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Intramolecular Attack on Coordinated Nitriles: Metallacycle Intermediates in Catalytic Hydration and Beyond

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ARTICLE

Intramolecular Attack on Coordinated Nitriles: Metallacycle Intermediates in Catalytic Hydration and Beyond

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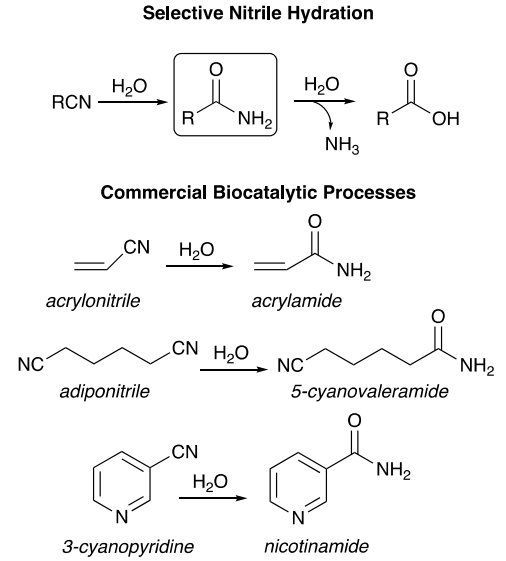
Hydration of nitriles is catalyzed by the enzyme nitrile hydratase, with iron or cobalt active sites, and by a variety of synthetic metal complexes. This Perspective focuses on parallels between the reaction mechanism of the enzyme and a class of particularly active catalysts bearing secondary phosphine oxide (SPO) ligands. In both cases, the key catalytic step was proposed to be intramolecular attack on a coordinated nitrile, with either an S-OH or S-O$^-$ (enzyme) or a P-OH (synthetic) nucleophile. Attack of water on the heteroatom (S or P) in the resulting metallacycle and proton transfer yields the amide and regenerates the catalyst. Evidence for this mechanism, its relevance to the formation of related metallacycles, and its potential for design of more active catalysts for nitrile hydration is summarized.

Introduction

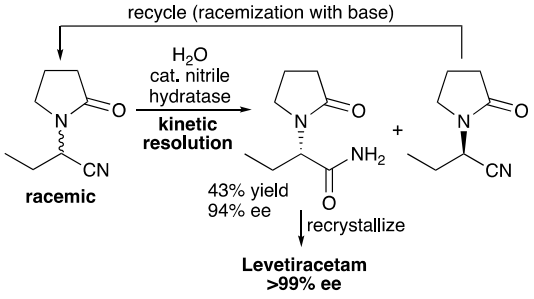
Amides are so important in biochemistry and organic synthesis that their preparation was the most common transformation in a recent survey of reactions used in the pharmaceutical industry.[1] Among the many methods for amide synthesis, the atom economical hydration of nitriles (Scheme 1), forming no waste, is attractive as an example of green chemistry.[2] This process can be mediated by simple acids and bases, but the product amides react more quickly with water to yield carboxylic acids, so selective hydration is challenging. Nevertheless, biocatalysts using the enzyme nitrile hydratase[3] have been commercialized for large-scale production of several amides from nitriles (Scheme 1).[4,5]

Similar processes have been applied to higher-value amide targets, such as the blockbuster anti-epilepsy drug Levetiracetam (Keppra, Scheme 2).[6] Under optimized conditions of pH, temperature, and concentration, a specially engineered nitrile hydratase catalyzed kinetic resolution of a racemic nitrile, yielding the target highly enantioenriched *S*-amide. The recovered unreacted *R*-nitrile could be recycled via racemization, further improving the yield.

Scheme 1. The Challenge of Selective Nitrile Hydration and Some Commercial Processes Catalyzed by Nitrile Hydratase Enzymes



Scheme 2. Enantioselective Synthesis of a Chiral Amide, Levetiracetam (Keppra), by Nitrile Hydratase-Catalyzed Kinetic Resolution of a Racemic Nitrile



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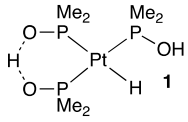
To complement such successful biocatalytic processes, analogous *chemical* ones would also be valuable, because they could be carried out at higher concentrations, over a wider temperature range, and in a variety of solvents. This approach would enable synthesis and use of both enantiomers of the catalyst, avoiding the high substrate specificity of biocatalysts.[7] Moreover, systematic tuning of the catalyst structure would be possible for rational improvements of activity and selectivity. For example, platinum complex **1** in Chart 1, reported by Ghaffar and Parkins in 1995,[8] is one of the most active metal catalyst precursors for nitrile hydration, with a turnover number (TON) of 77,000 and turnover frequency (TOF) of 1485 h^{-1} in hydration of acrylonitrile.[8c] Because it operates under relatively mild conditions in refluxing water, or in mixtures with organic solvents, and shows excellent functional group tolerance, it has been applied in many syntheses of natural products.[9] Precursor **1** is so useful that it is commercially available, although expensive (for example, $2419 for 2 g from Strem).[10] Its success has inspired development of related catalysts derived from secondary phosphine oxides (SPOs), whose tautomerization from $PHR_2(O)$ (P(V)) to P(III) ($PR_2(OH)$) is promoted by metal coordination.[11]

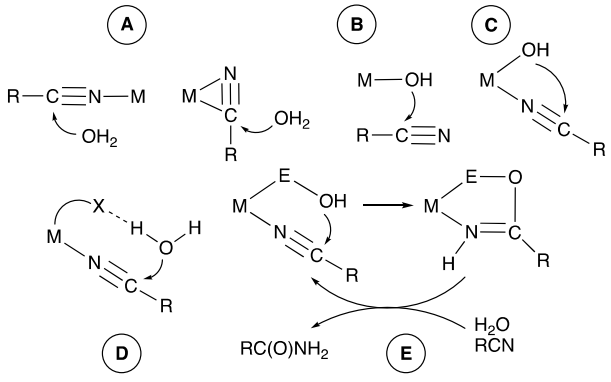
Chart 1. Structure of the Ghaffar-Parkins Catalyst Precursor for Nitrile Hydration



Mechanism of Catalytic Nitrile Hydration

Understanding the reaction mechanism could enable rational design of improved catalysts, either enzymatic or synthetic. Metal catalysts promote hydration by activating the nitrile electrophile (**A**, Scheme 3) or the water/hydroxide nucleophile (**B**). Coordinated nitriles are usually N-bound, although π-coordination is possible (**A**). Activating *both* components (**C**) brings them close together on the metal template to speed up the reaction. Instead of directly coordinating the nucleophile, some catalysts contain a pendant Lewis base (X) which can hydrogen bond to water (**D**), positioning it for attack on the nitrile.[12,2] Alternatively, an O-nucleophile in a ligand containing polarized E–O bonds (E = S, P, N) attacks a complexed nitrile, and water breaks up the resulting metallacycle to form the amide product and regenerate the E–O group (**E**).

Scheme 3. Mechanisms of Metal-Catalyzed Nitrile Hydration



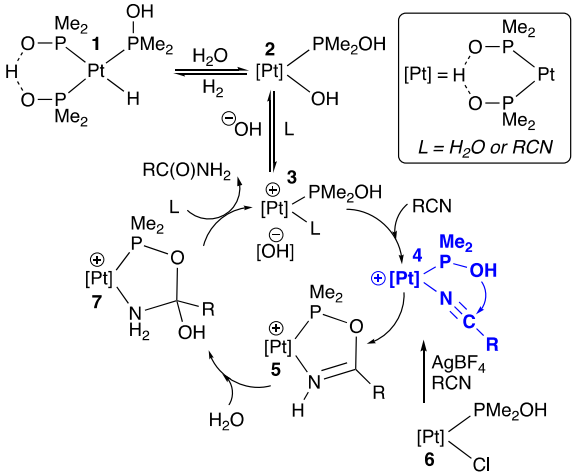
Although there is little apparent connection between the nitrile hydratases, which contain Co or Fe active sites,[13] and the Ghaffar-Parkins catalyst, with Pt and abiological SPO-derived ligands, recent studies suggest that both, as well as some related catalysts, operate by route **E** via metallacyclic intermediates. This Perspective summarizes the evidence for this mechanism and considers its potential for the design of more active and selective catalysts.

Mechanism of Nitrile Hydration Catalysis

Proposed Mechanism of Platinum-Catalyzed Nitrile Hydration

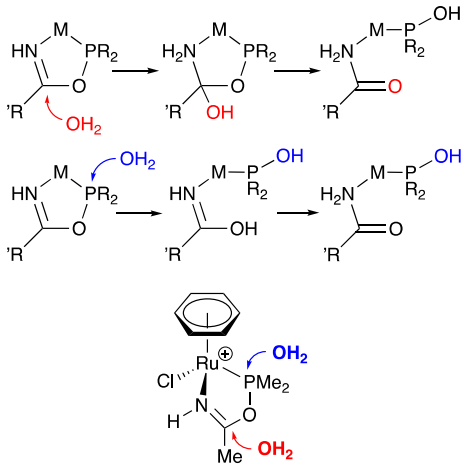
Ghaffar and Parkins suggested that protonation of the hydride in precursor **1** by water gave H_2 and platinum hydroxide **2** (Scheme 4). Ligand substitution (L = water or nitrile) would then yield cationic intermediate **3**, with a hydroxide anion presumably stabilized by water. The key step (**E** in Scheme 3, blue structure **4** in Scheme 4) is intramolecular nucleophilic attack of the hydroxyphosphine ligand on the coordinated nitrile to yield metallacycle **5**. This process would be promoted by the Lewis acidic nature of the cationic platinum center in **4**, which was also generated by silver-mediated halide abstraction from platinum chloride **6**. Addition of water across the metallacycle C=N bond then forms the amide product and regenerates the PMe_2OH group after proton transfers via intermediate **7**.[8]

Scheme 4. Proposed Metallacycle Mechanism of Nitrile Hydration by the Ghaffar-Parkins Platinum Catalyst Precursor **1**



Alternatively, and more generally, water could attack the metallacycle at phosphorus (blue route, Scheme 5), regenerating the PR_2OH ligand and completing hydration of the nitrile. In this sequence, water adds across the C≡N triple bond indirectly via attack and reformation of the P-OH nucleophile.

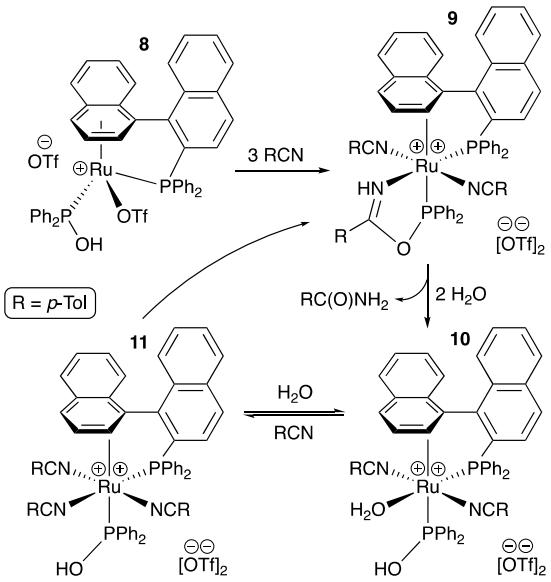
Scheme 5. Water Could Attack a Metallacycle at C (Red, Ghaffar-Parkins Mechanism) or at P (Blue, Favored by DFT Calculations on a Ru Complex)



Although this possibility was not considered by Ghaffar and Parkins, DFT calculations on a Ru catalyst (Scheme 5, bottom) showed that attack of water at phosphorus was a lower-energy process than attack at carbon.[14] In a complementary DFT study comparing analogous Ru and Os catalysts, differences in their reactivity were ascribed to subtle differences in the metallacycle ring strain.[15] Later isotopic labelling experiments on a related Pt catalyst (see Scheme 7 below) provided strong support for this mode of metallacycle ring opening.

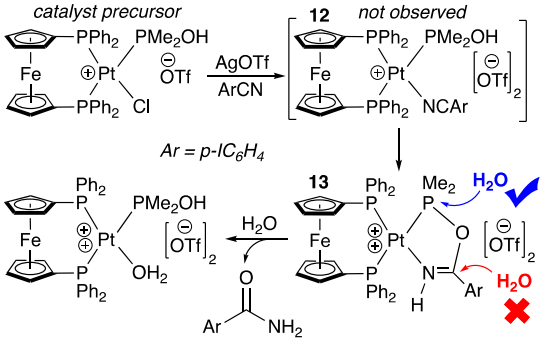
Metallacycle intermediates as proposed by Ghaffar and Parkins were unknown until isolation of this functional group via the postulated SPO attack on a Ru-coordinated nitrile, which presumably occurred in conversion of **8** to **9** (Scheme 6).[16] Significantly, metallacycle **9** reacted with stoichiometric water to form an amide and SPO-aquo complex **10**, which reacted with more nitrile to regenerate metallacycle **9**, presumably via intermediate **11**.[17] These observations led a review article to conclude that "there is now clear evidence for Parkins' intermediate proving the bifunctional action of SPOs on Ru."[18] However, under the catalytic conditions (5 mol % catalyst precursor, 100 °C in water), metallacycle **9** and aquo complex **10** were less active than **8**, with TOF values of 2.8 h^{-1} vs 4.0 h^{-1}. Therefore, Tomas-Mendivil and co-workers concluded that "this [metallacycle] reaction pathway does not appear to be the predominant one."[17]

Scheme 6. Formation of a Metallacycle by Addition of a Nitrile to a Ru-SPO Complex, Its Reaction with Water to Yield an Amide, and a Potential Catalytic Cycle



Studies of second-generation Ghaffar-Parkins-type Pt precursors[19] provided compelling evidence for the metallacycle mechanism (Scheme 7). Replacing the self-assembled hydrogen-bonded anionic $PMe_2OH\bullet\bullet\bullet OPMe_2$ chelate with a conventional neutral bis(phosphine) ligand yielded more active catalysts. After chloride removal from the catalyst precursor using silver triflate, the expected nitrile adduct **12** was not observed. Instead, metallacycle **13** was formed and characterized by X-ray crystallography. This intermediate reacted with stoichiometric water to yield the amide and a Pt-aquo complex, and it acted as a catalyst for nitrile hydration. Isotopic labelling using $PMe_2{}^{18}OH$ and $H_2{}^{18}O$, monitored by mass spectrometry, demonstrated that water attacked the metallacycle at P (blue route, Scheme 7) instead of at C (red route), as predicted earlier for a Ru catalyst (Scheme 5).[20]

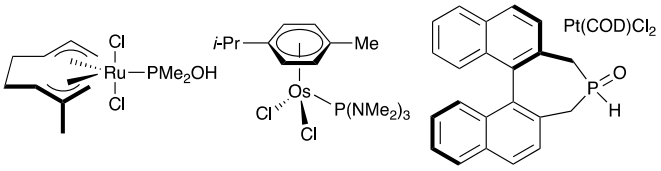
Scheme 7. Formation of a Catalytically Competent Metallacycle Intermediate in Pt-Catalyzed Nitrile Hydration, and Amide Generation via Attack of Water at Phosphorus



How general is this mechanism for synthetic catalysts? There is now strong evidence for it in the most active catalyst systems (Scheme 7), and, by extension, in the original Ghaffar-Parkins catalyst. It is

plausible that this mechanism is also important in the many other catalysts which feature P-OH ligands, formed by tautomerization of SPOs, or by hydrolysis of related precursors with P-Cl or P-NR_2 groups.[11] Chart 2 shows some examples;[21] see recent reviews for more.[11,22]

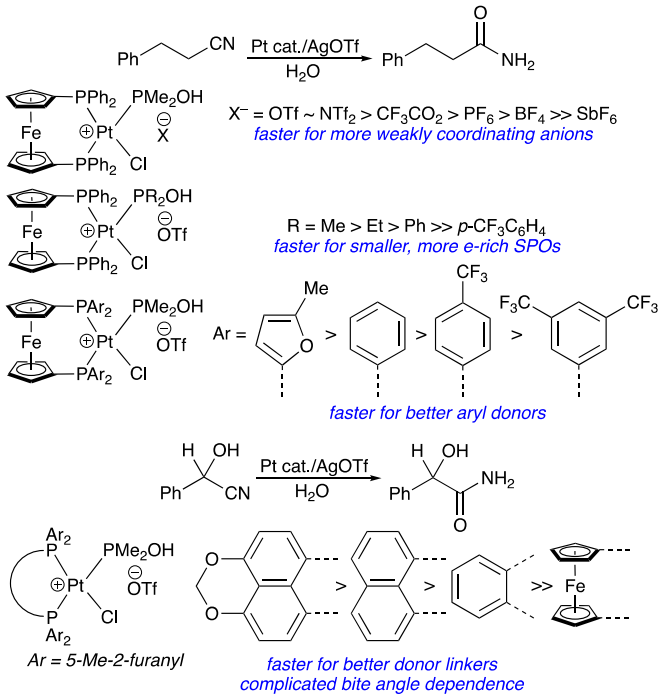
Chart 2. Nitrile Hydration M-SPO Catalyst Precursors



The activity of catalysts operating by this metallacycle mechanism should be maximized by these features: (i) a vacant coordination site for nitrile binding, (ii) a nucleophilic hydroxyphosphine ligand, (iii) an electrophilic, ideally cationic metal center to activate the nitrile for nucleophilic attack, and (iv) suitable supporting ligands. Structure-activity studies on the Pt catalysts have provided design principles to achieve these goals (Scheme 8).[20]

(i) Chloride abstraction with a silver salt generated a vacant site. As expected, more weakly coordinating anions yielded more active catalysts; the anomalously poor performance of $[SbF_6]^-$ may be due to its susceptibility to attack by water.[23] (ii) As in other systems,[8] dimethylphosphine oxide was a privileged SPO, presumably because it combines small size and alkyl donor groups, promoting nucleophilic reactivity. Either increasing the size of this group (Me vs Et) or making it a worse donor (Ph vs *p*-$CF_3C_6H_4$) reduced catalytic activity. (iii) The formal 2+ charge on Pt promoted nitrile coordination and nucleophilic attack on this ligand. (iv) The supporting diphos ligand played both steric and electronic roles. More electron-donating diarylphosphino substituents yielded faster catalysts, which was rationalized by a donor-acceptor argument. Pushing electron density from the *trans* diphos donor onto the PMe_2OH acceptor was proposed to increase the P-OH nucleophilicity, while increased polarization arising from such interactions promoted nitrile activation. Large diphos bite angles could force the P-OH nucleophile and the nitrile electrophile closer together, speeding up metallacycle formation, but this effect may be disadvantageous for hindered substrates. For hydration of the cyanohydrin mandelonitrile (Scheme 8, bottom), smaller bite angle bis(phosphines) were more effective than ferrocene-based dppf. Although these structure-reactivity relationships should be assessed cautiously because catalyst lifetime may also be important, they provide some ideas for design of related catalysts.

Scheme 8 Structure-Reactivity Relationships for Synthetic Platinum-SPO Nitrile Hydration Catalysts



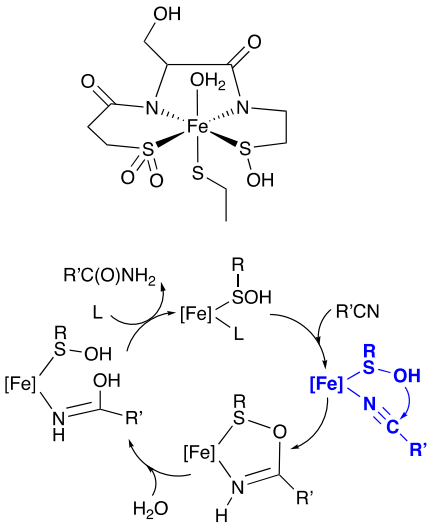
Proposed Mechanism for Nitrile Hydratase

The crystal structures of M(III) nitrile hydratases showed that both the Fe and Co variants contained octahedral metal centers with N_2S_3O coordination, with water, amide, and cysteine-derived ligands. Post-translational modification, required for catalytic activity, resulted in single (S-OH) and double (SO_2) oxidation of two of the cysteines.[24]

Although several mechanisms for nitrile hydratase have been proposed, the consensus pathway has several features in common with the one for synthetic catalysts described above.[25] The Fe(III) or Co(III) active sites (Scheme 9) feature a weakly bound ligand (water), or, for some Fe catalysts, an NO which may be removed photochemically.[26] These ligand dissociations are promoted by a *trans* thiolate donor. Cis to the coordinated nitrile is a sulfenic acid ligand (RSOH), which is proposed to play the same nucleophilic role as the R_2POH ligands in synthetic catalysts. After formation of a metallacycle, attack by water at sulfur yields the amide product and regenerates the key sulfur nucleophile.

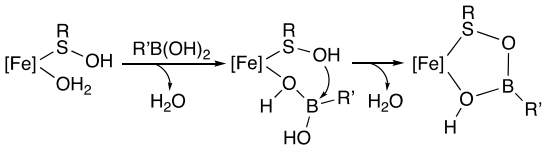
Although there is general agreement on these steps, the proposed mechanisms in the following Schemes are not completely consistent, reflecting variations in the enzymes, the reaction conditions, and the assumptions of the original authors. For example, Schemes 9-10 include an S-OH group, but in Schemes 11-12, it has been deprotonated. This feature is pH-dependent, and spectroscopic and mechanistic studies have considered both the neutral nucleophile and the anionic form, as well as hydrogen bonding from nearby protein residues to the S-O moiety.[26,27]

Scheme 9. Structure of the Iron Nitrile Hydratase Active Site and Proposed Metallacycle Mechanism for Catalytic Nitrile Hydration



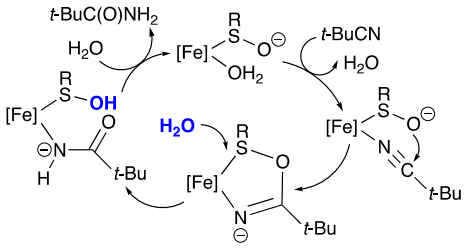
Several experimental and computational lines of evidence support this mechanism. For example, boronic acids are competitive inhibitors of the enzyme. X-ray crystallographic studies showed that they displaced water and then underwent nucleophilic attack by the S-OH group to form a metallacycle (Scheme 10), which suggested that a similar process was involved with coordinated nitrile substrates.[28]

Scheme 10. Metallacycle Formation with Boronic Acids, Competitive Inhibitors of Nitrile Hydratases



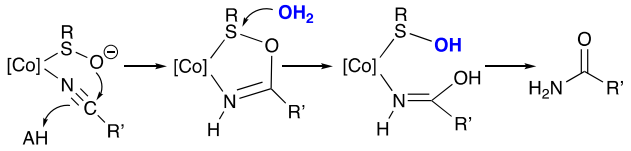
Similarly, a time-resolved X-ray crystallographic study on an iron nitrile hydratase enabled observation of the individual steps in the proposed mechanism. After substrate binding, in which pivalonitrile replaced coordinated water, intramolecular attack of the deprotonated sulfenate group gave a metallacycle. Attack of water at sulfur, evidenced with $H_2{}^{18}O$ by IR observation of the shifted SO stretching vibration, opened the ring, and a series of proton transfers and water binding regenerated the catalyst. The simplified Scheme 11 omits the complex hydrogen bonding networks proposed to mediate most of these processes.[29]

Scheme 11. Time-Resolved X-Ray Crystallographic Evidence for Metallacycle Formation in Nitrile Hydratase-Catalyzed Hydration of Pivalonitrile



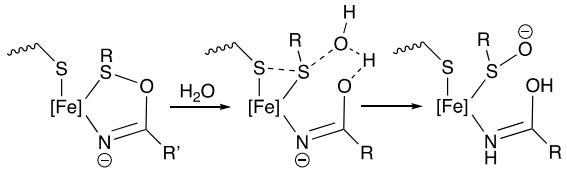
Mass spectrometric analysis of single-turnover nitrile hydration catalysed by a cobalt-containing nitrile hydratase demonstrated that the label in ^{18}O-water appeared not in the amide product but in the protein, also consistent with water attack at sulfur in the metallacycle (Scheme 12; compare Schemes 7 and 10 above with similar results for a synthetic Pt-P-OH catalyst and the reaction of nitrile hydratase with boronic acids).[30]

Scheme 12. Single-Turnover Experiments on a Cobalt Nitrile Hydratase Showed That the ^{18}O Label Was Incorporated into the Catalyst, Not the Amide Product



Computational studies identified a role of the thiolate active site ligand in metallacycle ring opening, involving nucleophilic attack at sulfur.[31] In an example (Scheme 13), this partial S-S bond formation promoted attack of water at sulfur.[26a]

Scheme 13. Thiolate-Promoted Metallacycle Ring Opening via Attack of Water at Sulfur



In summary, nitrile hydratase enzymes contain an unusual ligand set which helps to promote nitrile hydration. This includes the active sulfenate nucleophile, oriented cis to a vacant site for nitrile coordination and activation by the low-spin M(III) ion. The thiolate donor trans to the nitrile promotes ligand substitution to accelerate turnover, even for the relatively inert Co(III) center. As shown in Scheme 13, the thiolate may help to mediate metallacycle ring opening by attack at the nearby sulfur. Finally, the rigid chelate N~S ring holds the SO nucleophile in the right position for attack on coordinated nitrile.[26] Besides these primary coordination

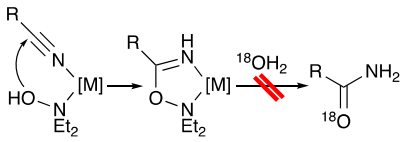
sphere features, hydrogen bonding to nearby residues is important in enzyme activity.[32]

Metallacycle Mechanisms for Attack on Coordinated Nitrile: Beyond P and S

Intramolecular attack on coordinated nitriles, especially in processes that form a five-membered ring, is a more general reaction. Besides the P-OH and S-OH or S-O^- nucleophiles described above, related E-O groups (E = N, C, O) yield analogous metallacycles, some of which may be intermediates in catalysis.

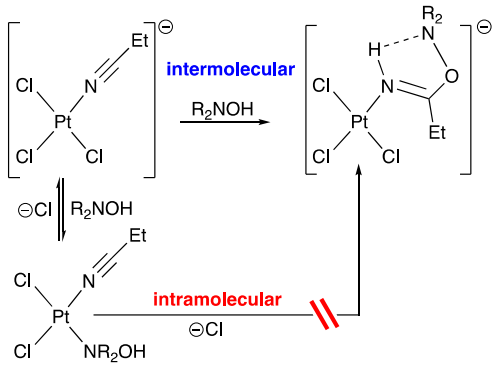
Copper(II) acetate catalyzed nitrile hydration mediated by a hydroxylamine. To rationalize the promoting effect of copper and other Lewis acids, N-OH nucleophilic attack on coordinated nitrile was proposed to yield a metallacycle. When ^{18}O-labelled water was added, no ^{18}O label was incorporated into the amide product, suggesting that water was not acting as a nucleophile (Scheme 14). Instead, a radical mechanism involving N-O cleavage, or a metal-mediated rearrangement, were suggested.[33]

Scheme 14. Proposed Metallacycle Intermediate and Lack of Incorporation of Labelled Water in Copper/Hydroxylamine-Catalyzed Nitrile Hydration



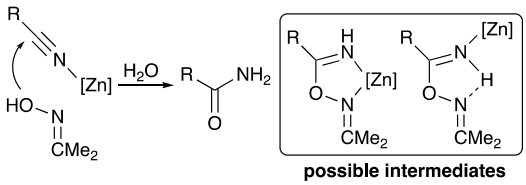
A related stoichiometric nitrile-hydroxylamine coupling in a Pt complex (Scheme 15) could occur by reversible displacement of chloride by the hydroxylamine, followed by intramolecular attack (red pathway), or by direct intermolecular attack on coordinated nitrile (blue route). Because the process was not inhibited by added chloride, the intermolecular pathway was preferred.[34]

Scheme 15. Proposed Intermolecular Mechanism of Hydroxylamine Attack on Pt-Coordinated Nitrile



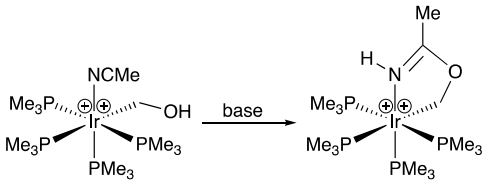
A related process may be involved in ZnX_2/ketoximine-catalyzed nitrile hydration (for example, X = Cl or NO_3, Scheme 16), for which a proposed mechanism involved oxime attack on coordinated nitrile, followed by hydrolysis.[35] This process might involve metallacycle formation or intermolecular attack of the N-OH nucleophile, as in Scheme 15.

Scheme 16. Zinc-Catalyzed Nitrile Hydration Promoted by Ketoxime Attack on Coordinated Nitrile



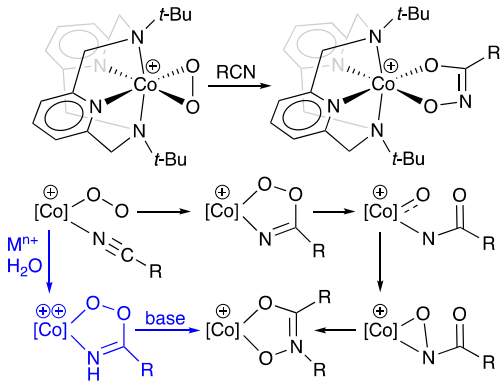
In a related process with a C-OH nucleophile, a metallacycle was formed via intramolecular attack of a hydroxymethyl group on coordinated nitrile in a dicationic iridium complex. Base catalysis was necessary, presumably to increase the O-nucleophilicity (Scheme 17).[36]

Scheme 17. Base-Catalyzed Attack of an Ir-Hydroxymethyl Group on Coordinated Acetonitrile Gave a Metallacycle



Even coordinated dioxygen has been proposed to react with a nitrile in a similar fashion. In a mechanism suggested on the basis of DFT calculations, after nitrile coordination, attack by the β-O yielded a metallacycle, which rearranged via a 1,3-sigmatropic process to cleave the O-O bond and form a new metallacycle.[37] A protonated form of the proposed metallacycle was isolated when the reaction was carried out in the presence of redox-inactive metal salts (blue pathway, Scheme 18). Deprotonation of the NH group led to the rearranged metallacycle observed previously (black pathway).[38]

Scheme 18. Proposed Mechanism of Reaction of a Co-Peroxo Complex with a Nitrile (Black) and Formation of a Metallacycle in the Presence of Lewis Acids (M^{n+} = Zn^{2+}, La^{3+}, Lu^{3+}, and Y^{3+}, Blue)



Conclusions

Despite the differences in metals and ligand sets between nitrile hydratase and related synthetic catalysts, their proposed mechanisms have some important similarities. Both include a weakly coordinated ligand, such as water, which can be displaced by the nitrile substrate. Both this step and subsequent ligand substitutions required for catalytic turnover and to avoid inhibition by water or the amide product are promoted by a supporting ligand with a large trans effect. The formal charge on the metal center (Fe/Co(III), or Pt(II)) activates the nitrile carbon for intramolecular attack by a polarized S-O or P-O bond to yield a five-membered metallacycle. Ring opening by attack of water at the heteroatom results in the counterintuitive conclusion that nitrile hydration occurs indirectly, without attack of water on the C ≡ N triple bond.

Despite these similarities, little communication seems to have occurred between scientists studying the mechanism of nitrile hydratase and those developing related synthetic catalysts. For example, although Ghaffar and Parkins first proposed their metallacycle mechanism in a 1995 paper,[8] its 170 citations so far do not include any publications about the enzyme mechanism.[39]

Nevertheless, these mechanistic ideas offer some design principles for future development of synthetic catalysts. Most importantly, replacing the precious metal platinum with earth-abundant metals is plausible, since cobalt and iron, at least in the enzyme environment, are active catalysts. Moving up the column from Pt to Ni with SPO-derived catalysts is logical, and both Ni(0)[40] and Ni(II) catalyst precursors[41] for nitrile hydration are known, although they do not contain P-OH groups. However, any metal should be able to bind nitriles and a pendant E-OH nucleophile (E need not be P) for metallacycle formation, suggesting that a broad range of catalysts using this motif will be available. To promote nitrile binding, catalyst precursors should be electrophilic, perhaps cationic, and have a vacant site. Suitable supporting ligands stabilize the catalyst, promote ligand substitution, and maximize the E-OH nucleophilicity. More sophisticated designs would include hydrogen bonding groups to promote proton transfer after attack of water on the metallacycle.[42] These ideas, along with further mechanistic investigations, may yield more active and selective catalysts for nitrile hydration and related processes.[43]

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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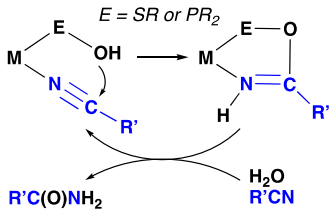
TOC Graphic & Text



Intramolecular S-OH or P-OH attack on a coordinated nitrile yields a metallacycle in the proposed mechanism of nitrile hydratase and related synthetic catalysts.

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