Metal-Carbon Bonds in Nature

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Synthetic organotransition-metal catalysts (species possessing a direct metal-carbon or metal-hydrogen bond) are frequently used in industrial processes to convert hydrocarbon fragments into industrially useful chemicals (1). Transition-metal alkyl (M–CR3) species may, in many instances, play an important role as intermediates in these reactions. In contrast, biology tends to utilize CO3 or CO to form metabolically useful compounds. There is, however, one biological system, which is fondly referred to as "nature’s organometallic catalyst," namely vitamin B12 (2), that makes use of a M–CR3 species. Vitamin B12 contains cobalt in a substituted corrin macrocycle (a flexible porphyrin relative) and contains an axial Co(III)–alkyl (CR3). The macrocyclic environment imparts special properties to the cobalt center that allow it to function as nature’s Grignard reagent (CR3 source), radical (CR, source), or Meerwein’s reagent (CR3 source). The reaction-type promoted by this site depends on the mechanism of C–O bond cleavage. The accessibility of several different oxidation states (+1, +2, +3) allows the versatile behavior of this site. On page 628 of this issue, a report by Kumar et al. (3) presents strong evidence for the occurrence of a second organometallic intermediate in biology that consists of a reactive Ni–CH3 fragment, which serves as a precursor to acetate acid through its reaction with CO and CoASH (acetate-CoA synthase reaction 1). Unlike vitamin B12, the nickel ion in this enzyme, carbon monoxide dehydrogenase (CODH), is coupled to an iron-sulfur Fe3S4 cluster (Fig. 1).

Iron sulfur clusters are ubiquitous in nature, and analogs are accessible by means of synthetic methods (4, 5). Up until the early 1980s, these clusters were thought to function solely as electron transfer and storage sites, delivering electrons to enzymes that promote substrate reduction (the most difficult being N2 reduction to ammonia). Later, it was shown that clusters of this type can serve as enzyme active sites (such as Aconitase) and bind and activate substrate (such as 6). Examples of Fe3S4 clusters linked to a more reactive substrate binding site (7), by what is referred to as a bridging ligand X (M–X–Fe3S4), are found in an increasing number of biological systems [for instance, M= Fe(siroheme) in sulfite reductase (8, 9). If the two sites are chemically linked, they can communicate so that substrate binding at the M site triggers facile multielectron transfer, thereby avoiding toxic or unstable intermediates. In some cases the M site is incorporated into the cubane core (MFe3S4) in place of one of the irons (10).

With CODH (4, 11), the properties (such as Mössbauer spectra) of the Fe3S4 core are not dramatically affected by the presence of the M = Ni site, suggesting that the nickel is bound externally to the cluster core. This led Lindahl, Ragsdale, and Münck to propose the cluster core structure shown in the figure (12). Synthetic modeling studies appear to support this structure (13). The identity of the bridging ligand X is unknown. Evidence for coupling between the Ni site and the Fe3S4 cluster derives from studies in which isotopic labels (6Ni, 2Fe, 3Ni) incorporated into the CO derivative perturbed the electron paramagnetic resonance (EPR) signal associated with this cluster site (14). Resonance Raman and infrared studies established that CO binds to one of the iron sites (15, 16). Reaction of the CO-bound derivative with a methylated corrinoid (MeCo) species results in methyl transfer to the nickel site with the formation of a CH3-bound intermediate (see figure). Evidence

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References
for CH₃ binding to the Ni site is presented in this issue of Science (3).

To complete the biological reaction, CoASH reacts with the intermediate shown in the figure to form the thioester CoASH-C(-OMe) (reaction 1). The mechanism by which this C-C bond-forming process occurs is still under scrutiny (16, 17). The simplest explanation would involve the formation of an intermediate acyl [M-C(O)CH₃] (M = Fe or Ni) species, and evidence does indeed point to an acyl intermediate in reaction 1. It is not clear whether an Fe or Ni acyl intermediate is involved. With synthetic organometallic systems, CO insertion into M-CH₃ bonds, to form M-C(O)CH₃, is one of the most fundamental reaction types (1). These reactions generally occur at mononuclear (single metal) sites that contain electron-accepting supporting ligands such as PR₃, C₅H₅(Cp) or CO. Acyl formation occurs by means of methyl migration to the carbon of an adjacent CO. The best known example of this is the Monsanto acetic acid process (reaction 2), the catalyst of which is shown in the figure. An obvious distinction between the biological system CODH and synthetic catalysts is the absence of electron-accepting PR₃, Cp, or CO ligands, because they are not biologically available. Instead, nature is limited to ligands L-S, N, and O, which are not typically found to encourage acetate formation. A few rare examples of synthetic models for the CODH Ni site containing biologically relevant ligands (S, N, or O) have been reported, however (18–21). Mononuclear (S, N)-ligated Ni–CH₃ species have also been shown (17, 18, 21) to react with CO to form acyl complexes, and then to convert to thioesters upon addition of thios. This is directly relevant to the proposed pathway of the CoASH-C(-OMe) synthase reaction. Complexes of Ni or CO with biologically relevant ligands are also known (18, 20).

The question that remains concerns the role of the Fe₄S₄ cluster in CODH. Given the synthetic models described above, it would appear that Ni is capable of undertaking the entire CODH reaction scheme without the aid of an Fe₄S₄ cluster. In fact, synthetic Fe₄S₄ clusters are unstable in the presence of CO under reducing conditions (22). It has been proposed (16, 17) that the more oxidized Fe₄S₄ cluster serves as a CO binding site, and that CO insertion, involving the Fe₄S₄–CO intermediate shown in the figure, is promoted by redox changes at the cluster site. This has yet to be synthetically modeled. Synthetic models have shown, however, that in order for thioester formation to take place at a Ni center, the Ni ion must be reduced by 2e⁻ [from Ni(II) to Ni(0)] (17). It is therefore possible that the Fe₄S₄ cluster in CODH serves to facilitate the removal of these two electrons, a step that appears to be critical to the stability of the Ni site. The recombination of the mononuclear pathway of acyl formation observed with synthetic systems, and the biradical pathway proposed to occur with CO with CO with CODH (16, 17), awaits further study.

References

Calculus Sparks in Vascular Smooth Muscle: Relaxation Regulators

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Many smooth muscle cells periodically exhibit spontaneous transient outward (hyperpolarizing) currents, or STOCs (1). Each of these events results from the opening of 10 to 100 potassium-selective channels, triggered simultaneously by a rise in cytoplasmic calcium concentration ([Ca²⁺]), because these STOCs can be suppressed by agents that interfere with the release of Ca²⁺ from intracellular stores, the triggering Ca²⁺ for the STOCs has been presumed to come from inside the cell (1, 2), but it is so far impossible to detect the rise in Ca²⁺ that activates the STOCs—presumably because the Ca²⁺ increase is highly localized and brief, and thus invisible in whole-cell Ca²⁺ recordings or Ca²⁺ images with low time resolution. Now, Nelson and co-workers report in this issue of Science the first sighting of these local increases in Ca²⁺ in the cytoplasm of single smooth muscle cells (3). This first glimpse of these “Ca²⁺ sparks” is exciting for understanding how STOCs are generated, but perhaps even more exciting is the demonstration that sparks are quite likely responsible for a specific cell function—a vasodilatory influence on small cerebral arteries.

The Ca²⁺ sparks of smooth muscle are not quite the same as those in cardiac muscle, the tissue in which sparks were first reported (4). The Ca²⁺ sparks in both muscle types do have a similar duration (−100 ms) and magnitude (a few hundred nM), and spatial extent (2 m diameter) at half-maximal [Ca²⁺ ]). In both tissues, the Ca²⁺ sparks arise from the opening of one or several ryanodine receptors and reflect the activation of an elementary Ca²⁺-release unit. In cardiac muscle, the sparks are recruited throughout the cell to produce the global rise in [Ca²⁺ ] that causes the synchronous activation of the contractile system and the consequent ejection of blood from the heart (5). However, the Ca²⁺ sparks in smooth muscle are generated in isolation principally near the cell surface, presumably reflecting the fact that in smooth muscle the sarcoplasmic reticulum (SR), enriched in ryanodine receptors, is near the cell surface (6). These ryanodine-sensitive release units are thus perfectly positioned to receive signals from the plasma membrane and to send signals in the form of localized Ca²⁺ increases. In cardiac muscle, the ryanodine receptor amplifies Ca²⁺ signals arising from the plasma membrane. The studies of Nelson and co-workers, however, show