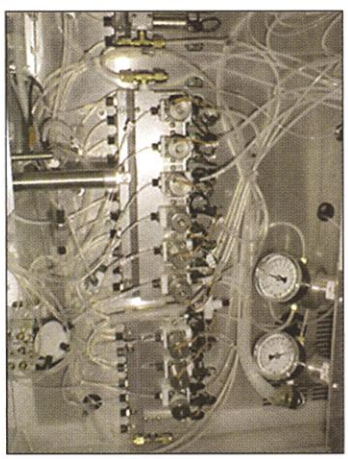
ORGANIC CHEMISTRY

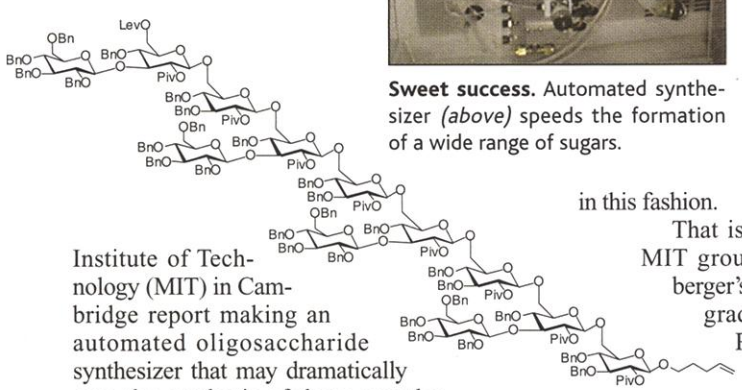
# Sugars Join the Automation Rush

For many biologists, sugars aren't so sweet. Chains of these simple molecules, called oligosaccharides, are vital to communication and binding between cells. But even short oligosaccharides are extremely difficult to synthesize. The inability to cook up large quantities of these molecules to conduct experiments has long kept researchers in the dark about what many of them do in the body. Indeed, when specialists in immunology, cancer biology, and developmental biology encounter oligosaccharides, they often just steer their research in another direction. "A lot of times they just stop working on the problem and do something else," says Carolyn Bertozzi, an oligosaccharide expert at the University of California, Berkeley. But now they are likely to get some help.

In a paper published online by *Science* this week (www.sciencexpress.org), Peter Seeberger and his students at the Massachusetts Institute of Technology (MIT) in Cambridge report making an automated oligosaccharide synthesizer that may dramatically ease the synthesis of these complex chains. Seeberger's team, for example, created one oligosaccharide made of 12 sugar units in 18 hours. Conventional methods would take months. Enabling researchers to mass-produce oligosaccharides and test their effects on cells, Bertozzi says, is likely to revolutionize the understanding of the role of these molecules in immunology, cancer biology, tissue development, and intercellular communication.



**Sweet success.** Automated synthesizer *(above)* speeds the formation of a wide range of sugars.



Similar widespread benefits ensued when researchers automated the synthesis of the two other classes of biopolymers, nucleic acids and peptides. Oligosaccharides, however, have remained automation's holdout—not for lack of interest, but because they link together in myriad complex three-dimensional shapes. Whereas the building blocks of nucleic acids and peptides bind in linear chains like boxcars on a train, the sugars in oligosaccharides have numerous points of attachment, like a child's Lego blocks. A single glucose unit, for example, has four hydroxyl groups that can bind to other sugars. What's more, each bond that forms between separate units can take one of two different shapes. As a result, just four sugars can be strung together in more than 5 million possible arrangements, says Chi-Huey Wong, an oligosaccharide chemist at the Scripps Research Institute in La Jolla, California.

Organic chemists typically deal with this problem by capping sugar molecules with "protecting" groups at all but one reaction site to block unwanted reactions. That precaution ensures that the bond is placed at the right spot when two sugars react. But it still leaves compounds with a mixture of bonds formed in different orientations, requiring laborious purification procedures after each new sugar building block is added. To streamline the process, numerous groups have recently experimented with growing oligosaccharides on solid supports and using protecting groups that force the molecules to bond in just one orientation. It can take just 2 weeks to make a 12-unit chain in this fashion.

That is the procedure that the MIT group has automated. Seeberger's team—which included graduate students Obadiah Plante and Emma Palmacci—converted an old peptide synthesizer to work with the new sugar-based reagents and reaction conditions. Along the way, the team invented new protecting groups that work better with solid supports, a novel linker group that holds on tight to the oligos but can easily be clipped at the end of the process, and novel reactants that knit sugar bonds together.

The team starts by hooking the linker to a polystyrene bead. The synthesizer then introduces an initial sugar building block that reacts with the linker. After a washing step removes unwanted byproducts, additional reagents remove a targeted protecting group on the sugar, opening a site for the next sugar unit to bind. The process is repeated until the desired oligo is made.

Thus far the MIT team has used the approach to make oligosaccharides with four of

CREDITS: (TOP TO BOTTOM) COURTESY OF O. PLANTE; PLANTE *ET AL.*; ITER

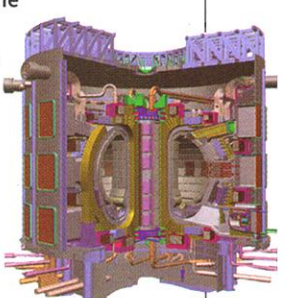
## ScienceScope

**Aussie Windfall** Researchers are applauding a $1.6 billion plan for Australian science. The 5-year government roadmap, released this week, largely follows recommendations from two reports issued last year by researchers and industry to reverse cuts and strengthen education, research, and the commercialization of new technologies (*Science*, 13 October 2000, p. 255).

The plan calls for doubling basic research spending by the Australian Research Council to $300 million in 2006 and nearly doubling funding for university infrastructure to $108 million. It also includes funds to support 21,000 new undergraduate students in math, science, and information technology, and for new IT and biotechnology research centers. Responding to complaints about earlier cuts, the government also plans to bump up tax credits and subsidies for industrial R&D.

Government chief scientist Robin Batterham, who wrote last year's scientists' report, is "delighted" by the plan. "Virtually all the recommendations of [our] report have come through," he says.

**Fusing Behind Fusion** European Union research ministers have united behind plans to build an International Thermonuclear Experimental Reactor (ITER). Last year, after the United States backed out of the megaproject, E.U. ministers couldn't agree on whether to move ahead with the $3.7 billion tokamak, a device designed to test the feasibility of fusion power. But at a special meeting in Brussels last month, officials agreed to put funding for the project—which is also backed by Japan and Russia—into the E.U.'s next 5-year Framework research plan, which begins in 2003.



Exactly how much Europe will spend on ITER, however, will depend on where it is built. Japan, France, and Canada are interested in hosting the machine, which means shouldering a greater share of the cost. E.U. officials say their existing $500 million fusion budget could handle an expected contribution to a machine built outside Europe, but not to a regional facility. ITER's partners hope to settle on a site by the end of 2002 and complete the device by 2014.

the nine sugar units found in mammals, says Seeberger. And most of the others are expected to follow quickly. Still, Seeberger acknowledges that the new synthesizer won't be able to provide all possible oligosaccharides, because the group has yet to find the chemistry that allows sugar bonds to form in certain orientations. "That's something we are addressing right now," he says.

Another hitch, Wong notes, is that the strategy requires that a wide variety of sugars with different arrangements of protecting groups be made in advance to serve as the building blocks for oligosaccharide assembly. And for now that must still be done by hand, using slow conventional chemistry. Although that's true, Seeberger notes, this used to be the case for peptide and nucleic acid building blocks, which became commercially available reagents as the machines grew in popularity. Seeberger and Plante say they plan to start a company this summer to commercialize their automated synthesizer and supply many of the needed reagents. **–ROBERT F. SERVICE**

WOMEN IN SCIENCE

## College Heads Pledge To Remove Barriers

**BOSTON**—The leaders of nine top U.S. research universities this week pledged to smash the glass ceiling that hinders women from advancing at their institutions. Meeting on Monday at the Massachusetts Institute of Technology (MIT), the all-male group stopped short of setting a specific agenda but acknowledged that women face greater obstacles in climbing the academic ladder. "It's momentous just to get these nine together," says Patricia Jones, a biologist and vice provost at Stanford University in Menlo Park, California, who attended the meeting. "Count me as a happy camper," adds Stanford economist and participant Myra Strober.

Hosted by MIT president Charles Vest, this week's meeting grew out of a 1999 internal report that found the small number of MIT women science faculty members had consistently less lab space, recognition, and leadership responsibilities than their male counterparts (*Science*, 26 March 1999, p. 1992). In a one-page statement, the presidents agreed that barriers exist, that more data are needed, and that they would work together to improve the situation. The discussions ranged from offering child care at academic conferences to monitoring the progress of young faculty and guarding against gender imbalances in hiring and promotions. Following the MIT model, a number of schools are putting together their own reports. Attending the meeting were the presidents, chancellors, or other senior administrators of Harvard, Princeton, Stanford, and Yale universities, the universities of California–Berkeley, Michigan, and Pennsylvania, the California Institute of Technology, and MIT.

A major focus was on quantifying the problem (see table). Shirley Malcom, education chief for the American Association for the Advancement of Science (AAAS, which publishes *Science*), laid out the issue in the day-long, closed-door meeting. "You don't collect what you don't want to know, and you can't make progress to a goal without measuring it," she told *Science*. Vest says that although the group did not endorse a collective approach to data gathering, participants agreed to find ways to fill in the gap. Such details likely will be discussed at a second meeting tentatively slated for 2002.

Financial backing for the meeting came from the Ford Foundation and an anonymous donor, each of whom gave MIT $500,000 last spring to address the issue of women and minorities in academic science. "They encouraged us to reach out," says Nancy Hopkins, an MIT biologist and a leader of the MIT study effort. MIT is chipping in a similar amount.

In California, meanwhile, state legislators planned a 5-hour hearing this week on equity and retention of female faculty members in the University of California (UC) system, the nation's largest. The hearing stems from concerns by UC faculty members that the recent abandonment of state affirmative action policies aimed at increasing the number of minority students and faculty members is also eroding the hiring of women.

At UC Davis, for example, 37 out of 44 professors hired in 1999 were male. And the percentage of women hired in the overall UC system has declined from 36% in 1996—when the policies were still in place—to about 24% in 2000. "The situation is now critical," says California Senator Jackie Speier (D), who was to chair the hearing. A state audit of UC's hiring policies is due out next month. **–ANDREW LAWLER**

**TOUGH TREK FOR WOMEN CHEMISTS**

| University | Full professor | Associate professor | Assistant professor |
|---|---|---|---|
| Berkeley | *38/3 | 4/1 | 9/1 |
| Caltech | 20/2 | 3/0 | 4/1 |
| Harvard | 16/1 | 0/0 | 4/0 |
| MIT | 21/3 | 2/0 | 6/1 |
| Michigan | 26/1 | 5/2 | 7/1 |
| Penn | 22/2 | 5/0 | 4/1 |
| Princeton | 21/0 | 2/1 | 2/0 |
| Stanford | 18/1 | 3/0 | 4/0 |
| Yale | 18/1 | 1/0 | 4/1 |
| TOTAL | 200/14 | 25/4 | 44/6 |
| Percentage | 7% | 16% | 14% |

* All ratios indicate total/women professors.

**No entrance.** Women chemists are filling the first rung at top schools at rates far below their share—31%—of the Ph.D. pool.

SOURCE: *CHEMICAL AND ENGINEERING NEWS*, 2000 SURVEY

MICROBIOLOGY

## Bakers' Yeast Blooms Into Biofilms

Standing alone, fungal and bacterial pathogens are relatively easy prey for antimicrobial drugs. But many of these germs cling together in resilient sheets and globs called biofilms that resist traditional chemical attack. Recently, microbiologists have been getting a fix on what causes bacterial microfilms to form—information that provides potential new targets for infection-fighting drugs (*Science*, 21 May 1999, p. 1302). But lack of a good model system has made fungal biofilms—which frequently contaminate medical devices, cause chronic vaginal infections, and lead to life-threatening systemic infections in people with hobbled immune systems—harder to study. New results should change that.

On page 878, Todd Reynolds and Gerald Fink of the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology report that they've coaxed a harmless fungus, bakers' yeast, to form a biofilm. Because bakers' yeast is so well studied—its entire genome has already been sequenced—researchers predict that this new biofilm model will expose vulnerabilities that can be targeted in other, pathogenic fungi. The work "expands [the study of biofilms] with a wonderful, genetically tractable organism," says microbiologist Roberto Kolter of Harvard Medical School in Boston.

Bakers' yeast occasionally forms a film on the surface of sherry, Reynolds says, but it doesn't naturally congregate into a form that fits the operational definition of a biofilm: simply, a film that sticks to plastic. To induce bakers' yeast to do this, the researchers tested several strains and tweaked the yeast's nutrients until they hit on a combination that produces a robust biofilm. The bakers' yeast built the largest biofilms and stuck most stubbornly to plastic when it was fed low concentrations of glucose, suggesting that lean times spur the yeast to change form. Once initiated, the yeast biofilm