thus, we saw information transfer in both directions. Our work with a chemical model system made it clear how a thiazolium salt such as thiamine could catalyze the biological reactions, and indeed, this turned out to be the correct mechanism for the biochemical process. At the same time, the discovery of this hitherto unsuspected species led to unprecedented chemistry and new and useful catalytic reactions.

We also explored the catalytic chemistry using thiamine analogs to see how well natural thiamine did in chemical model systems, an effort I have called “Nature appreciation.” Thiamine was the best of its close analogs for reasons that balanced reactivity and chemical stability (9). In a similar vein, we later synthesized what I called iso-DNA, based on 3-deoxyribose that makes 2,5-links instead of the normal 2-deoxyribose that makes 3,5-links (10, 11). In a sense, we wanted to see why Nature had selected the normal DNA structure. Iso-DNA makes a much weaker double helix with its conjugate, or with the conjugate based on normal DNA, because the helix has more hydrophobic surface exposed to solvent. Thus, it is not a suitable substitute for normal DNA as a genetic material, and organisms that may have tried it would not be competitive. However, iso-DNA does make a strong heteroduplex with normal RNA, reflecting the conformation of the ribose ring relative to that in deoxyribose.

Enzymes teach us many other inspiring principles. One is that geometry can dominate chemical reactivity. A good example is the conversion of lanosterol to cholesterol, in which three unactivated methyl groups are oxidatively degraded by enzymes of the class cytochrome P-450 while the much more reactive double bonds of lanosterol are left untouched until later (Fig. 2).

This inspired us to develop processes we called remote oxidation, in which we attached reagents and templates to substrates that could reach far from their attachment point (from ring A of the steroid all the way to ring D at the other end) and perform selective reactions on particular spots because of the geometry imposed by our attached reagent or template (12, 13). In more recent work, we have learned how to imitate the enzyme more fully, achieving geometrically controlled turnover catalysis (14–16).

The enzyme mimic we synthesized was a metalloporphyrin carrying cyclodextrin groups that would reversibly bind substrates such as steroids. These mimics of cytochrome P-450 performed selective oxidations that are of practical interest, with thousands of turnovers. The result...
was selective oxidation of particular C–H bonds that was hitherto possible only with natural biological enzymes.

Another of the important principles that natural enzymes use is bifunctional and sometimes even multifunctional catalysis. In simple chemical reactions, such processes are rare because they would involve the collision of two or more different catalytic materials with a substrate at the same time, but of course in enzymes, the catalytic groups are part of the binding molecule. In particular, in the enzyme ribonuclease A, both the imidazole of histidine 12 and the imidazolium ion of histidine 119 play such a bifunctional catalytic role in RNA cleavage.

We synthesized molecules that could perform the same kind of phosphate ester cleavage by attaching imidazole groups to the rim of a binding molecule, a cyclodextrin (17). With such a system, we were able to control the geometry of the process by fixing the positions where the two groups were attached. With a technique called “proton inventory,” we showed that the imidazole and imidazolium catalytic groups operated simultaneously in the cleavage process, as they do in the natural enzyme (17).

We made an important and surprising chemical finding. It was usually believed that ribonuclease uses a basic imidazole to deliver the hydroxyl group of carbon 2 to the phosphate as the histidine 119 imidazolium ion protonates the leaving nucleoside group, but this would require that the catalytic species be positioned essentially 180° apart. Our surprising finding was that such an isomer in our artificial enzyme was the worst of the three positional isomeric catalysts, and the best one had the acid and base groups as near each other as possible, on neighboring glucose residues.

This indicated that the mechanism was not a direct reaction, as is usually invoked in biochemistry textbooks, but instead a process in which water is added to the phosphate to produce what is called a phosphorane, a five-coordinated phosphorous species. At first, the imidazolium ion binds to the phosphate oxygen anion, and the water is delivered to this species by the imidazole. With further bifunctional catalysis, this phosphorane then decomposes to cleavage products in a second step.

In chemical kinetic studies, we were able to show that imidazole buffers used at high concentration could catalyze the hydrolysis of uridylyluridine, a fragment of RNA, and that this hydrolysis also proceeded through such a water addition to the phosphate group, rather than by a direct reaction (18). The imidazolium ion of the buffer again binds to the phosphorus, and the imidazole of the buffer then again delivers a water molecule to this species. The process resembles that in the hydrolysis of esters and amides, in which a tetrahedral intermediate is formed first. In phosphorus chemistry, such an intermediate is instead the five-coordinated phosphorane.

We pointed out that some of the evidence on the enzyme itself would be consistent with such a two-step mechanism of hydrolysis, where the water is added before the leaving group begins to depart or, in the case of the cyclization of RNA, where the C-2 hydroxyl group adds to the phosphate to make such a five-coordinated phosphorous species before the leaving group is lost in a subsequent step. It remains to be seen whether our addition mechanism proves to be correct with the enzyme, but it is certainly clear that we have learned important features of phosphate chemistry from the detailed study of an enzyme mimic inspired by ribonuclease.

Not only is bifunctional catalysis (by an enzyme mimic that binds a substrate next to two well placed catalytic groups) a useful process in chemistry, it also furnishes mechanistic information not available in other ways, as it did in the case of phosphate hydrolysis. As another example, we looked at the ability of such a bifunctional catalyst to promote the enolization of a ketone in a substrate that was bound into a cyclodextrin bisimidazole (19). Again, the catalysis involved one imidazole and one imidazolium group, but interestingly in this case, the preferential catalyst was the one with these groups farthest apart. This furnished detailed chemical information about how a base

FIGURE 2. In the conversion of lanosterol to cholesterol, cytochrome P-450 is able to oxidize the unactivated methyl groups while not attacking the much more reactive double bonds.
approaches and removes a proton in the enolization of a ketone (Fig. 3), information that was otherwise totally unavailable. The base attacks not along the C–H bond direction, but laterally to push the electrons toward the carbonyl group.

There is another important lesson that biological chemistry has taught us: the great value of water as a reaction solvent. There has been much interest in water as an environmentally benign solvent in the effort to make the manufacture of chemicals into a “green” process; we saw that the hydrophobic effect in water can also have very useful special applications in chemical processes. In the artificial cytochrome P-450 enzyme mimic described above, we used hydrophobic binding of the substrate steroid into the catalyst to achieve the well defined geometry that steered the oxidation to a particular spot, not the most reactive spot but simply the one that was accessible within the geometry of the complex (14–16).

In other work, we have shown that simple chemical reactions involving species with polar sections could be steered to high selectivity when they were performed in water, where hydrophobic binding oriented the reagents to the substrate, whereas in other organic solvents, the reactions were essentially random (20). Thus, water has become an attractive solvent for chemical reactions and processes. Not only is it environmentally benign, it is also special in inducing selective reactions out of what might otherwise be unselective processes.

In the course of this work, we also devised a way to diagnose that hydrophobic interactions were involved, taking advantage of additives to the water that either increased or decreased the hydrophobic effect. Substances that decrease this effect act as denaturants of proteins or nucleic acids, whose detailed conformations depend on hydrophobic binding of their components. We showed that species such as guanidinium salts, which are commonly used as denaturants, operate not by altering the properties of water, which was often suggested, but instead by furnishing solvation to the hydrophobic regions of the substrate. The species can bridge between the hydrophobic region and the water solvent (21).

Our inspiration for this was the findings in biology and biochemistry of such denaturant principles, but they inspired us to investigate the use of such phenomena in simple chemical systems. As part of this, we also showed that we could determine the detailed transition state geometries of a number of important chemical reactions, a goal of chemistry that was hitherto completely impossible, by using such denaturants in water solution (22). The magnitude of the denaturant effect on reaction rates proved to be directly related to the amount of exposed hydrocarbon surface in the transition states for the reactions relative to that in the starting materials.

Another principle from biology is that water-soluble enzymes have a hydrophilic exterior and a hydrophobic interior. This allows hydrophobic substrates to bind into the interior of the enzyme and also allows the chemistry to occur away from the water solution. Water sets up hydrogen bonds to acids, bases, and substrate groups, and in a catalytic process, these hydrogen bonds must be broken, as the groups are desolvated before they can directly interact. When the chemistry or biochemistry occurs inside a non-aqueous medium, desolvations are not required.

We saw this effect in a series of artificial enzymes we synthesized (23) based on the polyamines first investigated by Klotz and Suh (24). Nature taught us how to synthesize amino acids by using pyridoxamine phosphate coenzyme to perform a transamination with a keto acid, and we and others had studied models for such reactions. We constructed a model enzyme system for the process by using a hydrophobic derivative of pyridoxamine as the coenzyme mimic and a polyamine with an added hydrophobic core as the enzyme mimic. The coenzyme bound into this nonpolar region, and the substrates as well bound into it, especially if they carried hydrophobic groups, as in the keto acid that formed phenylalanine.

Our system followed Michaelis-Menten kinetics just as enzymes do, and with such kinetic studies, we were able to show that the hydrophobic core not only promoted the binding of the coenzyme and the substrate, it also increased the rate constant for the reaction within the complex (25). Thus, in an artificial enzyme, it is not enough simply to put together the appropriate catalytic groups or, for that matter, the catalytic groups and binding groups; it can also be important to achieve a change in

FIGURE 3. An artificial enzyme with imidazole rings attached to a cyclo-dextrin shows that the conversion of a carbonyl compound to its enol uses the base catalyst to remove the proton with a geometry that pushes the electrons toward their eventual occupancy of a p orbital.
medium by imitating such a change inside a globular protein. We were of course inspired to do this by thinking about how enzymes actually function.

We discovered a very effective way to perform the full cycle of transaminations, allowing the resulting pyridoxal species to be returned to the pyridoxamine form by a transaminative decarboxylation of an \(\alpha\)-methylamino acid (Fig. 4) (26). This is a relatively unusual biological process, although there is an enzyme that can perform it.

In the course of this work, we became aware of the fact that \(\alpha\)-methylamino acids are delivered from space to the earth by carbonaceous chondritic meteorites and that they have small but real excesses of the \(L\)-amino acids. We showed that we could perform a direct transaminative decarboxylation using such species to generate \(L\)-amino acids such as phenylalanine and alanine under credible prebiotic conditions, with prebiotically available substrates, and that we could also amplify the resultant chiralities to the high levels of enantiopurity needed for the synthesis of proteins and homochiral polypeptides.

In the full account of our studies, we point out the evidence for the source of these meteoritic amino acids (Strecker reactions with known interstellar components) and the source of their small chiral excesses (from directed circular polarized light generated by neutron stars) and have assembled a reasonable version of how homochirality first appeared on earth (27). This involves not only the work we have done but also studies in the past by meteorologists and others. It makes it clear how such homochirality in amino acids, for instance, could have occurred and made the origin of life possible. This is perhaps an extreme example in which chemistry is relevant to understanding the foundations of biology.

These are some examples in which thinking about biology, and sometimes solving the problems that biology raises, can also inform and enrich chemistry itself. It is easy to see the exciting prospects in the field of biomimetic chemistry. We need to know how to create self-organizing complex multicomponent materials that will imitate the living cell, at least in some of its aspects. The goal is not necessarily synthetic life, although that is clearly important. We can simply enrich chemistry by going increasingly to organized systems of several different components whose interaction leads to exciting new properties, moving away from concern with the properties of simple pure substances. This is a direction in which modern chemistry is going, inspired by the example of the biological cell itself.

Thus, we have by no means exhausted the level of inspiration we can derive by examining biology and trying to learn how to imitate it, to imitate its principles if not its exact details, to create new and exciting chemistry. At the same time, such explorations will continue to give us insights into biological chemistry itself. An important recent example is our creation of an approved anticancer compound, in collaboration with Paul Marks (28). This compound, which we call SAHA and is now marketed as vorinostat, inhibits a group of histone deacetylases. It was designed by considering what we knew about hydrophobic and metal-binding effects in enzymes. These prospects suggest that biomimetic chemistry will have a future at least as exciting as its past.

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Address correspondence to: rb33@columbia.edu.

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