

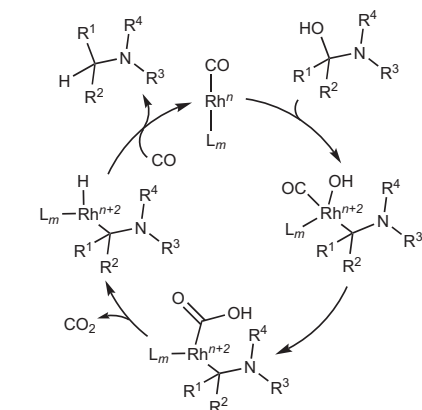
REDUCTIVE AMINATION

H₂ free reduction

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Many reductants are available to chemists, but molecular hydrogen is one of the most common both in academic labs and in industry. Though storage and transport can be a difficulty, hydrogen typically exhibits high reactivity, is cost effective on scale and can give perfect atom economy. Hydrogen is typically produced by steam-reforming of natural gas. The final stage of this process is the water–gas shift reaction: carbon monoxide reacts with steam to generate carbon dioxide and hydrogen. The carbon monoxide is oxidized and is therefore an indirect reductant.

Now, Denis Chusov from the Russian Academy of Sciences and Benjamin List from the Max Plank Institute have taken this process one step further using carbon monoxide as a reductant without the addition of an extra hydrogen source. They



chose to study a reductive amination — a widely used amine synthesis in which an amine and carbonyl react, followed by reduction of the resultant imine. Using carbon monoxide in combination with rhodium acetate catalyst for the reduction afforded good yields of product directly from amines and carbonyls. The methodology was applicable to a wide range

of substrates including both aldehydes and ketones, and in cases where other reducible functionalities (such as cyano and nitro groups) were present. Both primary and secondary amines were tolerated.

Mechanistic studies showed that, contrary to expectations, the reduction did not involve the generation of molecular hydrogen from carbon monoxide and water liberated from the amine–carbonyl condensation. Indeed, replacing CO with hydrogen under otherwise identical reaction conditions resulted in significantly reduced yields. Similarly, the addition of extra water, which would have been expected to boost hydrogen production, instead decreased the rate of reductive amination — raising questions about the active reducing agent. The authors propose a mechanism in which the hemiaminal intermediate — from the initial amine–carbonyl reaction — transfers a hydroxyl group to an *in situ*-formed rhodium carbonyl. Loss of carbon dioxide from the resultant species gives a rhodium hydride, which can then reduce the coordinated iminium. *EB*

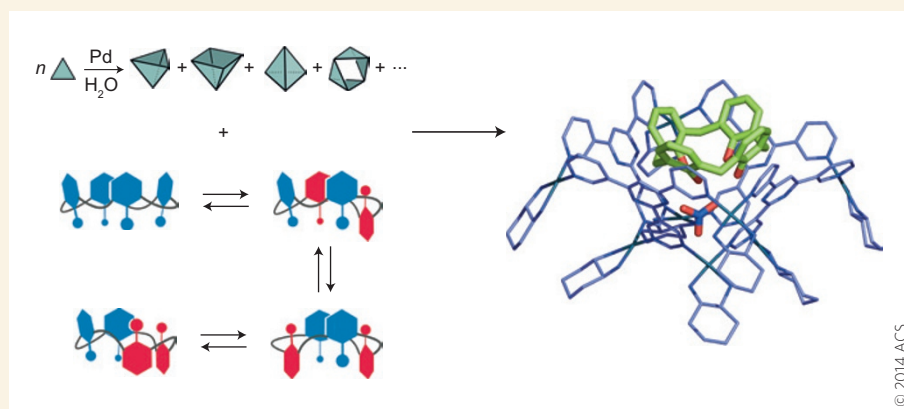
MOLECULAR RECOGNITION

Mutually exclusive

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Molecular recognition events often happen between two rigid molecules, called ‘lock-and-key’ recognition, or between a rigid substrate and a flexible guest that changes shape to fit into the binding site presented. These ‘induced fit’ mechanisms are taken one step further in protein–protein or protein–RNA recognition, where binding sites on both partners are flexible. In this case, mutually induced organization of both sites occurs such that only one conformation of the ensemble is observed. This mechanism is termed mutual induced fit, and, in contrast with examples from biomolecular systems, is rare in synthetic complexes.

Now, Makoto Fujita and co-workers at the University of Tokyo have designed a system that displays such a mutually induced fitting mechanism. They used two supramolecular hosts: flexible calix[4]arene, which rapidly interconverts between four possible conformational isomers, and a palladium–triangular ligand system able to form trigonal pyramidal, tetragonal pyramidal and box-shaped complexes (pictured, left). When the calixarene was added to the Pd–ligand complexation mixture, only a single species was observed. This was found to be a supramolecular



construct formed by one conformation of the calixarene fitting into the tetragonal pyramidal Pd–ligand structure — a ‘host-in-host’ complex. The crystal structure (pictured, right) confirmed that these particular conformations of the calixarene and Pd–ligand structure were present within the host-in-host complex and this can be explained by their mutual stabilization through π – π interactions.

In addition to showing that mutually induced fit can be achieved for synthetic systems similar to those seen in biomolecules, the binding of the calixarene

to a small guest molecule was shown to be altered in its ‘host-in-host’ state. In their free forms in solution, calix[4]arene does not complex nitrobenzene and the Pd–ligand complex accommodates several nitrobenzene molecules. In contrast, the host-in-host complex binds only one nitrobenzene molecule. This demonstrates that mutually induced fit could be a route to further tuning the binding properties of flexible host molecules, as well as a further consideration in designing ever more complex supramolecular constructs. *CH*