evidence of organic compounds and microbial life. In addition, part of Lederberg's vision for this instrumentation was also to close the loop by performing the analysis onboard the spacecraft to inform a next round of experiments without waiting for Earth-based instructions. This was, in part, the motivation for the DENDRAL project at Stanford in which an intelligent assistant hypothesized the molecular structure of organic molecules on the basis of mass spectrometry data (see the figure).

Intelligent assistants are currently numerous and well integrated into the activities of science and industry. In the longer term, however, new kinds of computer programs are needed to cope with the sheer volume of data that can be collected automatically (*7*–*9*) and with the volume of relevant information available in the literature.

Closing the loop from experiment design and data collection to hypothesis formation and revision, and from there to new experiments, will be one important way to cope with the volume of data. A new wave of programs will test the efficacy of using computers in closed-loop fashion and will explore the questions of which activities can be automated, and which ones we would even want to automate. Even for the relatively straightforward task of data collection, there are myriad questions to answer before streaming data from a laboratory instrument into a computer, including why particular data are being collected, which variables should be measured, and which instrument will measure them. If no such instrument exists, can it be designed and built?

Beyond coping with the volume of data, however, computers need to be called into service to cope with the volume of information and background knowledge relevant to any scientific question. Search engines and automated libraries will return more articles in response to a query than anyone has time to read. (For example, Google returns about 200,000 hits for the phrase "laboratory automation" and 10 million hits for the pair of terms "science" + "automation".) Programs that have the intelligence to read and interpret the online information for us will contribute to the next level of closing the loop. This is already an active area of computer science research (*10*).

For any such program to select the most cost-effective and informative hypotheses, prune hypotheses that cannot be realized experimentally, avoid repeating unsuccessful experiments that have already been tried by others, etc., it must include a rich model of the entire process of the loop, as well as knowledge of the specific scientific area being automated. This will increasingly involve a substantial modeling effort, as is already required for planning and interpreting experiments in systems biology or weather and climate.

For the foreseeable future, the prospect of using automated systems as assistants holds vast promise as these assistants are becoming not only faster but much broader in their capabilities—more knowledgeable, more creative, and more self-reflective. Human-machine partnering systems that match the tasks to what each partner does best can potentially increase the rate of scientific progress dramatically, in the process revolutionizing the practice of science and changing what scientists need to know.

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CHEMISTRY

Rethinking Water Splitting

A metal complex splits water into hydrogen and oxygen through an unusual series of steps.

Richard Eisenberg

Projections of global energy needs for sustainable development suggest a nearly 50% increase by 2030 (a mere 21 years hence) (*1*). This increase can be met satisfactorily by only one kind of alternative energy—the Sun. One approach to convert solar energy into a fuel is to use it to split water into H_2 and O_2. A number of strategies for the visible light–driven splitting of water are being pursued with varying levels of success. On page 74 of this issue, Kohl *et al.* (*2*) describe a very different reaction system for water splitting that uses light but also has thermally driven steps. The basis of this approach, in which key steps involve ligand modification, shows that reactions that harvest solar energy can be found among the unlikeliest of compounds.

Research in solar energy conversion follows three principal strategies. The first is the direct conversion of light into electrical energy, as in the photovoltaic (PV) devices that are currently being produced and installed around the world. Challenges here include increasing the efficiency and durability of such devices while reducing their cost to make them competitive with cheaper but environmentally problematic coal-fired power plants. The Energy Information Administration of the U.S. Department of Energy projects that global use of coal for electricity will grow relative to other sources in the next 21 years (*1*). Considerable research on dye-sensitized solar cells (*3*, *4*) has made them an interesting alternative to traditional silicon-based PVs, with demonstration units being deployed. Efforts also continue for new PV devices based on thin-film designs that use either amorphous silicon, cadmium telluride, copper indium gallium selenide, or organic charge-transfer compounds on flexible supports that can be manufactured on a massive scale (*5*, *6*).

The second strategy is to use nature's photosynthetic apparatus to produce biofuels from plants or waste agricultural by-products. Some of these approaches, such as corn-to-ethanol, are marginal in terms of economic and climate-change benefits (*7*). Other biomass sources, such as switchgrasses and agricultural by-products, may be economically more viable and have a sufficiently high positive net energy balance. To be feasible, methods must be developed for the facile catalytic

Department of Chemistry, University of Rochester, Rochester, NY 14627, USA. E-mail: eisenberg@chem.rochester.edu

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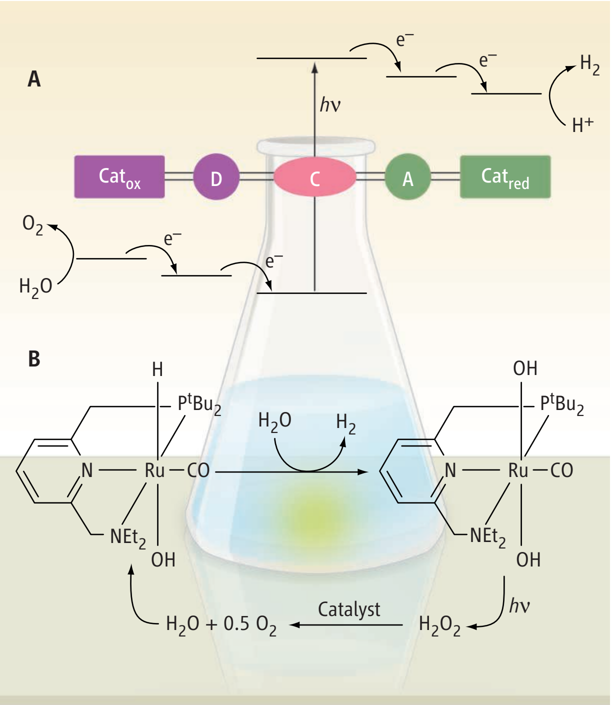

Two ways to split water. (**A**) In a simplified photosynthetic scheme, the absorption of a photon with energy *hν* by a chromophore C process generates a photoexcited electron and a hole state. Charge transfer of the electron is facilitated by the electron acceptor A and of the hole by the electron donor D. Proton reduction and hydrogen evolution occurs at Cat_{red}, which accepts electrons, and water oxidation and oxygen evolution occurs at Cat_{ox}, which accepts holes. The vertical scale qualitatively represents the electrochemical potential that drives the reactions. (**B**) The scheme of Kohn *et al.* departs from this scheme in a thermally driven reaction that generates hydrogen, and a subsequent photolytic step creates oxygen through decomposition of a hydrogen peroxide product. ^{t}Bu, tert-butyl; Et, ethyl.

or enzymatic breakdown of cellulose into its individual sugar units and the rapid conversion of those units into liquid fuels.

The third approach involves artificial (laboratory-designed) photosynthesis. Here, the splitting of water is the major reaction under study (*4*). The key photosynthetic steps in such a system are charge-transfer (CT) excitation, electron-hole separation by electron transfer reactions, charge accumulation, and catalysis. In a simplified diagram of such a system (see the figure, panel A), photoexcitation and charge transfer move an electron to a more reducing electrochemical level, leaving behind an oxidizing or electron-accepting hole. In the nonphotochemical electron transfer steps that follow, electrons move downhill and holes rise to drive the chemistry that occurs at catalytic centers

Because the electrons and holes separate in this scheme, water splitting can be divided into its two half-cell reactions that either consume or generate electrons, and each reaction can be investigated and optimized independently. In such studies, a sacrificial electron donor or acceptor is used to balance the half reaction (sacrificial in this context means that the compound decomposes once it donates or loses an electron). Research successes have been reported for both half-reactions. Although H_2 has been generated photochemically (*8–10*), the efficiency and durability of molecularly designed systems are far from effective levels for practical use. The formation of O_2 is even more difficult, because the reaction involves the loss of four electrons and four H^+ units in multiple steps that must be carefully choreographed to maintain charge balance and avoid going through high-energy oxygen intermediates (*11–13*).

The ruthenium (Ru) complex for water splitting reported by Kohl *et al.* builds upon several disparate observations they have made that are unrelated to other studies for H_2 and O_2 generation. The first is the reversible protonation of a "pincer" ligand arm that was bound to a ruthenium(II) ion; the facility of this usually difficult process is made possible through aromatization and dearomatization of the central ring of the pincer ligand (*14*). A pincer ligand coordinates to a metal through three points of attachment; the first and third are on opposite sides of the metal, or trans to each other, and the central or middle attachment is at 90°, or cis, to the other two. The added proton becomes a captive source of H^+ that can react with a ruthenium-bound hydride to yield H_2 by a hetero coupling reaction ($H^+ + H^- \rightarrow H_2$).

The second observation is that H_2O can add to a Ru pincer hydride complex by protonating the ligand arm (not the metal) and coordinating OH^- to the Ru metal center. Such addition reactions often change the oxidation state of the metal, but in this case, Ru remains in the 2+ oxidation state. The third observation is a reaction of the Ru pincer complex having hydride and hydroxide ligands—RuH(OH)(pincer)—with another H_2O molecule (see the figure, panel B). This reaction proceeds upon heating by initial H_2 liberation through hetero coupling and subsequent addition of H_2O as described above to form the dihydroxide complex *trans*-Ru$(OH)_2$(pincer).

The fourth observation is that in a photochemical step, *trans*-Ru$(OH)_2$(pincer) eliminates the higher-energy product hydrogen peroxide (H_2O_2) intramolecularly. Rapid disproportionation of 2 H_2O_2 molecules into O_2 and 2 H_2O completes the process of splitting water. Although the detailed mechanism of O_2 formation in more conventional water-splitting efforts, as well as in natural photosynthesis, remains a matter of ongoing study, it does not proceed via H_2O_2, which is a high-energy species (*11*, *13*).

The Kohl *et al.* system is notable in that the normally redox active metal ion maintains the same oxidation state throughout the course of the overall reaction. The heterolytic coupling step that forms H_2 is most unusual in how it involves the pincer ligand, but it connects to recent studies of H_2 formation in model hydrogenase compounds that are also thought to form hydrogen by hetero coupling of H^+ and a formal hydride H^- (*15*, *16*).

The water-splitting scheme that Kohl *et al*. describe presents challenges. It is not yet catalytic, and it has an uncertain energy balance depending on how the thermal steps are driven. Also, the system is not very durable because the phosphine arm of the pincer becomes oxygenated. However, the fact that a relatively simple molecular system can accomplish water splitting with steps not conceived of or brought together by other studies on water splitting is stimulating and thought-provoking.

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