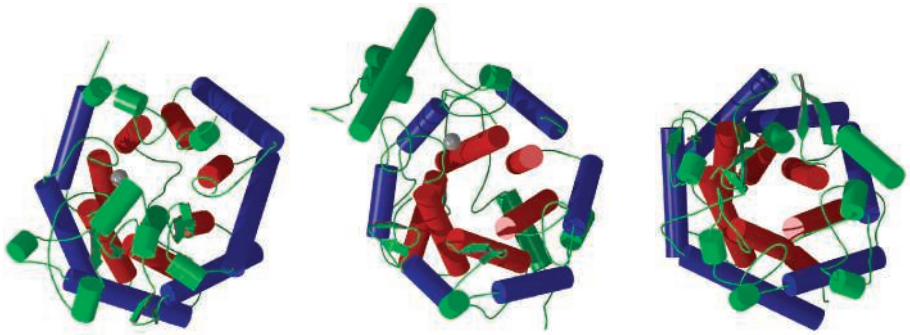

Nisin cyclase | Farnesyl transferase | Lanosterol synthase

Unexpected company. Nisin cyclase, farnesyl transferase, and the C-terminal domain of lanosterol synthase (a terpenoid cyclase), share similar double α-barrel folds (Protein Data Bank accession codes 2G02, 1KZO, and 1W6J, respectively) despite their lack of amino acid sequence similarity.

ies of nisin cyclase are clearly warranted to pinpoint the catalytic importance of Arg^{280}.

An equally surprising result emanating from the nisin cyclase structure (*5*) is the unexpected resemblance of its double α-barrel topology to that of farnesyl transferase (*7*) and of terpenoid cyclases such as squalene-hopene cyclase (*9*) and lanosterol synthase (*10*), despite low amino acid sequence identity (see the figure). The enzymes of terpene metabolism catalyze strikingly different chemical reactions using hydrocarbon isoprenoid substrates, yet they bear noteworthy structural and functional similarities with nisin cyclase. Farnesyl transferase uses a zinc-activated substrate thiolate for nucleophilic attack at farnesyl diphosphate (*6*, *7*). The terpenoid cyclases serve as stringent templates that enforce the folding of a long, flexible polyisoprenoid substrate in the conformation required for the proper sequence, regiochemistry, and stereochemistry of multiple carbon-carbon bond–forming reactions—just as nisin cyclase serves as a stringent template that enforces the folding of a long, flexible peptide substrate in the conformation required for the proper sequence, regiochemistry, and stereochemistry of multiple carbon-sulfur bond–forming reactions. However, the ring-forming reactions catalyzed by a terpene cyclase occur in a multistep carbocation-mediated cascade initiated by a single enzyme-substrate complex, whereas the ring-forming reactions catalyzed by nisin cyclase occur sequentially. That is, the substrate must shift in the enzyme active site to activate each cysteine residue, one at a time, for thioether ring formation. Thus, biosynthetic fidelity and promiscuity must be balanced in the nisin cyclase active site to accommodate the regiochemical and stereochemical requirements of multiple substrate-binding modes, much as fidelity and promiscuity appear to be balanced in the terpene cyclase active site to accommodate multiple carbocation intermediates in catalysis (*11*).

The occurrence of double α-barrel protein folds among disparate cyclases suggests that this particular fold lends itself to facile evolution and optimization as a template for complex cyclization reactions in biology. Another variation of the α-helical fold is found in terpenoid cyclases that generate smaller hydrocarbon products in the biosynthesis of menthol and the anticancer drug paclitaxel (taxol) (*11*). Future studies of these systems promise to exploit biosynthetic promiscuity and fidelity in cyclization reactions using natural and unnatural (*12*) substrates in the never-ending search for blockbuster antibiotics. Such studies may well prove the five thioether rings of nisin to be golden indeed.

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CHEMISTRY

Resonances in Reaction Dynamics

Richard N. Zare

Resonances—sharp changes in behavior when particles interact—in chemical reactions can reveal the vibration and rotation of reactants and products. This approach has been applied to the dissociation of formaldehyde and the reaction of fluorine with hydrogen.

Whenever one object collides with another, the objects can merely bounce off each other like billiard balls, or they can undergo some process of change and interaction (for example, a chemical reaction). The probability for such an interactive or reactive process to occur sometimes varies rapidly as a function of collision energy. Observing these sharp variations, known as resonances, is the most common way to detect short-lived intermediates in nuclear and particle physics. In the world of atomic and molecular physics, however, resonances are rarely observed, probably owing to the higher density of energy levels of the target system (which would smear out any resonance) and the experimental difficulty of obtaining sufficient velocity and angle resolution of the reactants and scattered products. It is very exciting, therefore, to see the observation of resonances in the reaction $F + H_2 \rightarrow HF + H$, reported by Qiu *et al.* (*1*) on page 1440, and the photodissociation of formaldehyde, reported by Yin *et al.* (*2*) on page 1443 of this issue. Such resonances may give us deep insight into how various elementary chemical steps actually occur. In each study, the intimate interplay between theory and experiment is needed to clarify what is actually happening.

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The first report of a scattering resonance in atoms was the observation by Schulz of a sharp change in the intensity of electrons transmitted through helium atoms (*3*, *4*). The incoming electron excites one of the two electrons of helium from its 1s orbital to a 2s orbital and then remains bound to the excited helium atom, forming a temporary helium negative ion. Below the energy threshold for promoting the helium 1s-to-2s transition, the temporary bound state can only decay by having the helium atom return to its $(1s)^2$ ground state, allowing the other electron to escape. Above this threshold, the temporary bound state of the helium nega-

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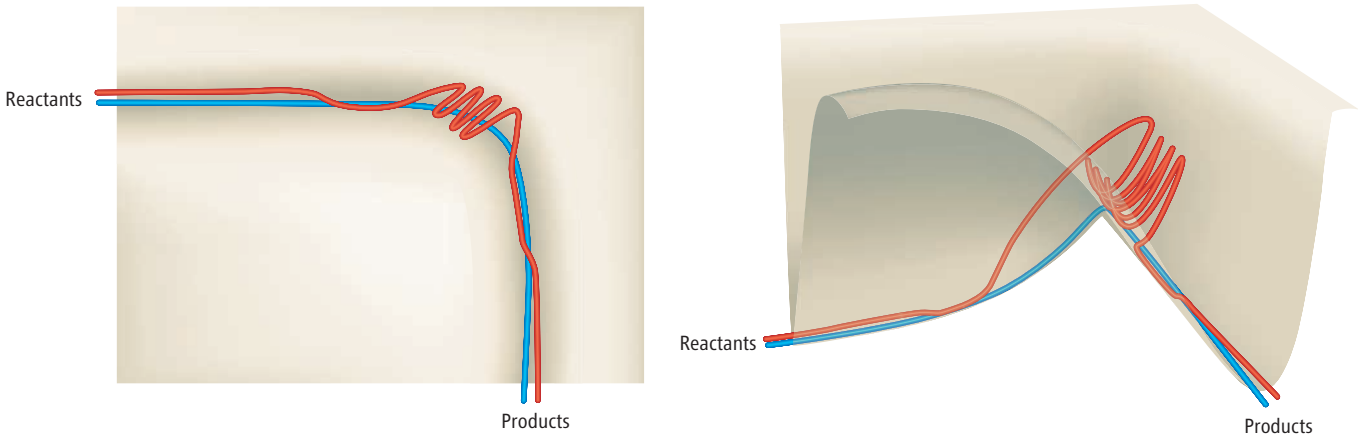

Over the top. In a bimolecular reaction, the transformation of reactants to products resembles a hike over a mountain pass (top-down view at left, three-dimensional view at right). The minimum-energy path (blue curve) is referred to as the reaction coordinate. In a resonance (red curve), relative motion of the colliding reactants becomes temporarily converted into internal motion of the collision complex not directed along the reaction path. This quasi-bound state persists until energy reflows into relative motion along the reaction coordinate. The drawings are very simplified—four dimensions are needed to portray accurately the motion, three for the internal degrees of freedom and one for the energy.

tive ion can also decay by having the electron escape while leaving the helium atom in its excited 1s2s electron configuration. The first decay mode is into a channel that hardly overlaps with the decaying state, whereas the second decay mode is into a channel with a much larger overlap. Consequently, the decay probability increases dramatically as the collision energy of the electron passes through threshold, an effect that is indicated by the width of the resonance as a function of the electron collision energy. Soon after Schulz's work with helium, the same type of phenomenon was observed in the scattering of electrons from molecules.

Scattering resonances might be regarded as rather esoteric, of intense interest to those who study simple atoms and molecules in isolation but of little relevance to living processes. This perception would be quite false. For example, most of the energy deposited in living cells by ionizing radiation causes the production of secondary electrons. These electrons, even at energies insufficient to trigger ionization, induce breaks in single- and double-stranded DNA, which are caused by rapid decays of transient molecular resonances localized on the nitrogen-containing bases of DNA (*5*).

A molecule is a collection of nuclei held together by electrostatic attraction. A bound system of N nuclei can vibrate in $3N - 6$ different ways (normal modes) in which the system's center of mass remains fixed while all nuclei move with the same frequency but in general with different amplitudes. Some of these motions are along the reaction coordinate—that is, they are directed from reactants to products—whereas many other motions do not couple to the reaction coordinate (see the figure). Energy in these noncoupled modes cannot be used to surmount the barrier that commonly separates reactants from products, and the system must wait some time (the decay time of the resonance) for its energy to redistribute itself and find its way to modes along the reaction coordinate for the collision partners to separate.

In the photodissociation of formaldehyde, CH_2O, the reaction products are HCO and H as well as CO and H_2. For the H_2 + CO channel, the H_2 molecule can be formed directly or it can result from the frustrated escape of the H and HCO fragments (*6*). In the latter case, the H and HCO partners fail to separate because part of the energy is tied up in vibrational motion of the HCO fragment, which does not couple to the H-HCO coordinate. The loosely bound H atom then bounces around in the attractive potential of the complex until it comes close enough to the H-end of HCO to pull off this H atom, yielding hot (vibrationally excited) H_2 and cold CO. This wandering behavior of the light H atom followed by the production of internally excited H_2 closely resembles what has been observed in the reaction of H + HBr → H_2 + Br (*7*). Two different pathways can yield the H + HCO fragments. One of them is on the barrierless ground-state singlet potential energy surface (S_0) for which the two electron spins on H and HCO are paired, and the energy is distributed statistically among the different vibrational and rotational motions of the products. The other is on the low-barrier triplet-state potential energy surface (T_1) for which the electron spins are unpaired, resulting in more impulsive dynamics that directs the energy into the separating photofragments in a distinctly nonstatistical manner. The combined experimental and theoretical studies by Yin *et al.* represent a major step forward in our understanding of how this simple molecule is decomposed by radiation to yield photofragments having so many disparate attributes. The coupling of electronic and nuclear motions in which more than one potential energy surface is accessed is particularly striking. Even for this relatively small molecule, breaking up is never easy.

The F + H_2 reaction, made famous by the pioneering crossed molecular beam experiments of Lee and co-workers (*8*), is of practical importance as the driver for the powerful infrared HF chemical laser. Qiu *et al.* fire a pulsed beam of F atoms at a pulsed beam of molecular hydrogen that is prepared almost exclusively in its vibrationless, rotationless ground state $H_2(v = 0, J = 0)$ (where v is the vibrational quantum number and J is the rotational quantum number). The resulting H-atom products are detected by converting them to high-lying atomic Rydberg states. By measuring the velocity distribution of the H atoms, it is possible to extract the corresponding vibrational-rotational internal state distribution of the HF products from conservation of energy. Moreover, the H atoms can be detected at different laboratory scattering angles, allowing the center-of-mass angular distribution of the HF products to be obtained. Qiu *et al.* find a pronounced forward-scattering peak for the HF($v = 2$) product, where forward means in the same direction as the incoming F atom—a result never observed before for this benchmark reaction system. This feature shows a rather abrupt change with collision energy, which is attributed to the trapped motion in the H-HF($v = 3$) vibrationally adiabatic potential energy surface before the opening of this channel. The authors suggest that both a ground-state and a first-excited-state van der Waals resonance in the exit channel constructively interfere to account for the observed behavior. This work is one of the most striking examples of the existence of resonances in a heavy-particle collision system.

Why study more resonances in reaction dynamics? They surely exist, as shown quite convincingly for the F + HD → HF + D reaction

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system (*9*). The answer is that resonances reveal the quasi-bound levels of the reaction complex with unique clarity. Until we are able to determine more confidently what theoretical approximations can be trusted, we need the close interplay between theory and experiment to help us understand how elementary chemical processes take place.

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BIOMEDICINE

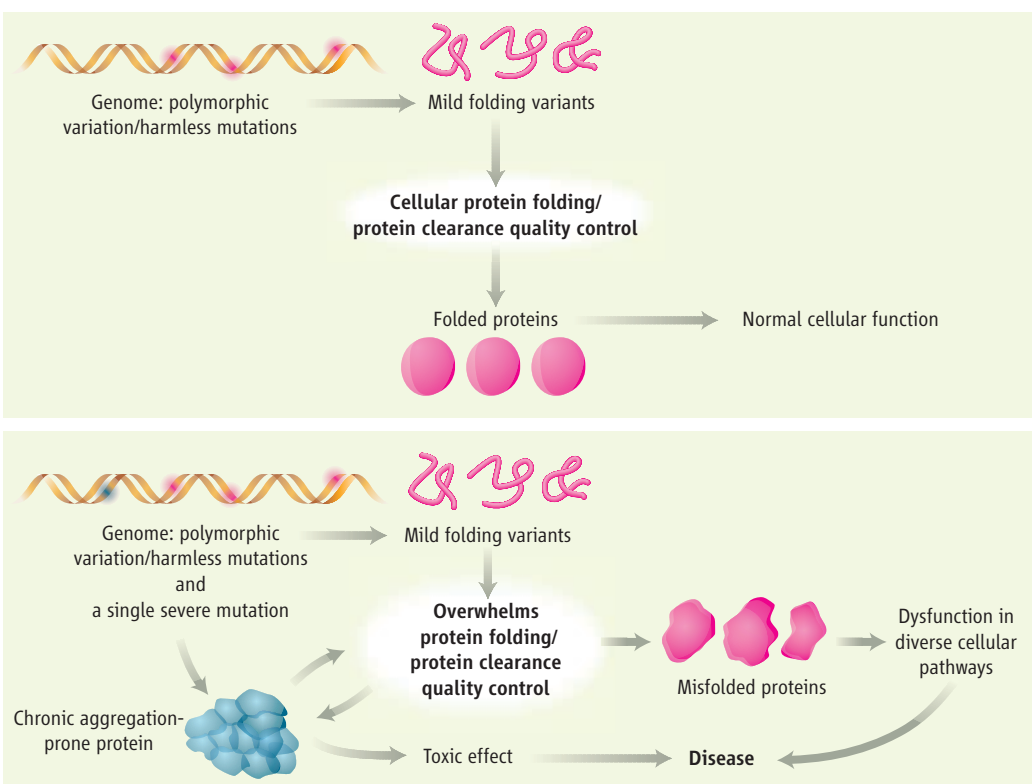
One Misfolded Protein Allows Others to Sneak By

Proteins prone to aggregate in cells have been linked to neurodegenerative diseases. As cells try to eliminate such aggregates, other misfolded proteins may go undetected, making the cell susceptible to their toxic effects.

Gillian P. Bates

Huntington's disease, Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis—these neurodegenerative disorders are among many inherited diseases that have been linked to genetic mutations that result in the chronic aggregation of a single specific protein. Cellular and animal models of these disorders are consistent with misfolded conformers, oligomers, and/or aggregates of the proteins huntingtin, α-synuclein, amyloid-β peptide, and superoxide dismutase-1 as the respective toxic culprits of these late-onset degenerations. What has been puzzling about the progression of each of these diseases is the perturbation of a wide range of cellular pathways (transcription, energy metabolism, microtubule transport, synaptic function, and apoptosis, among others), and this collective dysfunction of processes has also been proposed to underlie the pathogenesis of these diseases. Could a single "aggregation-prone" protein wreak so much havoc? A report by Gidalevitz *et al.* on page 1471 of this issue (*1*) has questioned whether there might be a general mechanism by which an aggregation-prone protein can have so many cellular effects.

The mutations that cause polyglutamine (polyQ) diseases, including Huntington's disease and a number of spinocerebellar ataxias, result in the expansion of a tract of glutamine residues to a length beyond a threshold of generally 35 to 40 glutamines, rendering the protein in which the tract is harbored as pathogenic. This correlates with a dramatic increase in the rate at which the polyQ tract can self-assemble into fibrillar aggregates (*2*). Morimoto and colleagues have previously used the nematode *Caenorhabditis elegans* to model polyQ disease by expressing pathogenic and nonpathogenic polyQ peptides that are fused to yellow or green fluorescent proteins in muscle (*3*) and neuronal (*4*) cells. Fluorescent polyQ aggregates and a corresponding phenotype were observed in worms expressing pathogenic polyQ, whereas nonpathogenic peptides had no effect.



The global consequences of an aggregation-prone protein on cellular protein folding homeostasis. (**Top**) Under normal physiological conditions, polymorphisms in genes can result in the expression of proteins that are mild folding variants that are correctly folded or cleared out of the cell by protein quality control mechanisms. (**Bottom**) In the presence of a chronic aggregation-prone protein such as those associated with neurodegenerative diseases, the protein folding and clearance process becomes overwhelmed. Proteins that are normally innocuous are no longer correctly folded, leading to dysfunction in a diverse set of cellular pathways. In turn, these structurally and functionally unrelated proteins generate a positive feedback loop and exacerbate the misfolding of the aggregation-prone protein, thereby acting as modifiers of this process.

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