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CHEMISTRY. Following the Flow of Energy in Biomolecules

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Some biological molecules, such as those in visual or photosynthetic systems, have evolved to efficiently convert energy from one form to another. How do these molecules channel energy rapidly and efficiently so that useful work can be performed without this energy being dissipated ineffectively into the surroundings? Dissipation of molecular vibrational excitation energy typically takes place on picosecond time scales, so biological molecules must be able to channel energy rapidly and efficiently if they are to be able to direct it in a useful manner. In biological systems excited by light, the nonradiative electronic transitions can occur on time scales ($\ll 10^{-12}$ ps) that are even faster than vibrational energy dissipation (1–3), hinting at how nature solves the problem of directing energy flow. On page 1006 of this issue, Kukura *et al.* (4) take an important step forward in defining the process of directed energy flow in the visual pigment rhodopsin.

Photoexcited biological molecules offer a unique opportunity to monitor the evolution of excitation energy as it transforms a reactant molecule into its final products. With the advent of appropriate femtosecond laser techniques (5), it has become possible to examine the underlying dynamics of the elementary vibrational and electronic excitations that guide the structural changes and, ultimately, the function of a variety of biomolecules (6–8). The work presented by Kukura *et al.* enhances our ability to monitor rapid structural changes in such molecules by introducing the technique of femtosecond stimulated Raman spectroscopy (FSRS). In their report, Kukura *et al.* follow the evolution of the retinal chromophore as it is excited to photorhodopsin and decays into bathorhodopsin, all within the first picosecond of the visual process. They do this by taking advantage of the broad spectral bandwidth of their probe pulse to obtain very high quality time-resolved stimulated Raman spectra over the range of 600 to 2000 cm^{-1} .

How does this experiment generate ultrafast time resolution, as well as the high spectral resolution associated with Raman spectra, without violating the uncertainty principle? Although not emphasized in the report by Kukura *et al.*, these authors are fully aware (9) that the underlying time scale for the generation of the Raman photon is dictated by the dephasing time of the coherence between the initial and final vibrational levels of the material undergoing the Raman process. A typical time scale for the vibrational dephasing time is on the order of 10^{-12} s, which translates to a 10 cm^{-1} Raman bandwidth. This means that the FSRS experiment reads out Raman radiation from the sample that is averaged over its vibrational dephasing time window (that is, the stimulated Raman signals continue to appear at the detector, even after the probe pulse has passed through the sample). Thus, there is no violation of the uncertainty principle. However, being able to control the “gating” of the Raman coherence by changing the time delay between the photochemical pump and the broadband probe allows the dephasing time window to be moved so that rapid structural dynamics can be monitored. Changes in the vibrational frequencies that take place within the dephasing time window affect the FSRS lineshape, and the authors have done a convincing job of simulating these lineshape changes as shown in the supporting online material of their paper.

A key conclusion of the work on rhodopsin is that low-symmetry hydrogen out-of-plane (HOOP) wagging motions allow the system to evolve extremely rapidly (~200 fs) onto the ground-state electronic surface of the product, where much of the ensuing structural change of the retinal chromophore (the cis to trans isomerization) actually takes place. This is a paradigm shift from the usual description of retinal isomerization reactions, where the electronic and nuclear structures are often taken to evolve together in time within a one-dimensional reaction coordinate model that involves multiple intermediate states. In contrast, a very rapid transition to the electronic ground state of the product leads to an impulsive nuclear response composed of those vibrational motions that are coupled to the electronic state changes (those nuclei that feel forces due to the change in the electron distribution are said to be “coupled”). Because these electronic forces are associated with the product electron distribution, they naturally direct the nuclei toward the final product structure with high efficiency following the rapid electronic transition. Intermediates on such a pathway are simply a measure of the progress of the structural part of the reaction on the product ground-state electronic surface.

Similar conclusions have been reached in femtosecond coherence studies of diatomic ligand dissociation from heme proteins (7,10). These studies show that it is the ultrafast transitions of the iron electrons that trigger and direct the resulting nuclear motion of the heme on its ground-state photoproduct electronic surface. The surface crossing “seam” for dissociation, shown in the top panel of the figure, is where the electronic part of the reaction takes place. The crossing seam is analogous to the conical intersection (11) mentioned by Kukura *et al.*, where HOOP modes couple the ground- and excited-state electronic surfaces. It remains unclear precisely what mediates the highly efficient coupling between the electronic surfaces in the heme system, but spin-orbit coupling, as well as coupling by out-of-plane heme-ligand stretching and bending modes, are likely candidates.

Electron-nuclear coupling also plays an important role in thermally driven ground-state reactions (see the bottom panel of the figure, left). After the system accumulates enough thermal energy to surmount the energy barrier at the crossing seam, the forces of the electronic state change will guide the nuclear motion along q . When the vibrational period (τ_q) of mode q is longer than ~1 ps, the system loses enough vibrational energy before returning back to the crossing seam that it becomes trapped in the bound state. Without the reaction coupling to q , the system would rapidly (within the ~60-fs iron-ligand vibrational period) return to the crossing seam along r with enough energy to escape from the bound-state region. The electron-nuclear coupling of q gives the biological system the time it needs to dissipate energy within the bound-state region so that the efficiency of the binding reaction is optimized.

As a result of these studies, a scenario for directed energy transport is emerging in which biomolecules have evolved to make use of the fact that electrons are light and fast, whereas nuclei are heavy and slow. For ground-state reactions, the modes triggered by the electronic forces can help to trap the system in the desired electronic state. For photoexcited states, the fast electronic decay (mediated by motion along specific modes of appropriate symmetry and frequency) takes place before excess energy can escape to the surroundings, and this triggers highly specific electronic forces on the nearby nuclei when the electrons change state. Probably there is a correlation between the localization of the electronic state change and the specificity and efficiency of the nuclear (that is, structural) response in the associated reaction. In the event that the electronic transition is more delocalized, and therefore structurally less specific, the surrounding protein conformation may be called upon to act as a restraining lattice that helps to direct the electronic forces so that the structural part of the chromophore reaction is guided to the desired outcome. In turn, this can set up action-reaction forces on the protein that lead to specific and desired conformational changes extending over the much longer length and time scales necessary for the proper function of larger biological assemblies.

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Figure. Good vibrations

(Top) A top-down view of the intersection of the initial photoexcited-state electronic surface (thin tan contour lines) of the heme in ligated myoglobin (labeled MbL*) and the photoproduct ground-state electronic surface (labeled Mb). After photoexcitation of the π -electrons of the heme chromophore (yellow region), the iron d-electrons rapidly reconfigure within their localized orbitals and go from a spin of $S = 0$ in MbL* to $S = 2$ in Mb. This exerts strong local forces on the nuclei surrounding the iron atom that move the system along the coordinate(s) q . The simplified picture depicts the photodissociation of the diatomic ligand (blue circles labeled L) along the iron-ligand coordinate r , as well as the coupling of the reaction to other chromophore and/or protein modes labeled q . The ensuing coherent vibrations of the reaction-

coupled q -modes are specific to the ground state and appear within 100 fs of the photochemical pump (7,10). **(Bottom)** The thermally activated reverse reaction as the ligand binds to the heme along the ground-state electronic surface. The diatomic ligand is “trapped” by electronic coupling to nuclear coordinate(s) q when the period (τq) for the return to the binding seam is longer than the time it takes to dissipate vibrational energy.