subunit toxins—*Clostridium spiroforme* toxin, the ADP-ribosyltransferase from *Clostridium difficile*, the ι-toxin from *Clostridium perfringens*, and the C2 toxin from *Clostridium botulinum*—are assembled on the host cell surface like anthrax toxin (*6*), and their activity could be blocked with a dominant-negative strategy. Furthermore, important cytolysins, such as the α-hemolysin from *Staphylococcus aureus* and aerolysin from *Aeromonas hydrophila*, assemble into heptameric ring structures at the host cell surface, inserting themselves into the membrane and forming pores (*7*). These toxins could be inactivated by mutant dominant-negative subunits. The VacA toxin of *Helicobacter pylori*, the bacterium that causes gastric ulcers, forms hexa- and heptameric structures. A deletion mutant of the toxin interferes with the formation of active oligomers when tested on cells in culture (*8*). It may be difficult to exploit this finding therapeutically, however, because VacA attacks epithelial cells deep within the gastric crypts of the stomach. In the case of anthrax, the toxin is carried in the blood and can therefore be blocked by injecting mutant PA into the circulation.

A major concern when treating bacterial infections with antibiotics is the appearance of increasing numbers of antibiotic-resistant strains. Vaccination is a possible alternative for some diseases, but is often impractical either because it does not provide long-lasting protection or because the disease is uncommon. It is therefore important to be able to treat bacterial infections as soon as they occur with therapeutics other than antibiotics. The paper by Sellman *et al.* is an innovative example of how this can be achieved.

References

1. B. R. Sellman, M. Mourez, R. J. Collier, *Science* **292**, 695 (2001).
2. S. H. Leppla, *Handb. Exp. Pharmacol.* **145**, 445 (2000)
3. J. Wesche *et al.*, *Biochemistry* **37**, 15737 (1998).
4. S. Olsnes, P. Ø. Falnes, *J. Gen. Physiol.* **115**, 417 (2000).
5. B. R. Sellman *et al.*, *J. Biol. Chem.* **276**, 8371 (2001).
6. *The Comprehensive Sourcebook of Bacterial Protein Toxins*, J. E. Alouf, J. H. Freer, Eds. (Academic Press, New York, 1999).
7. G. van der Goot, Ed., *Pore-Forming Toxins* (Current Topics in Microbiology and Immunology Series, Springer-Verlag, Berlin, 2001), vol. 257.
8. A. D. Vinion-Dubiel *et al.*, *J. Biol. Chem.* **274**, 37736 (1999).

PERSPECTIVES: LASER CHEMISTRY

Keeping Reactions Under Quantum Control

Sean M. Hurley and A. Welford Castleman Jr.

Many chemical reactions can follow more than one reaction pathway, each leading to a different product. Usually, only one of these pathways is desired, and the side reactions decrease the yield of the desired product. Chemists therefore strive to devise methods for controlling chemical reactions and increasing the yield of specific products. Traditionally, they have relied on manipulating macroscopic parameters such as temperature and pressure; a catalyst may also alter the course of a reaction. Recently, femtosecond lasers have emerged as a powerful tool for quantum mechanical control of reactions. On page 709 of this issue, Levis *et al.* (*1*) show that strong-field laser pulses can be used to control a dissociative rearrangement reaction, in which bonds are not only selectively broken but also selectively formed.

Virtually since their creation, lasers have been suggested as a possible tool for controlling chemical reactions. A decade or more ago, schemes were developed that involved excitation to specific states, which were then supposed to decompose to specific products. In most cases, however, the laser energy was distributed rapidly into various bonds throughout the molecule, hindering the ability to select a specific pathway. All this changed with the development of femtochemistry, which opened up completely new ways of altering the course of a chemical reaction (*2*). Several scenarios for laser control of reactions have now been developed and implemented.

On a microscopic level, atoms, molecules, and light behave both as a particle and as a wave. It is the wave nature of the atoms and molecules that allows for quantum control to be accomplished. Absorption of light must obey rules derived from the laws of quantum mechanics, including the resonance condition, which dictates that the difference between the ground state and an excited state of an atom or molecule must match the energy of a single photon or the total energy of multiple photons. Short (femtosecond) laser pulses contain components of several different wavelengths; the frequency range depends on the bandwidth of the laser and hence its temporal characteristics. A single molecule can absorb photons of any of the component wavelengths as long as the absorption obeys the selection rules. When a molecule is coherently excited by the laser, a wave packet is created that accounts for the motion of the molecule in the superposition of excited states. Quantum mechanics predicts that if the molecule has a probability of residing in any one of the possible excited states, then it is in all of the possible excited states simultaneously.

The goal of a quantum control process is to alter this superposition and thus the wave packets, such that maximum constructive interference occurs in the desired reaction path while maximum destructive interference occurs in all other reaction pathways. This allows selective control beyond the trivial effects obtained through varying the intensity or simple temporal characteristics of laser pulses often used to alter the course of photochemical reactions.

Quantum control can be implemented in several ways. Two-pathway control, developed theoretically by Shapiro and Brumer (*3*) and experimentally by Gordon *et al.* (*4*) and others, uses laser light of sufficiently long pulses to excite molecules by distinct routes that reach the same final state. For example, absorption of one photon of 200 nm light and absorption of three photons of 600 nm are energetically equivalent and both could lead to the same final state. Varying the phase difference between the two laser fields changes the phase of the superposition wave packet and allows for quantum control. Some success has been achieved with this method (*4*).

A more general approach to quantum control, optimal control, uses an optimized laser field to create and control the excited molecular wave packets (*5*, *6*). Optimal control theory is used as a design technique to solve the equations of motion for the molecule and the exciting laser field to determine the optimal laser pulse that will give the maximum yield of the desired reaction products while minimizing side reaction channels (*7*). Solving the equations of motion can be computationally difficult, however, and the calculated laser field may be experimentally difficult to implement. The equations of motion depend on having an adequate description of the molecule including its interaction with the laser field. Reductions in the complexity of the calculations have been attempted, but in the case of the isomerization of HCN, the current levels of simplification were not up to the task of de-

---

The authors are in the Departments of Chemistry and Physics at the Pennsylvania State University, University Park, PA 16802, USA. E-mail: awc@psu.edu

signing fields for controlling polyatomic molecular motion (*8*).

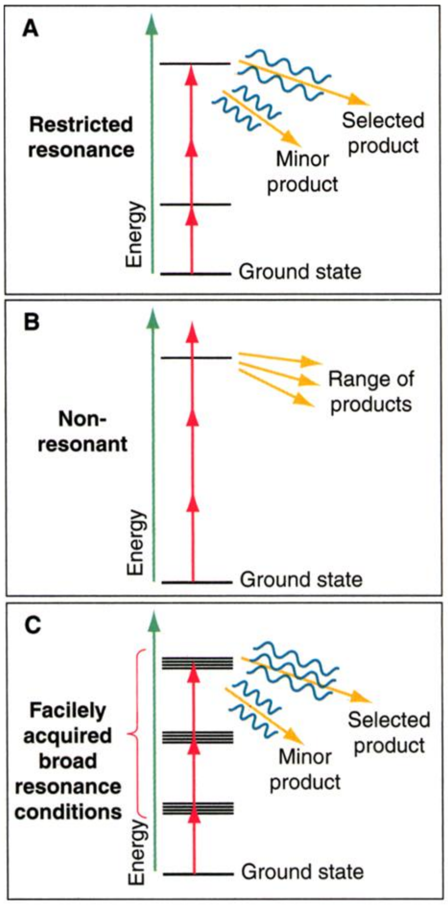
To overcome these problems, Judson and Rabitz (*9*) developed the concept of closed-loop optimal control, which uses a learning algorithm to guide the shaping of the laser field in the laboratory and requires no solutions of the equations of motion. An initial guess is made for the laser field, which is used to excite the molecules of interest and start the reaction. Products are detected and then analyzed by the learning algorithm. On the basis of the results, the learning algorithm makes changes to the components of the laser field such as pulse duration, phase, and amplitude. The adjusted laser field is then used to start the reaction again with a new sample, which completes the loop. The process is repeated until the results converge to a predetermined goal. In essence, the molecule bathed in the electromagnetic field "solves" the Schroedinger equation, and the algorithm uses the solution to guide the control of the reaction.

The initial demonstration of feedback control was the optimization of dye fluorescence (*10*). Optimal control of selective bond breaking in a polyatomic molecule was first shown using feedback-optimized phase-shaped femtosecond pulses in the photodissociation of $CpFe(CO)_2Cl$ (*11*). Other studies using shaped femtosecond pulses have included the optimization of the time-dependent ionization yield of Li_2 (*12*) and control of atomic transitions in Na atoms (*13*).

The methods discussed thus far were carried out with relatively weak laser fields, where substantial limitations are imposed by the necessity of working with the restrictive resonance condition (see panel A in the figure). Lasers typically only emit light over a small range of wavelengths. Only those chemical systems that absorb radiation in the wavelength range of the laser can be studied. Therefore, a consequence of obeying the resonance condition is a restriction of the chemical systems that can be studied (see panel B in the figure).

To overcome the weak-field limitations, Levis *et al.* have used a strong laser field to carry out their experiments (*1*). The magnitude of a strong field is comparable to the binding energy of a valence electron. When a molecule is subjected to strong-field radiation, the energy levels of excited states are shifted so that they may match the energy of a photon or multiples of photons, thus facilitating acquisition of the desired resonance condition. The broad distribution of possible superposed states generated in the superposition interferes constructively and destructively, leading to different reaction pathways (see panel C in the figure).

Strong-field control has not been widely implemented, but some experimental demonstrations have been reported. Bartels *et al.* have shown that shaped strong-field laser pulses can generate high harmonic soft x-rays (*14*). The advantage of strong-fields in accomplishing excitation is seen in the surprising results of experiments that revealed charge states as high as I^{+17} (all valence electrons lost!) and concomitant Coulomb explosion upon irradiation of HI clusters (*15*). Linearly polarized strong laser pulses have been used to enhance the branching ratio of the photodissociation of I_2 (*16*). Until now, however, reports of strong-field control of polyatomic molecular motion have been lacking. Prior intuition suggested that in the strong-field regime, high sensitivity to even small field variations might destroy the necessary wave packet structure. The recent high-field studies (*1*, *14*) show that this is not the case.



Quantum control of reactions. With the use of optimal control, selected reaction channel products can be formed through constructive interference. Destructive interference reduces or eliminates reaction products from other channels. **(A)** Weak field, restricted resonance condition. **(B)** Reaction control is not achieved. **(C)** Strong field, induced resonance condition.

Levis *et al.* (*1*) report strong-field optimal control of the photochemistry of acetone, fluoroacetone, and acetophenone. They show that selective bond breaking can be accomplished with strong-field shaped femtosecond pulses in closed-loop optimal control. While investigating the control of the photochemistry of acetophenone, $C_6H_5COCH_3$, a peak corresponding to toluene, $C_6H_5CH_3$, was observed in the mass spectrum. Toluene must be the product of photochemical dissociative rearrangement of acetophenone due to control initiated through strong-field effects. The toluene product intensity could be increased by a factor of 4 using strong-field pulse shaping techniques, showing that control of molecular dissociative rearrangement is possible. In further experiments, the ratio of toluene ion to phenyl ion was optimized and found to increase by a factor of 3, proving that nontrivial strong-field optimal control was operative. This is the first observation of quantum control of a dissociative rearrangement reaction.

Levis *et al.*'s experiments show that photochemical reactions of polyatomic molecules can be controlled through shaped strong-field optimal control. Resonance conditions are induced by using a strong laser field in the control scheme, thus making the use of the technique potentially universal. Molecular dissociative rearrangement has not been accomplished in the weak-field regime, and the use of a strong field opens up a new class of photochemical reactions that can be initiated using shaped strong-field closed-loop optimal control. The ability to influence not only simple processes such as dissociation and ionization but also complex ones such as dissociative rearrangement brings a new dimension and great promise to the future of the optimal control field.

References

1. R. J. Levis *et al.*, *Science* **292**, 709 (2001).
2. A. H. Zewail, *Angew. Chem. Int. Ed.* **39**, 2587 (2000).
3. M. Shapiro, P. Brumer, in *Advances in Atomic, Molecular, and Optical Physics*, B. Bederson, H. Walther, Eds. (Academic Press, San Diego, CA, 2000), vol. 42, pp. 287–345.
4. R. J. Gordon *et al.*, *Acc. Chem. Res.* **32**, 1007 (1999).
5. H. Rabitz *et al.*, *Science* **288**, 824 (2000).
6. H. Rabitz, W. Zhu, *Acc. Chem. Res.* **33**, 572 (2000).
7. S. Shi, H. Rabitz, *J. Chem. Phys.* **97**, 276 1992).
8. S. Shah, S. A. Rice, *J. Chem. Phys.* **112**, 6536 (2000).
9. R. S. Judson, H. Rabitz, *Phys. Rev. Lett.* **68**, 1500 (1992).
10. C. J. Bardeen *et al.*, *Chem. Phys. Lett.* **280**, 151 (1997).
11. A. Assion *et al.*, *Science* **282**, 919 (1998).
12. R. Uberna *et al.*, *Faraday Disc.* **113**, 385 (1999).
13. T. Hornung *et al.*, *Appl. Phys. B* **71**, 277 (2000).
14. R. Bartels *et al.*, *Nature* **406**, 164 (2000).
15. J. Purnell *et al.*, *Chem. Phys. Lett.* **229**, 333 (1994).
16. I. J. Larsen *et al.*, *Phys. Rev. Lett.* **83**, 1123 (1999).