Chemistry at the Uncertainty Limit**

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At the limit of time for chemistry (and biology), the femtosecond time resolution is fundamental for observing atomic-scale dynamics. With quantum uncertainty this paradigm may be questioned, but in fact, because of the powerful concept of coherence in the joint uncertainties, new limits in spatial and temporal resolutions have been reached. In this new regime of dynamics, the scope of applications has proven wide-ranging, encompassing the different areas of molecular sciences. The aim of this Essay is to discuss the concepts—with focus on the world of molecules, simple or complex—and the new knowledge possible at the limit of the uncertainty principle for atomic-scale dynamics.

Knowledge in our universe is not always certain. In everyday life we are familiar with classical mechanics and its description of *macroscopic* systems—the motion of objects with precise knowledge of where the object is (position x) and where it is going (momentum p, or speed v). In contrast, for the *microscopic* world, governed by the laws of quantum mechanics,[2] we cannot predict with the same precision the position and momentum simultaneously; such quantum effects also have a signature in phenomena of the very big, namely in cosmology. Mechanicians of both worlds, classical and quantal, accommodate the difference by recognizing two of the most powerful and uneasy to digest concepts: the uncertainty principle and the particle-wave duality of matter. Particles, even molecules, can behave as waves. The same duality holds for light: waves can behave as particles.

In the nineteenth century Maxwell showed the nature of light to be electromagnetic waves (1864), while Einstein gave light the particle-like description (1905) with a quantum of energy, which was called a photon by G. N. Lewis. (This idea of quanta has its roots in the earlier work (1900) of Planck which relates the energy E to the frequency ν of radiation by $E = h\nu$, where h is Planck's constant.) The connection to matter's duality was made by de Broglie in a brilliant analogy (1924), where he identified the wave character of particles with a wavelength given simply by Equation (1).

$$\lambda_{\text{de Broglie}} = h/p \qquad (1)$$

The complementarity of the two descriptions becomes clearer when the concept of coherence is introduced. Two or more waves can produce interference patterns when their amplitudes add up coherently, as shown two centuries ago by Young (1801) in his experiments on light propagating through two holes and resulting in fringes on a screen. This superposition results in a group of waves localized in space (Δx). For all waves, the group generally obeys the relationship $\Delta x \Delta k \approx 1$, where k is the resultant wave number; invoking the duality expression [Eq. (1)] makes $\Delta x \Delta p = \hbar$. For light waves, this behavior, which has also been observed for electrons, is discussed extensively in popular science writings; it embodies many abstract concepts from the microscopic world (such as the superposition of waves, particle and/or wave behavior, quantum measurements, quantum electrodynamics, and the uncertainty principle) and of the connection to macroscopic systems in what is called Schrödinger's cat.

For matter, superpositions analogous to those of light waves can be formed from matter wave functions. The solution of the Schrödinger equation (1926) yields wave functions and their probability distributions which are diffuse over position (x) space. However, if these waves are added up coherently with well-defined phases something remarkable emerges: the probability distribution becomes *localized* in space, as Schrödinger showed in 1926 using the quantum states of a harmonic oscillator. The resultant wave packet and its associated de Broglie wavelength has the essential character of a classical particle: a trajectory in space and time with a well-defined (group) velocity and position—a moving classical marble, but at atomic resolution! For a free particle ($E = p^2/2m$), it is evident that the group velocity of the packet ($\mathrm{d}E/\mathrm{d}p$) is simply v, namely the classical speed.

The association of a wave character to a particle motion through de Broglie's relationship, which leads to $\Delta p = \hbar \Delta k$ as discussed above, is entirely consistent with Heisenberg's mechanics (1925) which defines for all quantum systems the uncertainty in measurement—an imprecision in position (with a standard deviation $\sigma_x \equiv \Delta x$) and in momentum (with a standard deviation $\sigma_p \equiv \Delta p$), where both are related by

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$\Delta x \Delta p \geq \hbar/2$. When the equality holds, the packet is termed uncertainty- or transform-limited. Similarly, there is an uncertainty for energy measured over a finite period of time ($\Delta t \Delta E \geq \hbar/2$). This is the crux of the whole matter. With femtosecond resolution it is possible to make $(\Delta x/x) < 1$ and $(\Delta p/p) < 1$. The key concept is the coherent superposition and coherent state (wave packet) probing, in accord with these joint uncertainties (Figure 1).

Figure 1. The "ankh", the key of "life" in old Egyption religion—here the key has the codes, coherence and the joint uncertainties, which unlock mysteries of the relationship between quantum uncertainty and femtoscience.

Dynamic processes in chemistry and biology involve motions of atoms in the course of the transformation. The speed of atomic motion is approximately 1 km s^{-1}, and, hence, the time required to record atomic-scale dynamics over a distance of 1 Å is in the range of 100 fs. The very act of such motions as reactions unfold and pass through their transition states—the configurations between reactants and products—cannot be isolated without resolution in space and time on the femtosecond time scale. Thus, only on this time scale can we directly observe the fundamental processes of bond breaking and bond making of molecular structures; this is the central mission of the field of femtochemistry.[3]

If the concepts are clear, what created the perception that quantum uncertainty would limit the importance of femtosecond resolution? Two lines of arguments dominated the thinking.

The first of these is the use of the uncertainty relationship $\Delta t \Delta E \geq \hbar/2$. The energy uncertainty on the femtosecond timescale is "huge" and considered poor by the standards of high-resolution spectroscopy in the energy domain. For example, a 50-fs pulse (full-width at half maximum height) has an energy width ΔE of 294 cm^{-1} ($\sigma_t = 21.2$ fs, $\sigma_E = 125$ cm^{-1}, and $\sigma_t \sigma_E = \hbar/2$). It seems as though we would be "ruining" the quantized vibrational–rotational states of molecules by using femtosecond excitation or probes! The second issue is that of the spreading of localized wave packets in microscopic systems which was thought to be severe as a result of intra- and intermolecular interactions.

With these two issues in mind, predictions were made in the literature that femtosecond resolution for studies in chemistry and biology would be of limited utility. Had the energy states been prepared incoherently, this would have been true, but clearly it is not. The dispersion in time scales in the energy range of the packet gives a dephasing or spreading time that is longer than that of the nuclear motion—once again the uncertainty is in our favor!

The momentum distribution for a Gaussian-free particle wave packet having the minimum value of the uncertainty product, $\Delta x \Delta p = \hbar/2$, is also Gaussian, and the contribution of the momentum uncertainty to the widening of the packet as it moves is easy to express. We can have a feeling of the time needed for an appreciable spreading (by $\sqrt{2}$ or about 40%) to take place and express this time by Equation (2), where $t = 0$ is the time of minimum uncertainty, m the mass, and $\Delta v = \Delta p/m$.

$$t_s = \Delta x(0)/\Delta v = 2m\Delta x^2(0)/\hbar \tag{2}$$

When a free particle wave packet is initiated by an ultrashort light pulse so that it has the minimum value of the $\Delta x \Delta p$ uncertainty product, one can calculate the relationship between the pulse duration and the wave-packet spatial width. It turns out to be quite simple: $\Delta x = \langle v \rangle \Delta t$.

The size of $\hbar$, 1.05457×10^{-34} J s, means that the fuzziness required by the uncertainty principle is imperceptible on the normal scales of size and momentum, but becomes important at atomic scales. For example, if the position of a stationary 200-g apple is initially determined to a small fraction of a wavelength of light, say $\Delta x = 10$ nm, the apple's position uncertainty will spread by about 40% only after 4×10^{17} s, or 12 billion years, that is, the age of the universe! On the other hand, an electron with a mass 29 orders of magnitude smaller would spread by 40% from an initial 1-Å localization after only 0.2 fs. Clearly, from the above expression, the much greater masses of atomic nuclei make their wave packets spread orders of magnitude slower than the wave packet of the electron, and in fact this spreading is relatively minor on the femtosecond timescale.

We should recall the consequence of both of our uncertainty relations: A small Δt value is the way to obtain a small Δx value and hence *localization*! What is useful to keep in mind is the relationship of ΔE to the binding energies of atoms—for a 50 fs pulse, ΔE is about 1 kcal mol^{-1}, which is a small fraction of typical binding energies, which are on the order of 70 kcal mol^{-1}.

Experimentally, atomic-scale dynamics of molecules and their reactions have been observed and studied in all phases of matter; they span phenomena from the simple to the very complex, from diatomics to proteins, and from the gas phase to condensed media. The physics can be elucidated using the paradigm case of sodium iodide (NaI, Figure 2). The chemical

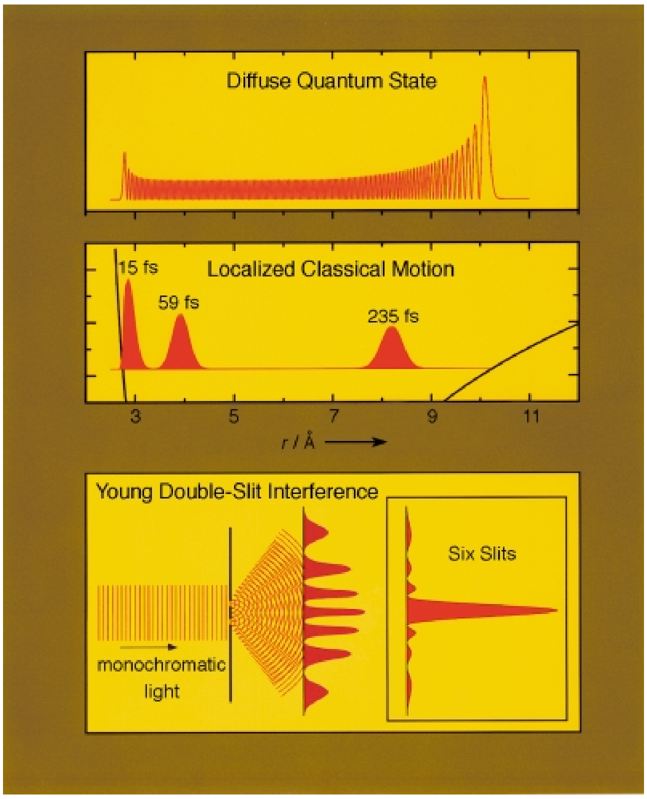

Figure 2. Comparison of localized (wave packet) and diffuse (wave function) representations of molecular systems. Here the results from real quantum calculations made for the NaI system are shown. Top: the stationary-state position probability density at an energy of 5300 cm^{-1}. Middle: the actual wave packet formed at about the same energy and at the same potential—covalent below r = 3 Å and ionic beyond 9 Å (black curves). The wave packet is made by a 15-fs pulse, and its evolution with time is indicated; note the narrow width of the moving wave packet. Bottom: the idea of Young's double-slit interference (1801) and the consequence of replacing two slits by six thin slits but keeping the same total distance. The more the interference channels, the more the localization.[6a]

bond in the diatomic NaI molecule changes character (covalent or ionic) with time, prior to the final breakage to yield atoms of Na and I. The bond also reforms after an electron is transferred.

In experiments at Caltech the wave packet was observed to oscillate periodically (resonance motion) and exhibited a particle-type behavior during the entire course of the reaction. The wave packet was found to be very robust, with relatively minor spreading (dephasing), and the ensemble of molecules behaves in harmony and exhibits "single-molecule" motion. Theoretically—by constructing the superposition of wave functions with their appropriate phases—one confirms that the initial wave packet is indeed highly localized (<0.3 Å) and remains intact for many periods of its motion. The de Broglie wavelength is also consistent with sub-angström localization: $\lambda \approx 0.1$ Å (from $p = 8.1 \times 10^{-18}$ erg sec cm^{-1} at $E = 5300$ cm^{-1}). This motion conforms to the $\Delta x/x$ criterion given above, with a value of about 0.1. Experiments in the condensed phase and in biological systems can be described with the same concepts, and coherent motions have been observed in all phases of matter.

Why is coherence robust? The observation of motion in real systems requires not only the formation of localized wave packets in each and every molecule, but also a small spread in position among wave packets formed in the typically millions to billions of molecules on which the measurement is performed. The key to achieving this condition is generally provided by the well-defined initial equilibrium configuration of the molecules before excitation and by the "instantaneous" femtosecond launching of the wave packet. The spatial confinement (typically about 0.05 Å) of the initial ground state of the system ensures that all molecules, each with its own coherence among the states which form its wave packet, begin their motion in a bond-length range much smaller than that executed by the actual motion (typically 5 – 10 Å). The femtosecond launching ensures that this narrow range of bond length is maintained during the entire process of preparation. The motion of the ensemble is that of a single-molecule trajectory unless molecular and ensemble coherences are destroyed by intra- and/or intermolecular perturbations.

At the 1972 Welch Conference, in a lively exchange between Eugene Wigner and Edward Teller, the uncertainty paradox was debated for picosecond time resolution. But, as has been seen, the uncertainty paradox is not a paradox even for the shorter timescale of femtoscience and certainly not for the dynamics of physical, chemical, and biological changes. Coherence in the femtosecond time regime, the vibrational timescale of a bond, is essential to the formation of localized, nonequilibrium molecular structures which then evolve with time in complete harmony with the uncertainty principle. At such ultrashort time we recover, by the power of coherence, the classical character of the motion in quantum systems.

Coherence was also not appreciated in the realization of the maser. Charles Townes encountered objections because of concern about the uncertainty principle: the claim was that molecules spend about one ten-thousandth of a second in the cavity of a maser and therefore it is impossible for the frequency of the radiation to be narrowly confined. When recognized, coherence of photons in the stimulated emission-feedback process removed this concern (see for example ref. [4]).

As we cross the femtosecond barrier into the attosecond regime we must recall the vital role of coherence, or otherwise the uncertainty in energy (which is now even larger than that of the femtosecond timescale) might again call into question its utility for electron dynamics, as initially transpired in the femtosecond realm.

Exploring for the Future

With the new limits of spatial and temporal resolutions reached, we are currently witnessing several exciting developments in the studies of the dynamics of complex molecular structures and in the number of molecules detected. One of the most significant advances made in recent years is the development of ultrafast methods for electron and X-ray diffraction to capture the entire molecular structure evolving with time. This approach will have a wide range of applications in chemistry and biology, as it opens up new vistas in the direct linkage of structures to functions.

At Caltech we have focused our effort on the development of ultrafast electron diffraction (UED); for recent references see ref. [5] and citations therein. In UED a femtosecond laser pulse is used to initiate a reaction, but unlike other ultrafast spectroscopies the subsequent laser pulses normally used to probe the progress of the reaction are replaced with ultrashort pulses of electrons. Diffraction patterns are then recorded to provide the evolution of the molecular structure in real time.

A number of experimental challenges had to be overcome for these UED studies to be successful. These include: 1) the problem of determining time zero of the reaction, namely the time of overlap between the pump and probe pulses for clocking the change; this is a nontrivial task as the speed of electrons and photons are different and an in situ detection must be made; 2) the problem of low electron flux required to minimize space-charge-induced temporal broadening of electron pulses; and 3) the problem of low scattering and sensitivity caused by the absence of long-range order (usually present in solids) and the low density of molecules in gases.

Over the past decade UED has been advanced[5] to now allow the direct imaging of transient molecular structures in reactions with a sensitivity to chemical change of about 1% or better. Intermediate and product structures can be observed in real time, with spatial and temporal resolutions of approximately 0.01 Å and 1 ps, respectively; electron pulses as short as 500 fs have been obtained. For example, electrocyclic ring opening of a complex cyclic hydrocarbon (with no heavy atoms) was observed directly upon femtosecond excitation.

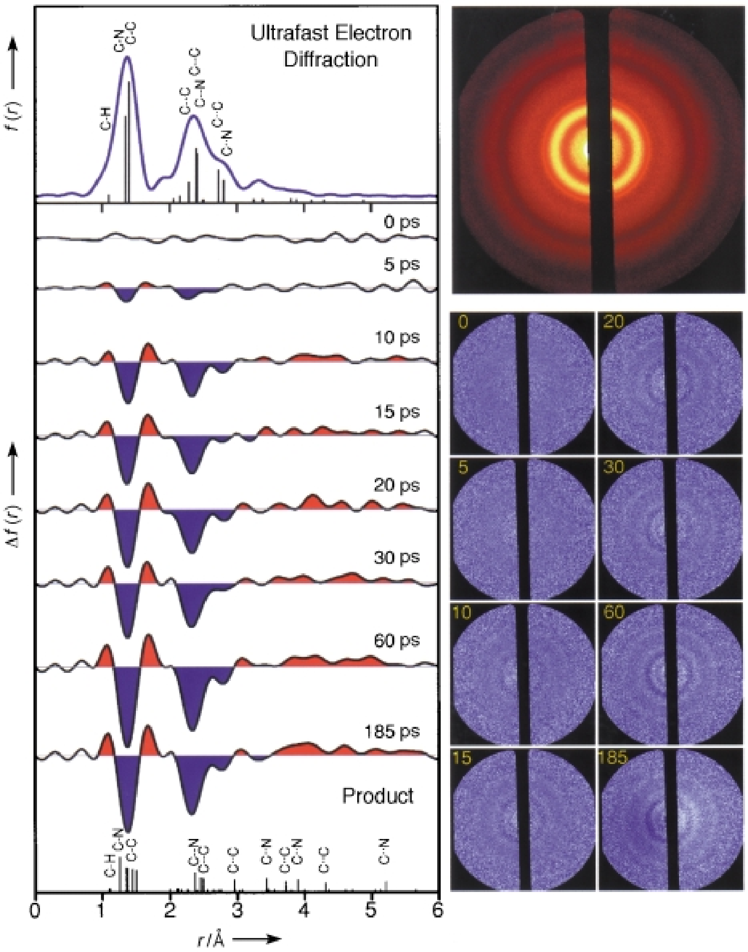

Figure 3. Ultrafast electron diffraction. These experimental images (right) provide the change of the molecular structure studied with time, and shows the evolution during the change. In this case, we directly observe, through the change in the radial distribution function $f(r)$ (left), the depletion of "old" bonds and the making of "new" bonds in the radiationless transition of pyridine molecules during the reaction of ring opening.[6b] Many other systems have been studied similarly using UED.

Similarly, we studied the reactive transition intermediate in the reaction of ethane to ethylene derivatives, the ligand dissociation in iron pentacarbonyl, the valence isomers of aromatic molecules, and nonequilibrium structures with large amounts of vibrational energy. A paradigm case for this development is that of ring-opening processes in isolated aromatic pyridine. With UED we can observe in real time the disappearance of "old" bonds and the appearance of "new" bonds as the molecular structure transforms from being reactant, to intermediate, and then to products (Figure 3). The progress made in this field demonstrates the new limit achieved in detection sensitivity, versatility, and resolution of UED, as well as the potential for its applications. The extension to even more complex systems, both theoretically and experimentally, represents one of our current research efforts in UED.

A second promising area of research is that of complex biological systems, but at the new limits of temporal and spatial resolutions. There have been already important contributions to femtobiology and these include: studies of the elementary steps of vision, photosynthesis, protein dynamics, and electron and proton transport in DNA. In proteins such as those of photosynthetic reaction centers and antennas, hemoglobins, cytochromes, and rhodopsin, a femtosecond event such as bond breaking, twisting, or electron transfer occurs. Global and coherent nuclear motions can be observed in these complex systems.

It is possible that the complexity is not as complicated as we think. For the chemistry and the efficiency to be unique, the system utilizes the organized structure around the "active center" with the necessary restraint on transition states and energy flow. Thus, the early femtosecond events are critical to understanding the function of complex systems as they reflect the important locality in biological dynamics. Our efforts in this direction have so far focused on DNA-twisting dynamics, electron transfer in DNA assemblies, DNA base-pair mimics, and on protein–ligand dynamics. We have recently completed studies on the dynamics of molecular recognition of DNA with drugs, such as anticancer daunomycin (and adriamycin), and of proteins with drugs and vitamins, and observed their elementary steps. For example, the observed charge-separation dynamics of DNA-nucleotides in drug solutions (Figure 4) elucidates the mechanism for the drug's enhanced cytotoxicity with oxygen and with light in experiments with cells—the aim is to provide a molecular basis of clinical observations.

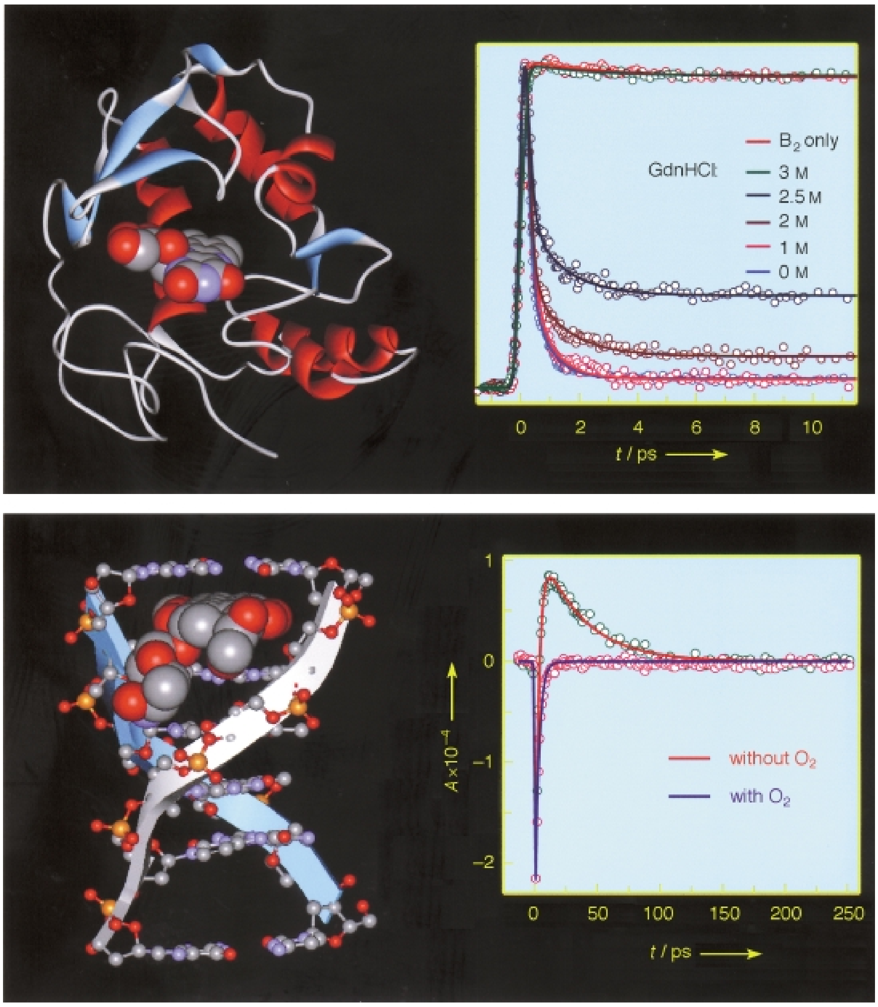

Figure 4. Structures of biological systems studied recently at Caltech: DNA-nucleotide (dGTP) with daunomycin (bottom), and riboflavin (vitamin B_2) with a binding protein (top) in water (buffer) solutions.[6c] The femtosecond transients displayed show the evidence for direct electron transfer and the influence of molecular oxygen. The influence of the denaturant GdnHCL, which unfolds the protein, on the dynamics of charge separation is also shown for the protein system (top).

In the future new extensions are anticipated. The nature and control of enzymatic reactions, the catalytic function of the transition state, and the design of artificial biological functions seem to be areas of great promise for dynamic studies. Also, it is envisaged that the recording of the change of a large biological structure with time and with atomic resolution may be realized. The ultimate goal is the recording of all coordinates in space and time. The impact on problems such as protein folding and molecular recognition is clear.

Finally, we should take advantage of the new limits achieved for applications in research areas such as the following: 1) the control of chemical pathways using prescribed temporal-, phase-, and polarization-specified pulses; 2) the crossing of the barrier to the attosecond regime for studies of electron motion (in 1991 we reported on the proposal of observing such motion in the benzene molecule, and this may be possible in the near future); and 3) extensions of femtochemistry studies to single molecules and at new extremes of pressure and temperature (micro-to-nano-kelvin by laser cooling, or very low temperature using helium clusters) to explore the dynamics outside the ambient conditions of our atmosphere. These are projections based on what we know, but we surely expect uncertainties of the future to bring about unforeseen breakthroughs.

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[6] a) A section of Figure 2 was adapted from ref. [3] and a paper co-authored with J. S. Baskin (J. S. Baskin, A. H. Zewail, *J. Chem. Educ.* **2001**, *78*, 737); b) Figure 3 was adapted from a paper co-authored with V. A. Lobastov, R. Srinivasan, B. M. Goodson, C.-Y. Ruan, and J. S. Feenstra, *J. Phys. Chem. A*, in press; c) Figure 4 was adapted from two papers co-authored with X. Qu, C. Wan, H.-C. Becker, and D. Zhong, *(Proc. Natl. Acad. Sci. USA*, in press); and with D. Zhong (*Proc. Natl. Acad. Sci. USA* **2001**, *98*, 11867). I wish to thank Spencer Baskin, Dongping Zhong, Xiaogong Qu, and Vladimir Lobastov for their help in preparing Figures 2–4.

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