CHEMISTRY

One-Pot Biochemical Cookery

The most ordinary biological cell, even a humble bacterium, is a chemical virtuoso, orchestrating ensembles of enzymes to build complex biomolecules that can control disease, disarm harmful chemicals, or serve as essential nutrients. Human chemists striving for the same goals have tended to try alternate routes of chemical synthesis—or they've transferred the genes for the enzymes to other organisms that can be grown in quantity and let them do the hard work of synthesis. But chemist A. Ian Scott of Texas A&M University has been trying to imitate that nonchalant cellular mastery directly.

At last month's meeting of the American Chemical Society (ACS) in Washington, D.C., Scott told attendees that he's been trying to pull off cell-style chemical syntheses by simply mixing the appropriate enzymes and other ingredients in a beaker. Scott promised little, admitting: "This seems unlikely [to succeed] given that we normally think of the cell as an exquisitely controlled system." Nevertheless, he told the ACS meeting, the mix-and-stir route to the synthesis of complex biomolecules has already taken him part of the way to targets such as vitamin B12 and indole alkaloids—a large class of plant compounds including vincristine, an anticancer compound derived from the periwinkle. In the coming decades, says synthetic organic chemist James A. Marshall of the University of Southern California, "this is one of the tactics people will be working with."

Conceptually, the strategy is simple: In a solution resembling a cell's cytoplasm, just combine some appropriate starting ingredients, such as amino acids, with all of the enzymes a cell uses to make a natural product—20 of them, for B12 synthesis. Then wait. With luck, Scott says, each enzyme will fulfill its little assembly-line chemical role, ultimately converting the starting ingredients into the complex product.

The strategy has yet to produce a complete product, in part because Scott doesn't yet have the full set of enzymes for any of these chemical assembly lines. In the most complicated example so far, Scott and his colleagues dumped 6 of the enzymes involved in B12's synthesis into a beaker, where their concerted action converted a simple starting ingredient—5-aminolevulinic acid—into intermediate structures called precorrins. Next, Scott hopes to get hold of all 20 enzymes to see if the complete enzyme cocktail yields bona fide B12. "We have purified 12 or 13 of the enzymes," he says, predicting it will take 5 years to get the rest.

Not that a complete synthesis-in-one-pot for vitamin B12 would challenge the cell-based biotechnologies that now cheaply churn out bulk amounts of the vitamin. "This is an exercise in feasibility," Scott says. But for other compounds, including vincristine and the anticancer compound taxol, which are produced in plant cells in only vanishing quantities, Scott predicts his technique could be a contender.

What's more, like any good cook, Scott looks forward to varying each recipe. The large amounts of enzymes needed for these syntheses would be collected from cells genetically engineered to overproduce the molecular tools. And genetic engineering opens the way to mutating the enzymes, yielding new ingredients to toss into the biosynthetic pot, Scott notes. That strategy could enable chemists to churn out dozens or hundreds of variants of a chemical compound that has shown therapeutic promise, in the hope of improving on the original.

First, though, Scott needs a few more basic recipes to play with. Only a few of the complicated, enzyme-tooled pathways that cells use to make their marvelous molecules are known. As a result, it will be a while before one-pot chemical synthesis reaches a boil.

–Ivan Amato

PHYSICS

Making Buckyballs Go Ballistic

Superconductors...molecular containers... super-efficient catalysts—the postulated uses for buckyballs seem never-ending. Now there's a new one to add to the list: high-energy projectiles. Researchers at the Institute of Nuclear Physics at Orsay, near Paris, working with a team from the University of Uppsala, have used a linear accelerator at Orsay to boost C_{60} ions to energies approaching 50 million electron volts (MeV).

That might sound arcane, but the French and Swedish researchers say that they're not simply riding the buckyball bandwagon. "This really opens a new field of research in the physics of collision processes," says Yvon Le Beyec of the Orsay institute. Agrees physical chemist Jerry Hunt of the Argonne National Laboratory: "It's a significant step forward" for physicists interested in what happens when high-energy ions slam into solid targets.

Buckyballs, say the researchers, make ideal projectiles. Clusters like C_{60}, in which many atoms are tightly linked by covalent bonds, can be used to deposit large amounts of energy right at the surface of a solid, because the mass of the cluster allows it to attain a high total energy while its velocity remains modest. This means that the clusters don't penetrate far below the surface when they hit a target—compared to smaller ions, it's the difference between a medicine ball and a bullet.

To make their buckyball beam, the Orsay researchers first fire cesium ions at a pellet of solid C_{60}, dislodging negatively charged buckyball ions, which then pass through a thin layer of nitrogen gas. Along the way, electrons get stripped away to form C_{60} ions ranging in charge from 1+ to 3+. The electric charge then provides a "handle" for the powerful electrostatic accelerator, which generates the beam.

Their success puts the group well ahead of other researchers. Robert Vandenbosch of the University of Washington has also fired cesium ions at a C_{60} pellet, but he's only been able to produce buckyball fragments, not intact ions. And though a German group led by Helmut Voit of the University of Erlangen has made beams of intact C_{60}, they've only been able to accelerate these to about 6 MeV.

Le Beyec and his colleagues—who have yet to publish their results—are now shooting their buckyball beam at carbon foils coated with thin films of organic compounds, studying how energy is transferred in the collisions. Argonne's Hunt says that the buckyball beam may also prove a useful tool in analytical chemistry: Aimed at a layer of fragile biomolecules adsorbed onto a surface, he says, it could eject intact molecules, which could then be analyzed by mass spectrometry.

On a more speculative note, the Orsay buckyball beam may also revive interest in a controversial process called cluster impact fusion. In 1989, a team from the Brookhaven National Laboratory claimed that when clusters of several hundred heavy water molecules strike a target loaded with deuterium, some unknown energy-concentration process triggers nuclear fusion. Shortly afterwards, several researchers speculated that bombarding a deuterated target with high-energy covalently-bonded clusters—such as C_{60} ions—might have similar effects.

This year, however, the cluster fusion enthusiasts have been in full retreat. In March, the Brookhaven team retracted its original claim, and the Orsay group is keeping its distance. Bo Sundquist, who leads the Swedish arm of the collaboration, for instance, describes the theory as "far-fetched." But others aren't quite so cautious. Washington's Vandenbosch found no evidence for an exotic energy concentration process when he used smaller carbon clusters as projectiles. But he says that if his group succeeded in making a beam of intact C_{60}, he'd soon be battering it against a deuterated target in search of fusion.

–Peter Aldhous