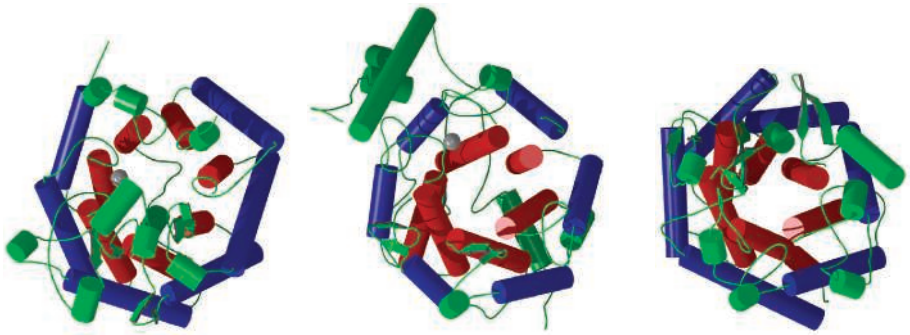

Nisin cyclase | Farnesyl transferase | Lanosterol synthase

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

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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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