VOLUME 69, NUMBER 8

JOC Perspective

APRIL 16, 2004

Some Got Away, but Others Didn't...

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Received December 2, 2003

A history of research projects undertaken in the group—ranging from mechanistic investigations to biomimetic chemistry to molecular devices and synthesis—is presented.

Introduction

On the happy occasion of writing this Perspective, I've decided to exhume some things that have been buried for a long time—up to 35 years; research projects that just didn't go as planned. These efforts led to no publications, and I would offer this manuscript as consolation to the co-workers involved, yet I can't help but think that they would rather not be named. There may be some hope for the research projects, but the trouble they caused me should be a warning to anyone who might want to follow them up. To keep balance and the readers' interest, I also include some successes.

Template Synthesis 1

This is not intended to be chronological, but I start with the first project that I took on as an assistant professor at UCLA in 1970. Larry Scott and I had just been hired under the premise (I can only guess) that if it worked out we might together fill one of Saul Winstein's shoes. The nearest I came to this destiny was earlier this year when I stood in the chemistry department at UCLA and delivered the inaugural Winstein Lecture. Back then, I was to trying to leverage my experience in peptide chemistry to synthesize cyclic tetrapeptides using squaric acid as a template. This molecule was then a commercially available curiosity but had not yet been recognized as a carboxyl isostere. Its methyl ester was known to undergo aminolysis, and we used this reaction to make an *N*-squaryl derivative of tetraglycine ethyl ester as shown in Figure 1. We had hoped that oxidation to the tetracarbonyl compound (or its hydrated equivalent) would cause the stepwise cyclization implied in the scheme to bring the two ends of the peptide together for easy intramolecular reaction. Subsequent diol cleavage could then release the cyclic tetrapeptide.

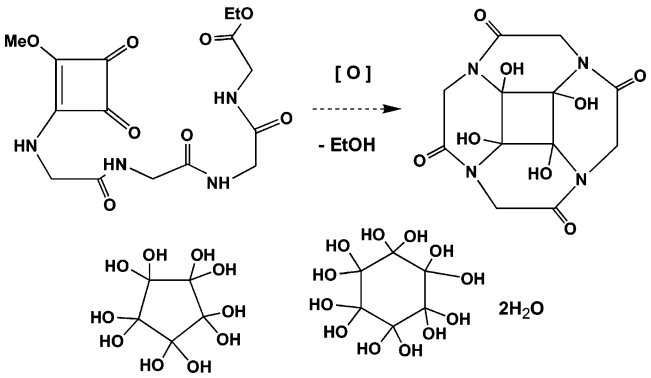

FIGURE 1. Attempted template synthesis of cyclic peptides.

The thought had more general appeal because the five-membered and six-membered versions (the latter with the irresistible name of triquinoyl octahydrate) were also commercially available. Moreover, an Edman-type degradation could be imagined that would clip up to hexapeptides from the N-terminus for sequencing. Well, we never got very much further than destroying the tetraglycine during the oxidation step; nothing at all came out of the direct condensation reactions that we could identify, despite Frank Anet's generosity with time on his home-made, 251 MHz NMR spectrometer.

Reactive Intermediates

Fortunately, another project running in the lab at the time worked out: the three-phase test (Figure 2). It was a fairly simple application of polymer-bound reagents to detect reactive intermediates. A precursor for the reactive intermediate was covalently attached to one solid phase while a trap was attached to a second such support. If transfer takes place between the solid phases, it heralds the existence of a reactive intermediate, free in solution. I will not dwell on the reactive species Francisco Gavina trapped this way—they are the subject of another

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10.1021/jo0303719 CCC: $27.50
Published on Web 04/12/2004

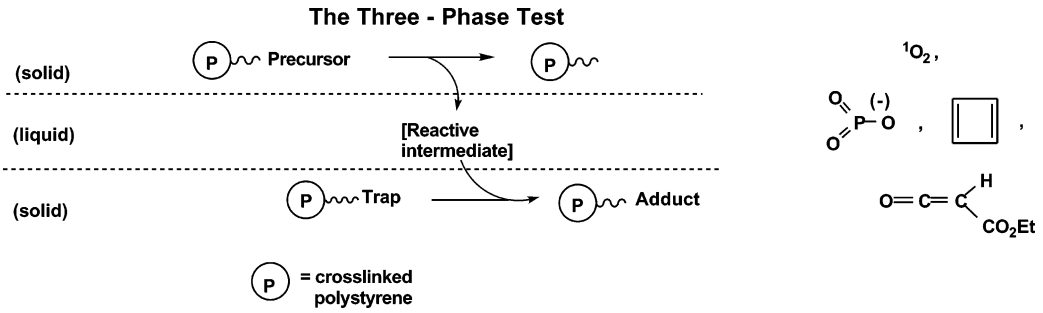

FIGURE 2. Method of detecting reactive intermediates using two insoluble supports suspended in the same liquid phase.

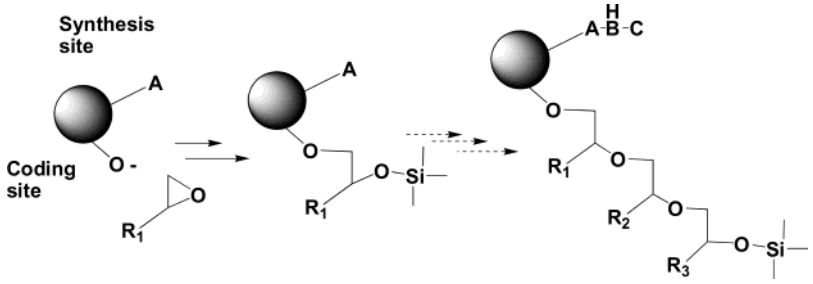

FIGURE 3. Scheme for coding reactions during synthesis on solid supports.

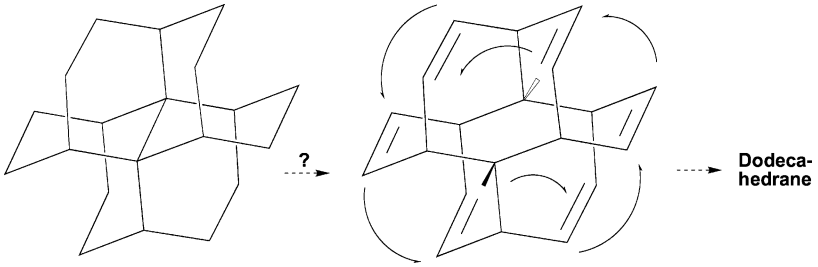

FIGURE 4. Notional dodecahedrane synthesis allowed by the Woodward–Hoffmann rules.

Perspective[1]—but I will mention that it was useful for acyl imidazoles and other reactive species which were under consideration as intermediates in nucleophilic catalysis of acyl transfers. In these cases, Dave Brown and Stephen Zimmerman used radiolabeled acyl derivatives and were able to follow the reaction by watching radioactivity decrease from one solid support and accumulate on another. We had the two solid supports suspended in the same solution and sometimes used teabags to keep them apart. Some time later (20 years) the teabag trick was rediscovered.[2] Twenty-five years later, when polymer-bound reagents were making a comeback in the service of combinatorial chemistry, the resin-to-resin transfer reaction also had a brief resurrection.[3]

Coding Schemes

While on the subject of combinatorial chemistry, I must confess to another failure that was related to the coding required for split-bead combinatorial synthesis. In the early 1990s, we had seen the Lerner and Brenner[4] proposal of coding using a nucleic acid tag and had heard that Still[5] had developed another method, but we did not know the details. This was—to us—a case of "idea diffusion", a phenomenon where the existence of an invention inspires you to devise a different version of it.[6] We felt that a tag on the solid support must be compatible with most reactions one might want to do on polystyrene beads; the tag had to be inert, featuring those functions that are found in solvents: hydrocarbons and ethers. Accordingly, we set out to do what is shown in Figure 3, where sequential reactions elsewhere on the bead were encoded by the opening of terminal epoxides with alkane groups that would be the code. The polyether would be read by mass spectrometry after cleavage from the resin. Incomplete reactions, however, thwarted us at every step, and eventually this project ground to a halt.

Dodecahedrane 1

In the late 1970s, dodecahedrane came into the news and I could not help but think of alternatives to Paquette's[7] published synthesis. One scheme that looked possible, or at least permitted by the Fieser models then on offer, is outlined in Figure 4, where three intersecting *trans*-decalins provide the general framework shown.

Now if one cleaves the common bond and inverts the centers, then the skeleton jumps immediately into a dodecahedron-shaped entity. Admittedly, there are a few too many hydrogens but double bounds could be strategically placed along the periphery, and the final bonds would be made through a cyclic array of antarafacial

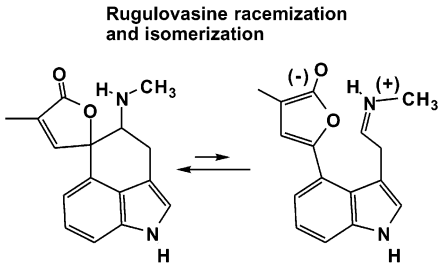

FIGURE 5. Racemization and interconversion of the rugulovasines.

FIGURE 6. Attempt at carboxyl ortho ester protection.

additions by light or heat (I forget which). On revisiting this approach with the less forgiving Dreiding models, we lost confidence: the strain involved in the structure actually caused some models to become unsoldered. This approach attracted no takers, but I continued to be haunted by the structure (about which, more later).

Natural Products

In the mid-1980s, the wholesale defection of a certain contingent from my department left a vacuum that pulled me toward that which that community most admired: the total synthesis of natural products. While Jean-Claude Gehret, Dar Fu Tai, and Steve Shaber synthesized a few,[8,9] I doubt that it shored up the department's reputation. Besides, I did not enjoy doing this very much. To be sure, there is a sense of closure when you compare the synthetic milligrams with the countless metric tons Nature makes every day. But there was a letdown since there was no further use for the molecule. Rarely, we found something to do with the synthetic product. For the optically active rugulovasines,[10] Youe-Kong Shue was able to examine their racemization/isomerization and found evidence for the brilliant mechanism proposed by Weinreb and Clardy (Figure 5).[11]

Still, I felt much better about synthesizing something to test a behavior, or deciding what structure was likely to show a given function. The heart of biomimetic chemistry is just this and involves molecular behavior such as recognition, replication, catalysis, and transport—words that have no structural content, they do not tell you what to build. The enterprise is fundamentally different from: How do I synthesize a natural product? There, the structure is known, the existence theorem has been proven, *the molecule can be made.*

Carboxyl Protection

Another early project (so early that Baldwin's rules were not yet available for violation) intended to prepare a carboxyl protecting group that remained stable to base (Figure 6). We thought that a glycidyl ester such as shown and easily prepared from epichlorohydrin would rearrange to the less-strained, compact ortho ester. A number of acid catalysts gave the same result: intractable materials from which even the reaction vessels

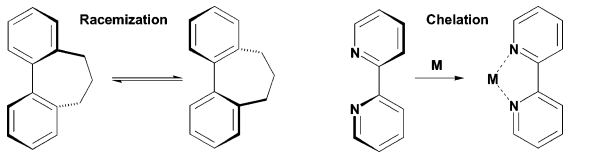

FIGURE 7. Racemization transition state corresponds to maximum binding of a metal and bipyridyl.

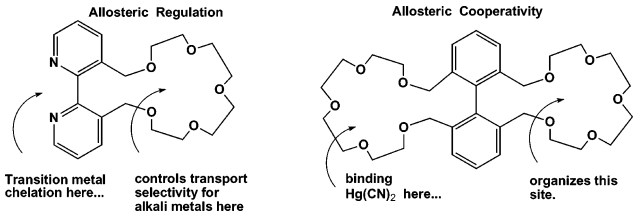

FIGURE 8. Two types of allostery.

could not be recovered. We subsequently found an unusually large number of publications on this reaction, ominously in the patent literature, that converged on a common theme—epoxy glue. Evidently, the [2.2.1] system still has too much strain to prevent further reaction. Though I didn't know it at the time, we had independently confirmed one of Westheimer's rules: a few weeks in the lab will save you a couple of hours in the library.

Molecular Devices

The Pauling principle of enzyme catalysis—maximum binding to the transition state—is, at first glance, a tautology. But, after a longer, puzzled stare it is really a retreat: what, exactly, does a transition state look like? The transition structure for the S_N2 reaction of chloride with methyl chloride had to feature D_{3h} symmetry, but for other reactions even the most confident computational chemists hedged on the details. Accordingly, I had, had had, some doubts in 1978 that the Pauling principle could be modeled in a chemical system. But physical processes, such as restricted bond rotation offered transition structure information that most chemical processes—bond making/bond breaking—did not. The thought was to arrange binding forces that coincided with structural changes along the coordinate. Consider the racemization of the biaryl shown in Figure 7, for which the transition state is reasonably expected to feature coplanar aryl rings. Consider next the chelation of a metal by a bipyridyl, also expected to show maximum metal ligand attraction at the coplanar geometry.[12,13] The two processes were coupled by John Trend through synthesis, and metals did enhance the racemization rate. But is a biaryl bond anything like a fulcrum? Can binding induce mechanical stresses elsewhere in a molecule? How rigid, stiff, rubbery, or plastic is, say, an aromatic? The resistance of cyclohexane CPK models to ring inversion may be satisfying to the hands, but do molecules really behave like balls and sticks? Or are we bound by the very models that we use?

We used this to devise a purely synthetic device to illustrate allostery, through construction of a system which had two points of affinity for metal types: a bipyridyl and a crown ether (Figure 8). When a transition metal binds to the bipyridyl segment (leading to its

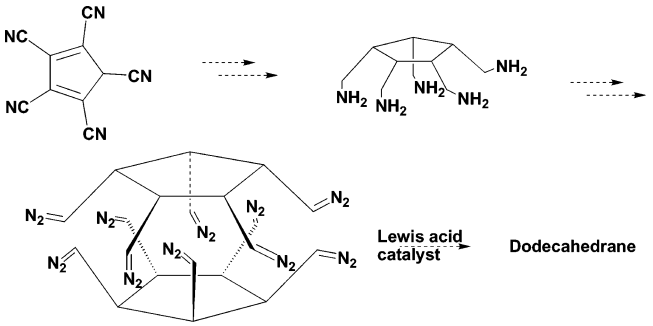

FIGURE 9. Notional dodecahedrane synthesis based on the polymerization of diazomethane.

flattening) the transport properties of the crown ether segment are altered.[14] This simple and interpretable model led Bob Gadwood, Ruth Wattley and Tim Costello to another involving two identical binding sites that showed positive cooperativity in binding of covalent mercury compounds.[15]

Dodecahedrane 2

An interlude, offering a second approach to dodecahedrane. This was loosely based on the polymerization of diazomethane but was never attempted, either (Figure 9). A pity, since the starting material, hexacyano cyclopentadiene was well-known, cheap, and had an acidity to rival H_2SO_4.

Recognition

While crown ethers represented the bulk of early efforts in molecular recognition, their targets were almost always ions. For recognition of small biorelevant targets we pursued cleft-like shapes.[16] Synthetic receptors tend to be concave and it is well-known that reactions on concave surfaces are much more difficult than those aimed at convex surfaces. Accordingly, it was best to create the functions and then assemble them in the proper shape overall. The key to recognition, we felt, was to have functional groups that would "converge" to create the recognition site, just as the amino acid side chain functional groups converge to create enzyme active sites. The grooves of nucleic acids are also concave and lined with convergent functions.

We took advantage of a substance introduced in 1981—Kemp's triacid.[17] This molecule had an unusual U-shaped geometric arrangement between the three carboxyl groups (Figure 10). Mary Killoran developed a large-scale synthesis from trimesic acid, and by condensing two of these to a diamine spacer, Louann Marshall, Ben Askew, and Dave Nemeth were able to get bisimides that showed converging carboxyl groups; the two OH bonds (the acidity of the function) are directed inward toward cavities of various dimensions. The conformation is maintained by the eight methyl groups of the molecule's periphery.

An excellent fit for pyrazine was found for the acridine diacid, for example, (Figure 11). The chelation of the small molecule was deduced by NMR shifts during titrations[18] of host and guest; it was subsequently confirmed by crystallography[19] in the solid state and even computationally in the gas phase.[20,21] Some unexpected guests

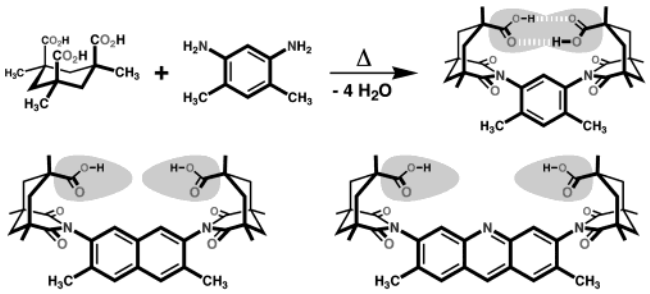

FIGURE 10. Kemp's triacid and aromatic spacers provide convergent carboxylic acid functions.

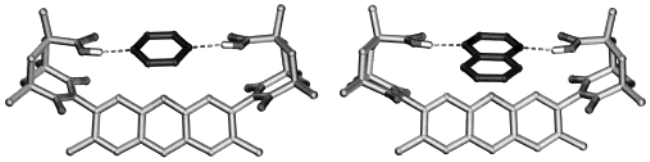

FIGURE 11. Chelation of pyrazine and its benzo derivative in the crystalline state by a synthetic receptor.

also found their way into these clefts. Who would have predicted that two of these acridine diacids would wrap around phenylalanine and extract it from water into $CHCl_3$?

Carboxylic Acids

Stereoelectronic effects were also in vogue about then, and we were not immune to the fashions. We chased an issue concerning the basicity of *E* versus *Z* lone pairs at carboxylate oxygen,[22] and Bob Duff, Jeff Huff, and Kevin Parris examined it in a number of contexts shown in Figure 12.[23] The Kemp triacid provided a means to do so, and for a while we believed no one else could. The effects were measurable, but modest. Our disappointment was not at all diminished by finding we were not alone in this research area.[24]

I have never been comfortable with the notion of effective molarity (EM),[25] even though EM figures appear in my publications. They do so only because the reviewers or the Editors ask about them. The comparisons of first- and second-order reactions inevitably involve different trajectories and approaches of the two components.[26] There is also an inherent entropic prejudice that contributes to high effective molarities for cyclization reactions. Intramolecular reactions usually involve a single molecule giving two products, say, a cyclic structure and a leaving group. In the comparison bimolecular reaction two molecules give two products, as in an SN_2 reaction. For the special case of intramolecular general base catalysis the prejudice carries with it the difficult to arrange endocyclic transition states. This also contributes the modest effective molarities observed by Mitra Tadayoni and Jeff Huff.[27]

The extraordinary versatility of the Kemp triacid continues to provide functional groups in increasingly confined spaces. Adam Renslo fused a triacid onto a cavitand to give an inwardly directed "introverted" functional group[28] (Figure 14). The acidity is directed into a chiral space that can more or less completely surround a guest and isolate it from influences outside. Paul Wash

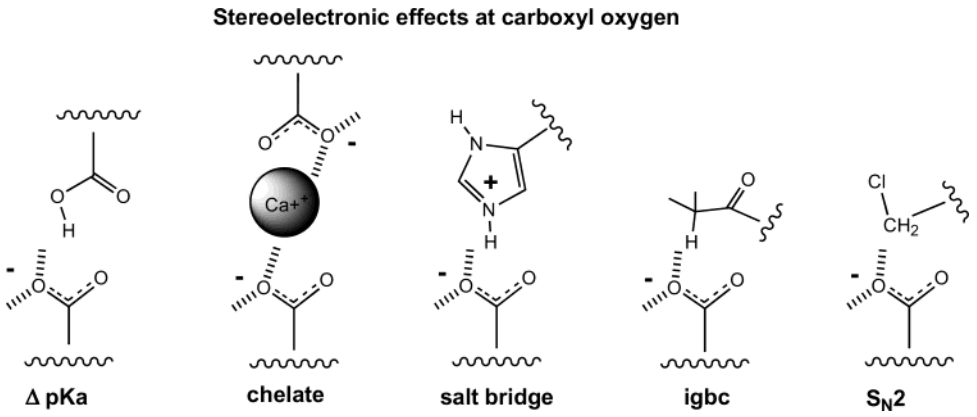

FIGURE 12. Kemp triacid derivatives present the *Z* lone pairs to groups of interest (igbc = intramolecular general base catalysis).

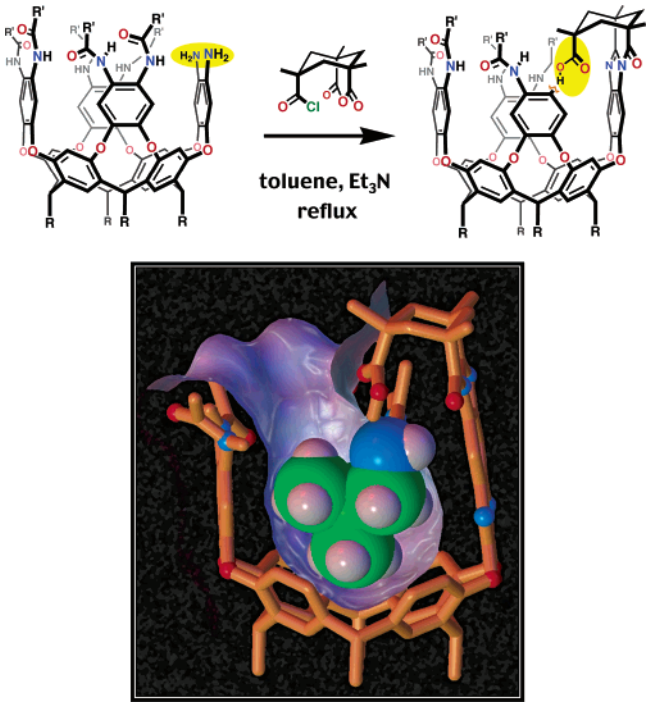

FIGURE 13. Synthesis of a cavitand/Kemp triacid hybrid (top); acid–base interactions and the filling of space are involved in the molecular recognition of isobutylamine (bottom).

showed that amines that filled the cavity and were pinned there by the acid/base interactions had their inversion dynamics radically altered by the close quarters.[29] An illustration is offered in Figure 13.

Nucleic Acids

The structure of DNA, published 50 years ago, made it clear how one strand in the double helix acts as a template for the other. It provided the inspiration for the polymerization studies of oligonucleotides in the Orgel[30] laboratories, but more than 30 years passed before von Kiedrowski[31] showed that a simple, self-complementary hexadeoxynucleotide could catalyze its own formation. Molecular replication had, at last, been achieved without enzymes. This autocatalysis was not of much interest to biochemists: after all, everybody

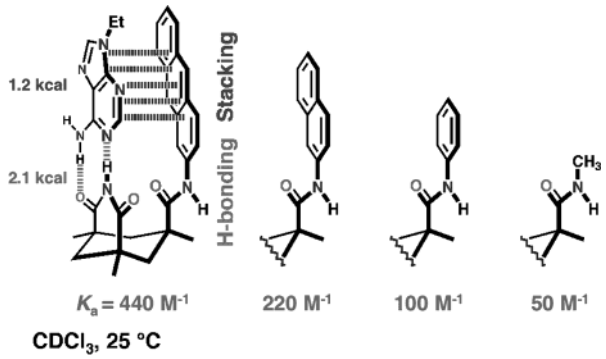

FIGURE 14. Molecular recognition forces in the binding of adenine in $CDCl_3$.

knew that nucleic acids could replicate, and nobody doubted that they did. But the result did stimulate organic chemists and inspired possibilities for replication that went far beyond the conditions imposed by practitioners of prebiotic chemistry.

Before I get to our synthetic replicators, please either recall or be informed that the group had refined the molecular recognition of adenine derivatives to a very high standard. Chris Buhr, Kyu-Sung Jeong, Sharon Jones, Tae Kyo Park, and Kevin Williams fashioned receptors for the heterocyclic portions of nucleic acids in organic solvents. In particular, they found that simple imides of the Kemp's triacid served as functional thymines, and any number of aromatic surfaces could be appended on these to provide additional binding through π-stacking interactions.[32–34] What we were measuring was the polarizability of these large aromatic surfaces when the dipole of adenine was held next to them by the hydrogen-bonding thymine group (Figure 14). Typical examples of adenine recognition in chloroform are shown in Figure 15.

The main recognition driver in this case was hydrogen bonding; the stacking was secondary. On the other hand, with the series of water-soluble derivatives in D_2O solution (Figure 15), Brian Murray, Vince Rotello, and Elisabetta Viani found these roles were reversed: the hydrophobic effects forced the molecules together with only a minimal contribution from the hydrogen bonds.[35]

As we—and many others—became more proficient at sculpting complex, concave surfaces for targets, it became manifest that completely surrounding one molecule by

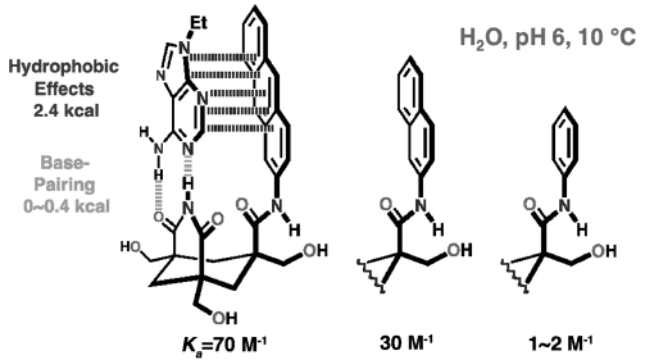

FIGURE 15. Molecular recognition forces in the binding of adenine in water.

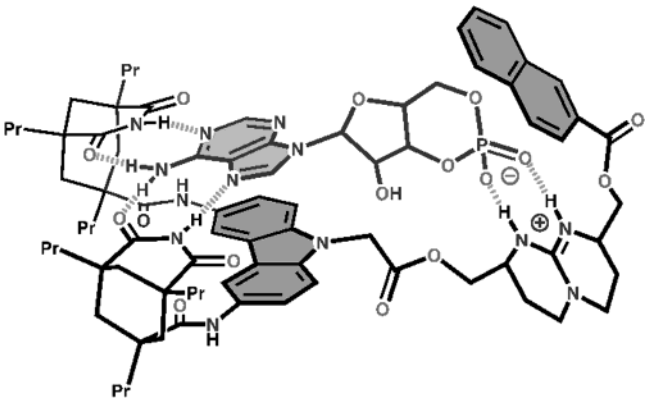

FIGURE 16. Simultaneous Watson−Crick and Hoogsteen base pairing, aryl stacking, C−H/π interactions and a salt bridge provide selective recognition of cyclic AMP.

another would be possible using weak, intermolecular forces. For example, Ghislain Deslongchamps and Amalia Galan, collaborating with Prof. Javier de Mendoza in Madrid, created a receptor for cAMP, which provided simultaneous Watson−Crick and Hoogsteen hydrogen bonding, aromatic stacking, and even a salt bridge to the appropriate complements of the target. (Figure 16).[36]

Template Synthesis 2

Two molecules that recognize each other through weak, reversible intermolecular forces might find themselves positioned for an intracomplex reaction that would leave them irreversibly bound to each other. I thought maybe a "covalent accident" could bridge recognition and replication.[37] For example, a synthetic receptor was outfitted by Tjama Tjivikua with a functional group that reacts irreversibly with a chemically complementary group on its target. Specifically, the receptor was an imide that recognizes adenine derivatives by hydrogen bonding and aryl stacking of the purine to the imide and naphthalene surfaces of the receptor, respectively. The target (Figure 17) delivered a nucleophilic amine to an active ester positioned on the receptor. The first synthetic, self-replicating system was based on just these structures and conditions.[38] It is tautologous that the union of complementary molecules gives a self-complementary one, but in the case at hand, the product has an additional attribute—it can act as a template for its own formation.

The significance of template effects in this reaction rests on the autocatalysis shown by the system. The initial rates of the reaction were studied by James Nowick, Qing Feng, and Ed Wintner at varying concentrations of added product; the rate enhancements are not directly proportional to product concentration, but rather to its square root.[39] This "square root law" was described by von Kiedrowski[40] to characterize nucleic acid replicators in which the autocatalytic entity exists largely in dimeric form.

How does it work? The simplest explanation that embraces the experimental results involves a template effect: the product provides a surface on which the reaction components can find a faster path for product formation than free, in bulk solution. A termolecular complex or the complex with the reversibly formed tetrahedral intermediate is grasped at both ends as shown in Figure 18.[41]

In any sequence, the configuration shown favors the expulsion of the phenolate from the center to give the product. It may be possible that the amide of the template, in proximity to the tetrahedral intermediate, provides some chemical catalysis as a general base,[42] but it can only do so when presented within the complex. When base pairing is precluded, as with an *N*-methylated imide, no rate enhancement is seen. Additional studies by Reinhoudt[43] show that dimethylation of the purine amino group has the same effect: catalysis shuts down. The substitution of methyl groups for the hydrogens involved in recognition gives molecules that neither self-replicate nor act as catalysts for the replication of the original. The covalent accident created a *minimalist* replicator that can help make identical copies of itself, and the molecule catalyzes its own formation through molecular recognition.[44]

The catalytic efficiency was too low to observe exponential growth of the product, but the system was

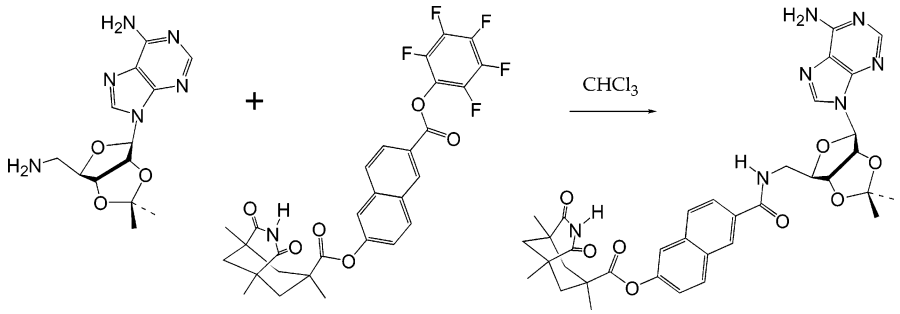

FIGURE 17. Autocatalytic aminolysis reaction.

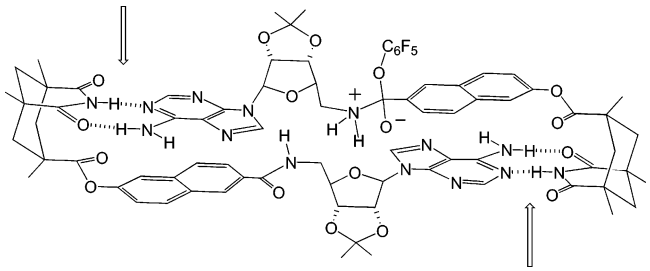

FIGURE 18. Proposed mechanism of template autocatalysis, the product recognizes both components of the reaction.

structurally refined to give a modified replicator with this behavior.[45] In addition, many other synthetic, self-replicating systems including peptides[46] and Diels–Alder adducts[47] have been devised, using the self-complementary template paradigm.

But there remain two shortcomings we (and others) continue to find challenging. The first problem faced by the prebiotic chemist is developing synthetic, informational sytems and there has been no good news on this front. The second is the problem of product inhibition. This is a seemingly inevitable consequence of template-mediated replication even in biology. The bimolecular complex of product molecules is likely to be favored over a termolecular reactant complex. Although this seems inescapable, last year my colleague Jerry Joyce selected a self-replicating ribozyme for which the product does not compete for reagent sites.[48] Turnover, rather than product inhibition, is the consequence.

Encapsulation

In the organic laboratory there is now some progress—albeit modest—on this front as well. It involves autocatalysis based on a quite primitive form of recognition, reversible encapsulation. But first, this is the time to introduce you, the reader, to "molecules within molecules". This is a form of molecular recognition invented by Cram[49] and Collet[50] in which a small molecule guest is more or less completely surrounded by a large molecule host. I was intrigued to find recently that "host" and "guest" appeared at least 45 years ago in the Fiesers' book *Steroids*.[51] The subject was the behavior of choleic acids and their inclusion compounds, but our own look at these complexes gave no well-defined structures in solution. Logically enough, Louis Fieser was Cram's mentor at Harvard, and host/guest interactions were popularized by Cram in the 1980s using crown ethers. More recently, Don DeLillo wrote it nicely: " ...'guest' and 'host' are words that intertwine... Converging, mixing, reciprocating. ...Guests bring ideas from outside".[52] My own preference is for pairing host with "hostage". At any rate, the Cram and Collet systems, the carcerands and cryptophanes, are held together by covalent bonds and have lifetimes of up to decades. The recent versions, reversibly formed capsules,[53] are assemblies held together by weak intermolecular forces and are dynamic.

Having spent more than a decade on molecular recognition, or how molecules fit together, I became engaged by the question of why molecules fit together. Molecular surfaces that are in contact with each other are shielded from solvent and dissolved reagents. This protection of the interface enhances stability; in prebiotic terms, enhances survival. In its double-helical forms, DNA presents mainly the very stable phosphates and some grooves to the solvent; the information is protected by base-pairing and stacking. The longer the individual lifetimes, the better the chances for functions such as autocatalysis to develop.[54] Molecules capable of molecular recognition over extended surfaces could be held in complexes hidden from hydrolysis; molecules completely surrounded by others enjoy the ultimate in protection.

The forces comprise hydrogen bonds, C–H/π interactions, van der Waals forces and even stronger metal–ligand binding.[55–58] The lifetimes of the complexes vary from milliseconds to days, a range that makes them useful as nanometric reaction chambers,[59] as means to stabilize reagents,[60] sources of "complexes within complexes,[61]" and as spaces where new forms of stereochemistry can emerge.[62,63] When encapsulated, guests are unreactive to dissolved reagents, since the capsule provides a mechanical barrier. Exchange between the environments inside and outside the capsule becomes a means of regulating reactivity.

The system that shows promise in recognition-based autocatalysis involves a reagent in a cylindrical capsule of nanometric dimensions[64] (Figure 19).

Encapsulation of appropriate guests occurs best in those solvents that cannot fit inside the capsule, and deuterated mesitylene is appropriate for most guests and provides a convenient solvent for NMR spectroscopy. Thomas Heinz and Dmitry Rudkevich showed that this capsule can accommodate two molecules of typical solvents such as benzene, toluene, or *p*-xylene but it also shows an unexpected selectivity: when offered a choice of these solvents as a competing mixture, it selects one benzene paired with one *p*-xylene. Longer, congruent guests are also carefully selected by the capsule, provided that they fill the space appropriately.[65]

Chain Reaction

Steffi Koerner and Jian Chen found this capsule binds the popular dehydrating agent dicyclohexylcarbodiimide (DCC). The corresponding urea (DCU) is even a better guest (Figure 20), as is the *p*-ethylanilide of *p*-toluic acid. The shorter anilide is an excellent guest for the capsule, However, the slightly longer *p*-ethylanilide of *p*-ethylbenzoic acid (not shown) is not a guest of the capsule. Unlike flexible guests that can adopt coiled conformations,[66] the longer anilide has no way to shorten its dimensions, short of folding to a *cis* amide that is too fat to fit, anyway. In solution, the DCC dehydrating agent shows equal reactivity to *p*-toluic and *p*-ethylbenzoic acids, but strange behavior results when the DCC is encapsulated.

With encapsulated DCC in deuterated mesitylene, the reaction of *p*-toluic acid and *p*-ethyl aniline shows a distinctly sigmoidal reaction profile (Figure 21). At NMR concentrations of capsule and DCC, the equilibrium amount of free DCC is too low to detect by NMR experiments. Nonetheless, the reaction proceeds slowly through whatever concentration of DCC is available in solution. The DCU and the shorter anilide are both good guests for the host, and each of these products, once formed, displace the DCC from the capsule into the bulk

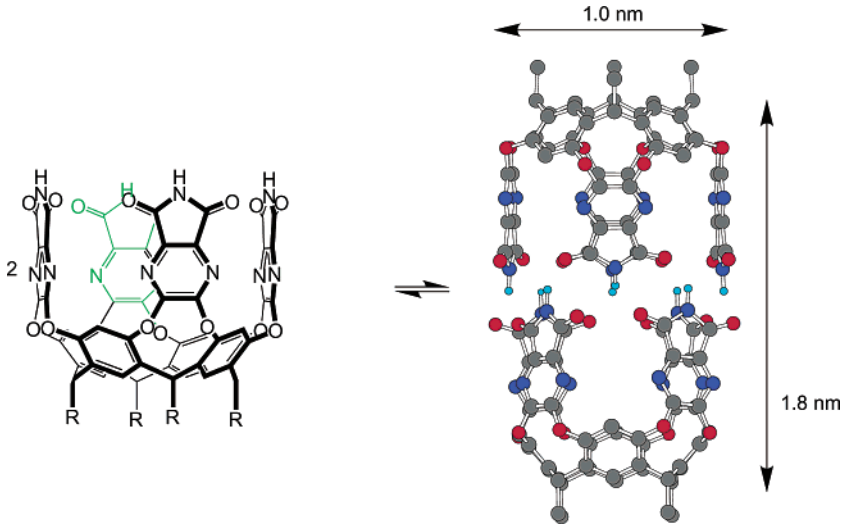

FIGURE 19. Cyclic tetraimides dimerize through bifurcated hydrogen bonding.

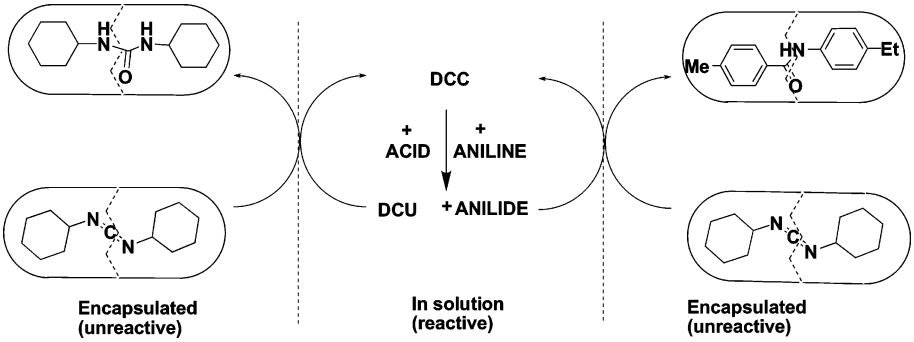

FIGURE 20. Reaction products accelerate their own formation through release of encapsulated reagent. The autocatalytic behavior results from feedback loops in a self-regulating reaction cycle and involves molecular recognition by the capsule.

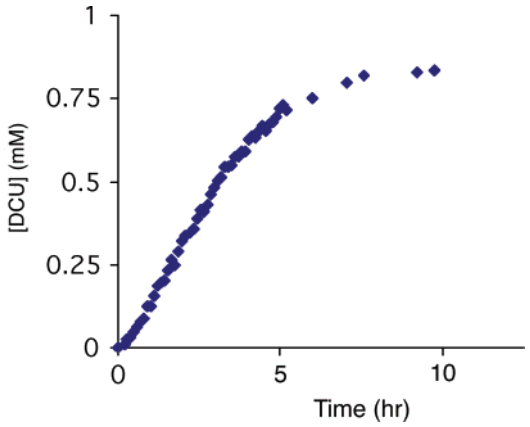

FIGURE 21. Encapsulated chemical reagents can result in nonlinear kinetics and autocatalytic behavior. The reaction of encapsulated DCC with toluic acid and *p*-ethyl aniline in deuterated mesitylene at 295 K. The graph shows the generation of encapsulated DCU as a function of time during the course of the reaction system shown in Figure 20.

solvent where it can react with the acid. A single molecule of DCC reacts to yield one molecule each of the urea and anilide, which then displace additional DCC, leading to more urea and anilide, and result in chain reaction kinetics. The capsule gradually fills with the product DCU and product anilide. With the longer *p*-ethyl benzoic acid, no such anomaly is seen. When the reactions were performed in the presence of the anilide products, the shorter anilide accelerated the rate of its formation, but the longer anilide did not.

The capsule does not influence the reaction between acid and DCC; it only limits the rate at which reagents encounter each other, leading to kinetics that accelerate with the increase in free, "reactive" DCC. Stephen Craig and Shirley Lin showed that the sigmoidal shape in the graph is dependent on two conditions: (1) at least two products must be generated which are better guests for the capsule than the DCC, and (2) the release of DCC must be at least 1 order of magnitude slower than the coupling reaction.

Amplification

Autocatalysis based on molecular recognition is the very definition of molecular replication: the product is a template on which the reactants are positioned. The encapsulated system does resemble autocatalysis, but there are subtle differences in two respects. First, specific molecular products are selected from many reactive possibilities in templated autocatalysis.[67−75] Such systems have a backdrop of direct competition of individual molecules. Encapsulated reagents, once released, are equally likely to encounter any partners present in solution. Accordingly, the autocatalytic behavior emerges

from the components of the system rather than depend on recognition of a specific molecule. Since we were unaware of a specific term that describes this effect, "chemical amplification" was proposed.

This behavior requires compartmentalization, and the benefits of compartmentalization are no news to Nature, where it is believed to be an essential characteristic of living systems. Autocatalysis and chemical amplification give rise to behaviors such as increased sensitivity, responsiveness, and self-replication. The autocatalysis based molecular recognition by encapsulation has two other consequences: the products are encapsulated and thereby protected, and product inhibition is not a problem.

Conclusions

If you've made it this far, you're probably a former member of the group wondering if references to your work will show up. I did adopt a self-referential, postmodern style as is inevitable in reviews, but no more names appear in the narrative. The reader may be a student worried about the next cumulative exam. If so you're playing the odds: the published results have tortured many students. I know, because the torturers gleefully send me the exam questions; do they really think that I want to be resented by yet another generation of graduate students? My own torment comes from the juxtaposition of Figures 2, 8, 10, and 20 . Is there only one idea—simple, recurrent, and defining—here? You, the reader, can decide.

Acknowledgments. I am deeply indebted to the Skaggs family: generous with support, warm in their friendship, and graceful with their interpretation of chemical biology, they are the very best examples of philanthropy. The National Institutes of Health (GM 50174, GM 29372) and the NASA Astrobiology Institute provided funds as well. I am most happy to acknowledge the contributions of the other members of the group, currently in or recently released from the trenches and to Fraser Hof for the cover graphic. Finally, I'm grateful to Ron Breslow for inventing the word "biomimetic," and to the American Chemical Society for this opportunity to celebrate Ron's career.

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JO0303719