Catalyst Makes A Novel Switch

Catalysis: Small-molecule iron complex has mixed activity that was exclusive to nature

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Fe(PDP) catalyzes hydroxylation/desaturation of carboxylated substrates. The hydroxylation product
lactonizes and the desaturation product forms a hydroxylactone.

Researchers have discovered that a small-molecule iron catalyst has unusual reactivity previously seen only in nature.

The researchers find that Fe(PDP), an iron-based agent known to catalyze hydroxylation, can also catalyze mixed hydroxylation and desaturation reactions of C–H bonds in carboxylated aliphatic substrates, yielding mixed hydroxyl- and alkene-derived products. Outside of enzymes, this is the first time this type of reactivity switch has been observed for unactivated C–H bonds in aliphatic compounds.

Mixed catalytic activity is often not ideal for chemical synthesis and is not normally sought, the researchers note. But they show it can be useful for synthesizing analogs of medicinally important natural products, such as picrotoxinin, with diverse properties.

The study was carried out by associate professor of chemistry M. Christina White and grad students Marinus A. Bigi and Sean A. Reed at the University of Illinois, Urbana-Champaign (Nat. Chem., DOI: 10.1038/nchem.967).

Mechanistically, White and coworkers propose that Fe(PDP)-catalyzed reactions of carboxylated substrates abstract hydrogen to form short-lived radical intermediates and then branch into two outcomes—hydroxylation to form hydroxylated products or second hydrogen abstraction to form alkenes. Under the reaction conditions used, the products react further to form derivatives.

To support the radical-mechanism hypothesis, the researchers show that Fe(PDP)-catalyzed oxidation of a taxane derivative proceeds by the same type of radical intermediate, which then adds hydroxyl to form a nortaxane. They hypothesize that a P450 enzyme catalyzes the production of nortaxane in plants by the same type of radical mechanism, which has not previously been proposed.

The work “expands the range of transformations that can be carried out by cheap metal catalysts in C–H activation” and could be useful for complex-molecule synthesis, says Robert H. Crabtree of Yale University. Crabtree was part of a collaborative team that reported on small-molecule catalyst switching last year, but only on C–H bonds activated by aromatic groups.

The findings “diversify the kinds of things one can imagine doing with complex organic substrates,” says metalloenzyme specialist Lawrence Que Jr. of the University of Minnesota, Twin Cities.