The *E. coli* fumarate reductase structure is clearly modular. Subunit A is in physical contact only with subunit B, which is attached to the membrane anchor. The modular composition indicates that the enzymes of the complex II family have originated from a soluble monomeric flavoprotein, a 2Fe-2S ferredoxin, a 7Fe-8S ferredoxin, and an integral transmembrane protein possibly with two b hemes and functioning in transmembrane electron transfer. Soluble monomeric fumarate reductase with a noncovalently bound FAD is found, for example, in promitochondria of the yeast *Saccharomyces cerevisiae* (*6*), and water-soluble ferredoxins are common, particularly in anaerobic bacteria. The first complex formed has been gradually modified over time to optimize succinate oxidation or fumarate reduction under the metabolic conditions prevailing in different cells.

It is the integral membrane domain, however, that is perhaps the most exciting part of the fumarate reductase structure. This is where quinone oxido-reduction occurs and where remarkable diversity is seen among the different members of the complex II family. Why is heme present in most of the enzymes when *E. coli* fumarate reductase and a mutant variant of *E. coli* succinate dehydrogenase (*7*) are functional without it? Are there undiscovered functions in these enzymes? The C and D polypeptides of fumarate reductase each provide three tilted α-helical membrane-spanning segments: helices I, II, and III from subunit C, and helices IV, V, and VI from subunit D. The amino termini are on the same side of the membrane as the AB dimer. Helices I, II, IV, and V are arranged in a right-handed helical bundle, whereas helices III and VI are peripheral to the bundle. The two bound menaquinone molecules in the fumarate reductase, Q_P and Q_D, are located at the respective ends of the helix bundle. Q_P is in a polar pocket ~11 Å from the 3Fe-4S cluster, whereas Q_D is in an apolar environment ~27 Å away from Q_P on the opposite side of the membrane dielectric.

The two low-spin hemes, b_H and b_L, in the diheme membrane anchor of, for example, *Bacillus subtilis* succinate dehydrogenase and *Wolinella succinogenes* fumarate reductase are predicted to have bis-histidine axial ligation and to be located within the four-helix bundle (*8, 9*). The two axial ligands for b_H are on helices II and V, whereas those for b_L are on helices I and IV. Applied to the *E. coli* fumarate reductase structure, the two hemes in the diheme anchors would be positioned between Q_P and Q_D, filling the ~27 Å gap. This is amazingly similar to the situation in complex III, where the function of the two hemes is to provide efficient electron transfer between two quinone binding sites as part of the Q-cycle energy-coupling mechanism (*3*). A major difference is, however, that the heme b_H in complex III is on the positive side of the membrane, whereas in complex II it is on the negative side.

The two hemes in succinate dehydrogenase seem to be the key to an apparent bioenergetic dilemma. *Bacillus* species can grow on succinate (E_m' for the succinate/fumarate redox couple is +30 mV) but only contain low-potential quinones like menaquinone ($E_m' \approx -80$ mV). Electron transfer from succinate to menaquinone is thus thermodynamically highly unfavorable. The succinate oxidase activity in *B. subtilis* drops drastically when the cells are disrupted (*10, 11*). This phenomenon is also observed if uncouplers are added to intact *B. subtilis* cells, but is not observed with mitochondria or *E. coli* cells. The explanation is most likely that the electrochemical potential across the cytoplasmic membrane, which is lost when the cells are disrupted, drives electron transfer from b_H ($E_m' \approx +16$ mV) to b_L ($E_m' \approx -130$ mV), which then can reduce menaquinone. The energy invested for the reduction of menaquinone is regained, and in excess, by the action of coupled terminal oxidases. This mechanistic model is supported by data from mutant enzymes. For example, a variant of *B. subtilis* succinate dehydrogenase deficient in heme b_L but containing b_H does not support growth on succinate and lacks Q reductase activity (*8*).

The *E. coli* fumarate reductase structure is indeed wonderful. It brings us a big step closer to a full understanding of the aerobic enzyme succinate dehydrogenase but also to respiration without molecular oxygen.

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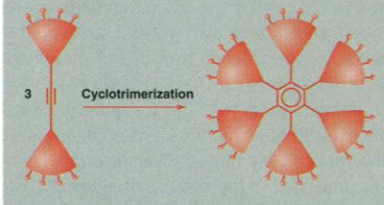
NOTA BENE: CHEMISTRY

Completing the Cycle

Dendrimers are treelike molecules that branch out from a central core and subdivide into hierarchical branching units (*1*). They are potentially useful for diagnostic and therapeutic applications, for example, as contrast agents in magnetic resonance imaging (*1*), because of their ability to anchor many substituents on their surface. Dendrimers can be synthesized in two ways. In the divergent method, the dendrimers are built up step by step from the core. With the convergent method, the dendrimer segments are constructed first and then assembled around the central core. Now, Hecht and Fréchet (*2*) report a new approach to convergent dendrimer synthesis. Previous studies reported trimerization via supramolecular interactions, based on the formation of metal complexes, ionic interactions, or hydrogen bonds (*3*). Hecht and Fréchet now achieve covalent cyclotrimerization of dendritic precursors. The alkyne spacers connecting two dendrimer branches (see figure) trimerize to form a benzene core with six dendrimer ligands.



Clean dendrimer synthesis. A benzene dendrimer core is formed in situ, catalyzed by a cobalt catalyst, from alkyne spacers between dendrimer units. [Adapted from (*2*)]

This approach is very clean, as no side products or partially reacted products are formed. Precise macromolecular structures can be constructed and easily purified. The method should prove particularly valuable for making hybrid dendrimers from differently substituted precursors. Such clean, versatile syntheses will greatly enhance the potential for successful applications.

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