that there are also genetic components to the common late-onset forms of PD (*14*, *15*). Until we attain a full understanding of the causes of PD—a prerequisite for preventing the disease altogether—L-dopa and cell therapies supplemented with GDNF gene therapy may become the treatments of choice for PD patients. Unlike the first two treatments, GDNF gene therapy has the added promise of maintaining the wiring diagram of dopamine neurons in the brain's nigrostriatal pathway. Cocktails of genes encoding a medley of neurotrophic factors, delivered by safe inducible vectors to target areas in the brain and spinal cord, hold promise as a treatment not only for PD but also for an entire spectrum of other central nervous system disorders.

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PERSPECTIVES: CHEMISTRY

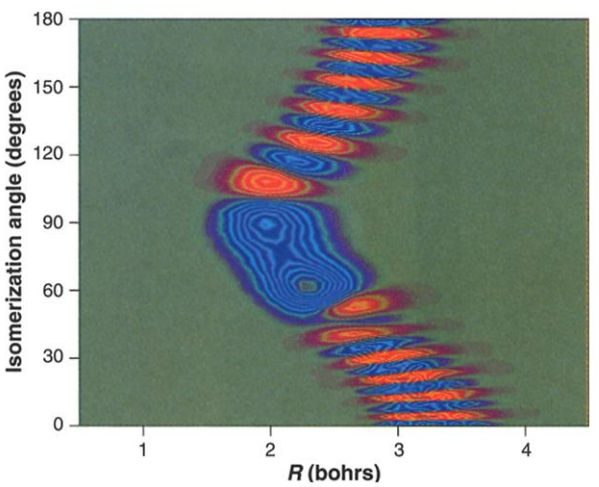
Beyond Platonic Molecules

Joel M. Bowman

Nearly every issue of *Science* contains beautiful depictions of molecules. But these depictions are "platonic," showing idealized, static structures. Real molecules are not static: They move and may do so in a regular or a complex, almost chaotic fashion. A well-known example is the cis-trans isomerization in retinal, which is of central importance in vision. Chemical reactions are a more general example of atoms on the move.

Recent studies suggest that it may be possible to control this motion with lasers, thus influencing the reaction outcome. To understand and manipulate molecular motions, however, we have to first find a way to describe (and computationally model) them. To do so rigorously requires the use of quantum mechanics, especially in the case of the ubiquitous, light hydrogen atoms, which can, in many situations, tunnel over large distances with significant probability. The correct quantum mechanical and the idealized platonic picture of a molecule can sometimes be reconciled in a structure depicting the expectation values of the bond lengths and bond angles at 0 K or in a perfect crystalline state. In most other instances, however, the platonic and quantum mechanical pictures cannot be reconciled, and molecular vibrations cannot be ignored. The resulting theoretical and computational challenge is formidable.

Two recent workshops (*1*, *2*) focused on how molecules behave when they are vibrationally excited. Highly excited molecules can undergo large-amplitude motion that leads to isomerization (that is, they sample a variety of structures other than the lowest energy one) or the breaking of bonds. It may even have dramatic effects on the rates of chemical reactions—the very heart of chemical dynamics. Several talks highlighted new theoretical connections between the quantum and classical pictures of highly excited molecular motion. Others described new experimental methods that allow isomerization to be probed directly and even the weak interaction of particle physics to be detected in chiral molecules.



The lowest energy wave function exhibiting HCN-HNC isomerization. Linear HCN corresponds to an isomerization angle of 0°, linear HNC is at 180°, and the transition state (the barrier between the two minimum energy structures) is at 67°. *R* is the distance of the H atom to the center of mass of the CN fragment.

The accepted quantum treatment of molecular vibrational motion is based on the Born-Oppenheimer approximation, which rests on the fact that atomic nuclei are much more massive than electrons and thus nearly fixed with respect to electron motion. First, the Schrödinger equation for the electronic energy and the nuclear-nuclear repulsion is solved many times for many different positions of the nuclei in the molecule. The variation of this electronic energy with nuclear geometry, referred to as the potential energy surface (PES), then determines the quantum mechanical behavior of the nuclear motion and gives the complete description of the molecular vibrational dynamics. (The molecular geometry with the minimum electronic energy is often what is represented by the platonic picture mentioned above.)

This dual procedure is extremely computationally demanding. For many years, it was greatly simplified by doing a small-amplitude normal mode analysis (NMA), which approximates the vibrational motion as a collection of uncoupled harmonic oscillators vibrating around a single reference geometry. It is used in such diverse fields as acoustics, structural engineering, geophysics, solid state physics, and chemical physics. The most widely used software packages in quantum chemistry rely on this kind of analysis. But the results of an NMA are not exact and may give a totally inadequate picture of molecular vibrations, because the nonlinear couplings and the anharmonic nature of true molecular vibrations are ignored. Over the past 15 years or so, it has been demonstrated (*3*) that these couplings are crucial in molecular vibrations, especially for excited states.

A striking departure from the NMA occurs for example in the isomerization between HCN and HNC. The three-dimensional wave function shown in the figure samples both the HCN and HNC structures and the transition state. This type of wave function cannot even be approximated by the harmonic oscillator assumption of the NMA, which is limited to the description of either HCN or HNC, but not both. (Another example of the breakdown of NMA is the catastrophic failure of the Tacoma Narrows bridge in 1940.)

Highly accurate ab initio calculations of molecular forces and dynamics have until recently been limited by computational power to three-atom molecules, because the coupling of the vibrational modes enormously expands the scope of the calculation. Increas-

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es in computing power and a rethinking of the problem have aided the development of new codes that can provide vibrational energies and wave functions far more accurate than the NMA (*4*, *5*). Using our MULTIMODE code (*5*), which allows the user to choose between different levels of accuracy, we have obtained essentially exact results for five- and six-atom molecules and less accurate but still realistic results for much larger molecules.

The basic approach underlying these codes is the representation of the potential as a hierarchical set of mode-mode interactions, such that the full N-mode PES is represented by a sum of two-mode, three-mode, and four-mode interactions and a mean-field (so-called vibrationally self-consistent field) treatment of vibrational interactions (*6*). Gerber and co-workers recently introduced the effect of mode correlation into their code using second-order perturbation theory (*7*). Carter and Bowman's newest code (*8*) treats mode correlations with "configuration mixing" methods that can give essentially exact results. The codes have been linked to popular electronic structure codes, enabling direct calculation of forces and vibrational dynamics (*9*–*11*). For example, calculations of the vibrational energies of the Cl–H_2O complex were able to confirm the results of one experiment over another (*11*). MULTIMODE has also been extended to treat internal rotation in molecules (*12*), which is widespread in large molecules but notoriously difficult to treat computationally.

The stage is thus set for more realistic and accurate calculations of molecular vibrations of fairly complex molecules and molecular systems, such as adsorbates, complexes, and small molecules encapsulated in confined environments. Isomerizing states of molecules are sure to receive more experimental attention in the near future, and the understanding and interpretation of these experiments will benefit from such an accurate theoretical treatment of vibrational motion.

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PERSPECTIVES: SIGNAL TRANSDUCTION

N-WASP Regulation—the Sting in the Tail

James Fawcett and Tony Pawson

The proteins of signaling pathways in eukaryotic cells selectively interact with one another and with small molecules such as phospholipids. These interactions frequently require modular domains that retain their capacity to recognize defined peptide motifs (or phospholipids) when they are expressed separately in cells (*1*). Signaling proteins often possess many of these domains and so are capable of multiple interactions with other proteins and phospholipids. Furthermore, domains within the same protein have the potential to interact with each other, providing a sophisticated means of switching signaling proteins on and off.

Members of the WASP (Wiskott-Aldrich syndrome protein) family regulate the assembly of actin monomers into filaments, and thus are key regulators of the cytoskeletal organization and motility of cells. When activated, many cell surface receptors induce alterations in the organization of intracellular signaling complexes leading to changes in actin assembly (polymerization) and cell motility. But it is still not clear how signals from these myriad receptors are integrated within the cell to yield a coherent cytoskeletal response. Recent findings suggest that a limited number of cytoplasmic proteins including WASP family members provide focal points at which multiple signals converge to control the dynamics of actin polymerization. Three recent papers (*2*–*4*), including the report by Prehoda *et al.* on page 801 of this issue, explore how activation of WASP (found in lymphocytes) and its relative N-WASP (expressed in many cell types) connects several signaling pathways to the initiation of actin assembly.

The carboxyl terminus of WASP and N-WASP contains a conserved VCA region consisting of a verprolin homology region (V), a cofilin homology region (C), and an acidic region (A) (see the figure). The acidic motif and cofilin homology region bind to the actin related protein complex Arp2/3, which initiates actin polymerization by promoting addition of actin monomers to the barbed ends of actin filaments (*5*). The V region binds to monomers of unpolymerized actin, which can then be passed to the neighboring Arp2/3 complex for assembly into filaments (see the figure). The amino-terminal region of WASP contains an EVH1 (WH1) domain, followed by a short basic region and a guanosine triphosphatase (GTPase) binding domain (see the figure). The GTPase binding domain associates with the GTPase Cdc42, which regulates organization of the cytoskeleton. Between the amino- and carboxyl-terminal domains of WASP lies a proline-rich sequence that can bind to profilin and to the Src homology (SH) 3 domains of signaling proteins (such as, Grb2 and Nck) and cytoplasmic tyrosine kinases.

This profusion of interaction motifs suggests that WASP and N-WASP are regulated by multiple molecules that associate with their amino-terminal and central domains, resulting in activation of a single response (actin polymerization) mediated by the carboxyl-terminal VCA region. In the absence of appropriate signals, WASP's activity is blocked by cooperative folding of the amino-terminal GTPase binding domain with the carboxyl-terminal C motif (*6*). This folding may prevent the Arp2/3 complex from binding to WASP's A and C motifs as well as potentially blocking binding of actin monomers to the V region. Binding of GTP-Cdc42 to the GTPase binding domain induces unfolding of WASP and liberation of the VCA region, which is then free to bind and activate Arp2/3, resulting in the initiation of actin assembly (*5*). A more potent way to initiate actin assembly is through the cooperative activation of WASP proteins by GTP-Cdc42 and the phospholipid, phos-

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