Regulating Access to Active Sites via Hydrogen Bonding and Cation-Dipole Interactions: A Dual Cofactor Approach to Switchable Catalysis

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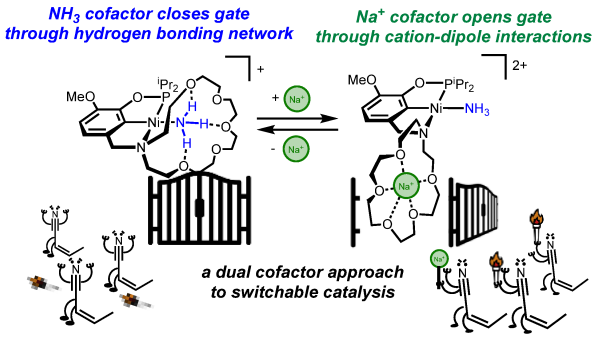


Abstract: Hydrogen bonding networks are ubiquitous in biological systems and play a key role in controlling the conformational dynamics and allosteric interactions of enzymes. Yet in small organometallic catalysts, hydrogen bonding rarely controls ligand binding to the metal center. In this work, a hydrogen bonding network within a well-defined organometallic catalyst works in concert with cation-dipole interactions to gate substrate access to the active site. An ammine ligand acts as one cofactor, templating a hydrogen bonding network within a pendent crown ether and preventing the binding of strong donor ligands such as nitriles to the nickel center. Sodium ions are a second cofactor, disrupting hydrogen bonding to enable switchable ligand substitution reactions. Thermodynamic analyses provide insight into the energetic requirements of the different supramolecular interactions enabling substrate gating. The dual cofactor approach enables switchable catalytic hydroamination of crotononitrile. Systematic comparisons of catalysts with

varying structural features provide support for the critical role of the dual cofactors in achieving on/off catalysis with substrates containing strongly donating functional groups that might otherwise interfere with switchable catalysts.

Introduction

In biological systems, catalytic reactions are often modulated by "gating" mechanisms that regulate substrate access to active sites, based on allosteric interactions between enzymes and small molecule or ion cofactors.[1–5] Synthetic chemists have long sought to replicate allosteric gating to achieve controlled or switchable catalysis in artificial systems.[5–8] The most common gating mechanisms involve physical blocking groups, such as supramolecular constructs with switchable steric bulk or supramolecular cages with switchable access, catalyst solubility, and configurational changes like cis/trans isomerization or metal-ligand bond-breaking reactions.[5,9–13] These designs have enabled breakthroughs in copolymer synthesis, established methods for switching product selectivity in small molecule synthesis without needing to synthetically modify the catalyst, and enhanced capabilities for multi-catalyst cascades.[5,9]

One important gating mechanism employed by enzymes is tunable hydrogen bonding (H-bonding) networks.[14] For example, ß-carbonic anhydrase is proposed to regulate the hydration of CO_2 using a complex network of hydrogen bonds (**Figure 1A**).[15,16] In one state, carbonate engages in hydrogen bonding in one part of the enzyme while aspartate binds to a Zn^{2+} ion, inhibiting the catalytic reaction. When the bicarbonate cofactor is released (by change in pH or surrounding carbonate concentration), the H-bonding network near the active site rearranges. This

reorganization enables a water molecule critical for catalysis to bind to the Zn^{2+} ion and initiate catalysis.

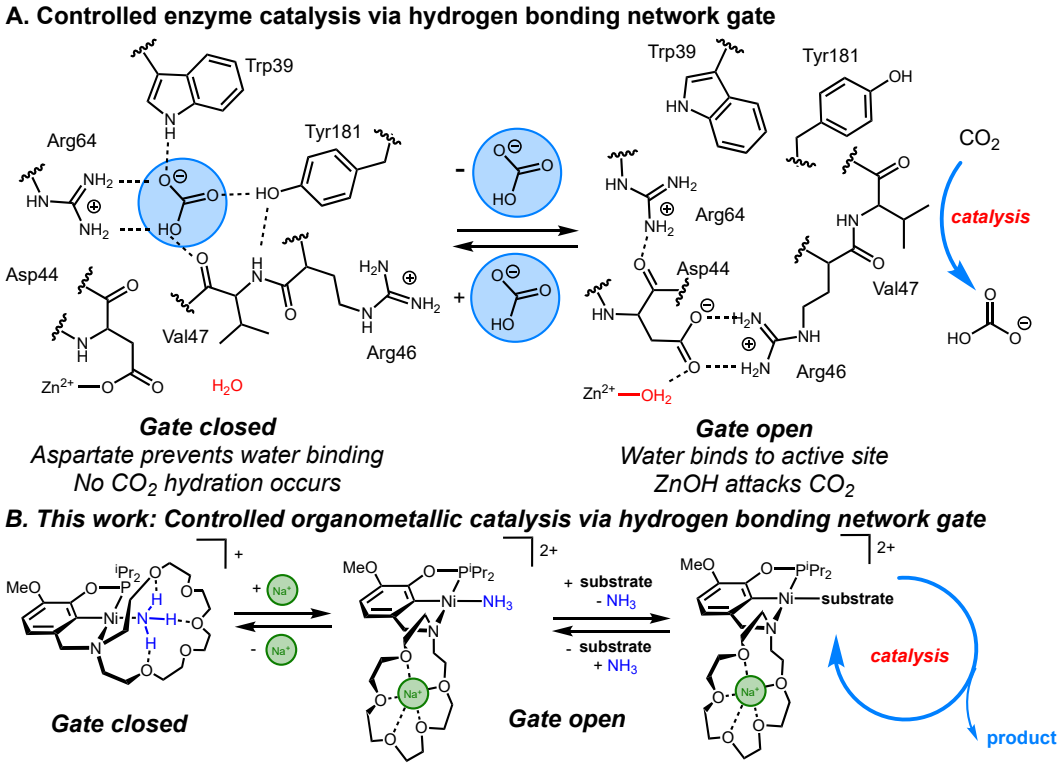


Figure 1. (A) Proposed hydrogen bonding gate in ß-carbonic anhydrase for controlled bicarbonate formation. (B) New approach to switchable catalysis using hydrogen bonding gate in pincer-crown ether complexes.

Although H-bonding networks in the secondary coordination sphere have been explored in bio-inspired synthetic chemistry for stabilizing and fine-tuning reactive species,[17–19] examples where H-bonding networks are used to control substrate access in the context of allosteric model systems or switchable catalysis remain surprisingly rare.[5,20–23] Most examples involve organocatalysts in which the H-bond donor is also the active site; to our knowledge, the only examples involving transition metal active sites utilize H-bonded DNA hybrids that change conformation upon interaction with complementary strands to enable access to the active site or bring two synergistic catalysts into proximity.[24,25] Considering the key role of H-bonding networks in regulating the conformational dynamics and allosteric interactions of enzymes, we saw an

opportunity to similarly utilize H-bonding networks in switchable catalysis of first-row organometallic complexes.

Our group has developed cation-responsive pincer-crown ether complexes that use ion-tunable hemilability as a gating mechanism for switchable reactivity.[26,27] These complexes feature an aza-crown-ether macrocycle incorporated into a pincer ligand, allowing for ether oxygen interactions with either the metal center or specific cations added to solution. In the closed state, the ether binds to the metal center and prevents substrate coordination. Cation cofactors open the gate, because the combined free energies of cation-dipole interactions and substrate binding to the metal center are thermodynamically favorable. Reactions of alkenes have been a focus of catalysis studies with pincer-crown ether complexes, with iridium systems in particular exhibiting excellent control over the rate, stereoselectivity, and regioselectivity of positional isomerization of olefins.[28–30]

One drawback of this system is that controlled catalysis is only possible with substrates that bind relatively weakly to the metal center. Strongly donating ligands can displace the hemilabile crown-ether donors even in the absence of cationic additives, leading to the breakdown of the gating mechanism: the rate is the same with or without cations, so no control over catalysis is possible. This is apparent in prior efforts to develop pincer-crown ether nickel-catalyzed reactions. The insertion of aldehydes into a C–H bond of acetonitrile proceeded even in the absence of alkali metal salts, due to acetonitrile displacing the hemilabile ether oxygen, preventing predictable control over nickel catalysis with our current systems.[31] Thus, new strategies are required to expand the scope of controlled nickel catalysis.

Inspiration for a new strategy for improved catalyst control came from the unexpected observation that adding water enhanced the activity of iridium pincer-crown ether catalysts for the

transposition of alkenes containing donor groups.[29] Crystallographic studies of iridium aquo complexes revealed an intriguing H-bonding network between the water ligand hydrogen atoms and the aza-crown-ether macrocycle.[29] We hypothesized that the right hydrogen-bond-donor small molecule could act as a secondary cofactor in nickel complexes to modulate the ability of substrates to bind the active site to access catalytic reactions featuring strong donors. This would solve a challenge in switchable catalysis involving tunable hemilability, and also provide fundamental insight into design strategies in switchable catalysis. It is rare for synthetic catalysts to employ multiple cofactors for switchable catalysis,[22,32] providing an opportunity for understanding how cation-dipole and H-bonding interactions with crown ethers can influence and control substrate access to active sites (**Figure 1B**).

In this work, we show how pendent crown ethers can establish H-bonding networks within organometallic complexes as part of a dual cofactor approach to controlled catalysis. When both ammonia and sodium ions are used as cofactors, balancing H-bonding and cation-dipole interactions enables a robust gating mechanism for switchable substrate binding and catalysis. The thermodynamics of these interactions are investigated and reveal insights into the switchable gating process. The importance of both H-bonding and cation-dipole interactions for switchable reactivity is examined through a series of comparison complexes, including a complex analogous to previously reported nickel pincer-crown ether complexes lacking the ammonia cofactor. The dual cofactor approach is leveraged to demonstrate switchable ligand substitution reactivity and catalytic alkene hydroamination reactions.

Results and Discussion

Synthesis of nickel complexes and characterization of H-bonding networks

Figure 2 describes the synthesis of the target nickel complexes. The aza-18-crown-6 ether macrocycle was selected based on crystallographic studies of iridium aquo complexes that showed excellent encapsulation of the water ligand.[29] Pincer ligands with and without macrocycles were chosen to better understand the role of crown ethers in enabling switchable reactivity. Halide abstraction from (κ^3-^{18c6}NCOP)Ni(Br) (**^{18c6}NiBr**) with $AgPF_6$, followed by salt metathesis with $NaBAr^F{}_4$, provided [(κ^4-^{18c6}NCOP)Ni][$BAr^F{}_4$] (**^{18c6}Ni**). Complexes **^{18c6}NiBr** and **^{18c6}Ni** are similar to previously published variants,[33] with the exception that they contain a methoxy group in the backbone of the pincer ligand to prevent unwanted metalation byproducts.[26]

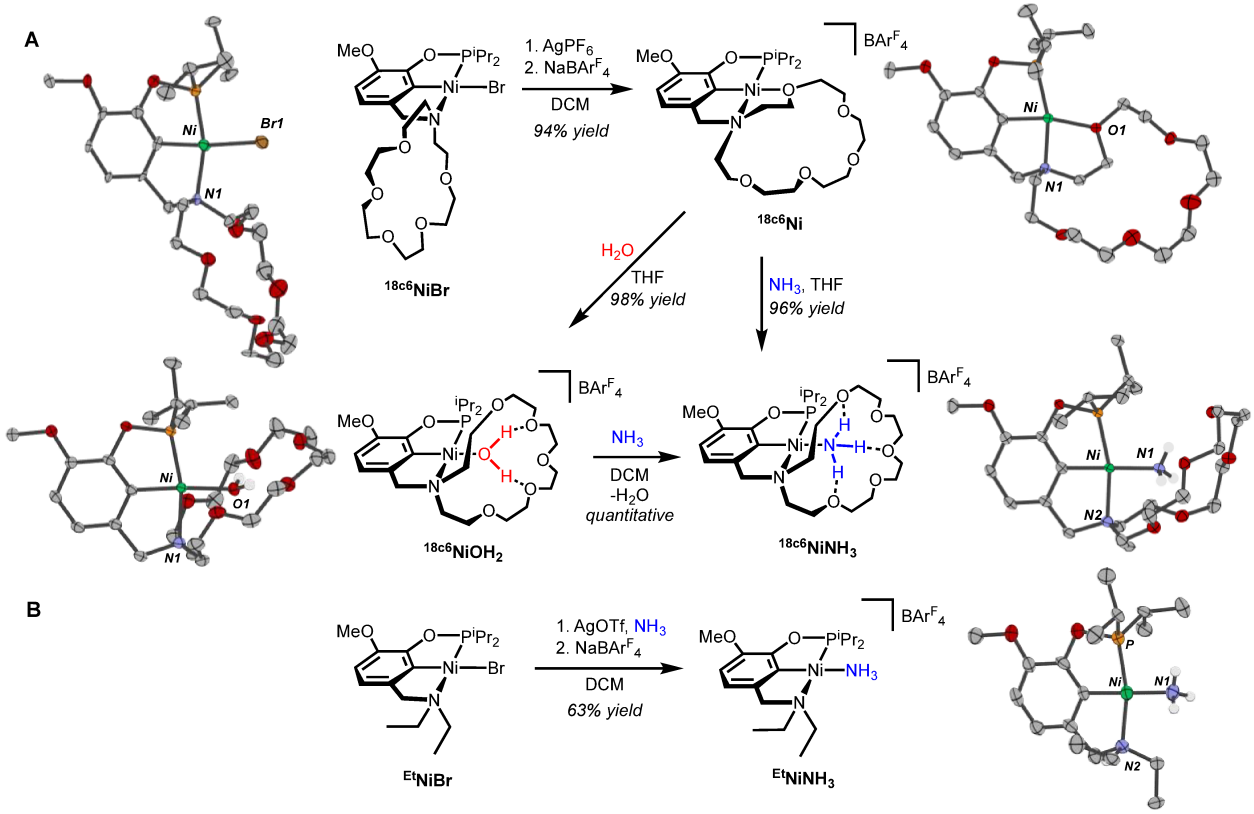
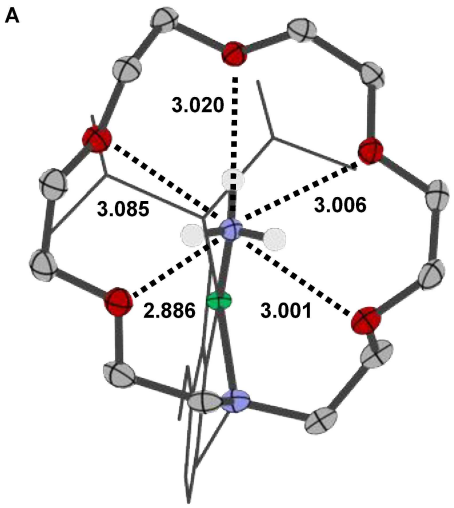


Figure 2. (A) Synthetic route to pincer-crown ether nickel ammine and aquo complexes. (B) Synthetic route to diethylamino pincer nickel ammine complex. Structural representations from single crystal X-ray diffraction, with ellipsoids at 50% and hydrogen atoms (except on aquo or ammine ligands) and anions omitted, are shown adjacent to the line drawing. Note that single crystals of **^{Et}NiNH$_3$** and **^{18c6}NiOH$_2$** were obtained as PF_6^- salts, see SI for details.

Treatment of **^{18c6}Ni** with 10 equiv of ammonia in THF led to the formation of the desired complex [(κ^3-^{18c6}NCOP)Ni(NH_3)][$BAr^F{}_4$] (**^{18c6}NiNH$_3$**), which was obtained as a yellow powder in 96% yield (**Figure 2A**). The ^{15}N-labeled isotopologue, [(κ^3-^{18c6}NCOP)Ni($^{15}NH_3$)][$BAr^F{}_4$] (**^{18c6}Ni^{15}NH$_3$**), was generated analogously. The diethyl-amine-containing complex [(κ^3-^{Et}NCOP)Ni(NH_3)][$BAr^F{}_4$] (**^{Et}NiNH$_3$**) lacks a crown ether and thus serves as an important control (**Figure 2B**).

The X-ray structure of **^{18c6}NiNH$_3$** reveals a remarkable H-bonding network. The crown ether curls up to encapsulate the Ni-NH_3 and bridge the primary and secondary coordination sphere (**Figure 2A**). This conformation is different than other reported four-coordinate nickel pincer-crown ether structures, which are oriented with the crown ether away from the metal center.[34] **Figure 3A** shows a detailed view of the H-bonding network of **^{18c6}NiNH$_3$**. All five oxygen donors on the macrocycle are within H-bonding distance, with five O-N distances ranging from 2.886(2) to 3.085(3) Å.[35] These distances are similar to reported X-ray structures of ammonium cations interacting with 15-crown-5 ether and transition metal ammine complexes interacting with external crown ethers.[36–39]



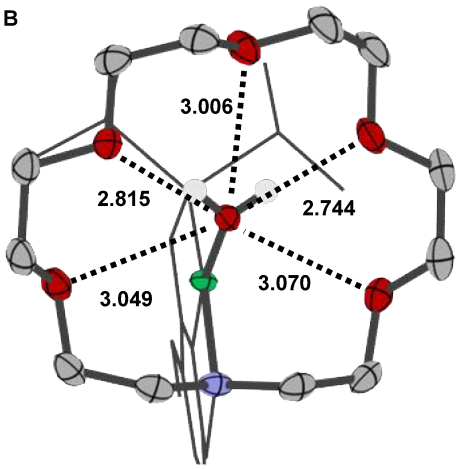
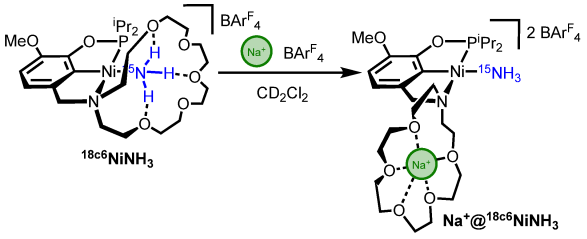


Figure 3. Perspective highlighting the H-bonding network in (a) ^{18c6}**NiNH$_3$** and (b) ^{18c6}**NiOH$_2$**. Structural representations from single crystal X-ray diffraction, with ellipsoids at 50% and hydrogen atoms (except on aquo or ammine ligands) and anions omitted, are shown adjacent to the line drawing. Inter-atomic distances given in angstroms (Å).

To compare H-bonding interactions with other ligands, the nickel aquo complex [(κ^3-^{18c6}NCOP)Ni(OH$_2$)][BAr$^F_4$] (**^{18c6}NiOH$_2$**) was also synthesized (**Figure 2A**). The crystal structure of **^{18c6}NiOH$_2$** also features a H-bonding network, with donor-acceptor distances shown in **Figure 3B**. The flexibility of the macrocycle is apparent in the distinct conformations adopted by **^{18c6}NiNH$_3$** and **^{18c6}NiOH$_2$**, as well as in the wide range of other structures observed with pincer-crown ether complexes: those with no H-bonding (empty crown), bound alkali metal cations, or with additional ether donor(s) binding to the transition metal center.[33,34,40]

Scheme 1. Addition of NaBAr$^F_4$ to **^{18c6}Ni^{15}NH$_3$**.



Multinuclear NMR spectroscopy can provide insight into the conformation of the crown ether. The ^{15}N NMR spectrum of **^{18c6}Ni^{15}NH$_3$** exhibits a quartet at –400.2 ppm vs CH_3NO_2 ($^1J_{NH}$ = 67

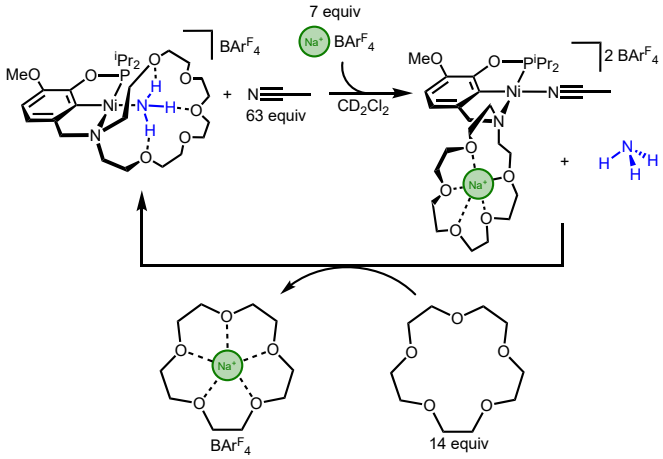
Hz), typical of ammine complexes (**SI Figure 16**).[41,42] To disrupt the H-bonding, 1 equiv $NaBAr^{F}_4$ was added to **^{18c6}Ni^{15}NH$_3$** in dichloromethane solvent (**Scheme 1**), resulting in the immediate formation of a new nickel species assigned as the Na^+ adduct **Na^+@^{18c6}NiNH$_3$**. The ^{15}N resonance shifts downfield by 0.5 ppm and additional coupling to phosphorus is observed (–399.7 ppm, qd, $^1J_{NH}$ = 67 Hz, $^2J_{NP}$ = 2.5 Hz). Significant shifts and changes in multiplicity are also observed for the crown ether proton resonances in the ^{1}H NMR spectrum, consistent with Na^+ localization in the macrocycle (**SI Figure 62**). Additionally, the NH_3 proton resonances shift from 2.3 to 1.3 ppm for **Na^+@^{18c6}NiNH$_3$**. Spectroscopic parameters of the complex without a crown ether, **^{Et}Ni^{15}NH$_3$**, which is not capable of H-bonding, are very similar to those of **Na^+@^{18c6}NiNH$_3$**, providing further evidence that Na^+ disrupts the H-bonding network.

Switchable ligand substitution of nickel ammine complexes

With a better understanding of the H-bonding present in the crown-containing complexes, we set out to examine how dual cofactors with distinct noncovalent interactions influence ligand substitution reactions. No reaction was observed upon treating the H-bonded ammine complex **^{18c6}NiNH$_3$** with 63 equiv of acetonitrile (**Scheme 2**). Similar behavior was observed when **^{18c6}NiNH$_3$** was treated with other neutral donor ligands such as pyridine. Yet, when 7 equiv of $NaBAr^{F}_4$ was added to the reaction solution, rapid substitution of ammonia with nitrile was observed to generate $[Na@(\kappa^3\text{-}^{18c6}NCOP)Ni(NCCH_3)]^{2+}$ (**Na^+@^{18c6}NiMeCN**) with the Na^+ cation in the crown ether (**Scheme 2**). This formulation of the Ni complex was confirmed by comparison to an authentic sample from an alternative synthesis, which was fully characterized by multinuclear NMR spectroscopy and elemental analysis (SI Figures 40-42).

The nitrile binding event can be reversed with a chemical stimulus. Previous studies have shown that free crown ethers bind alkali metal cations with higher affinity than analogous pincer-crown ether complexes.[34] Accordingly, the addition of 14 equiv free organic macrocycle 15-crown-5 ether (15c5) to **Na$^+$@^{18c6}NiMeCN** led to ejection of the nitrile ligand and ammonia recapture to reform starting complex **^{18c6}NiNH$_3$** (**Scheme 2**).

Scheme 2.



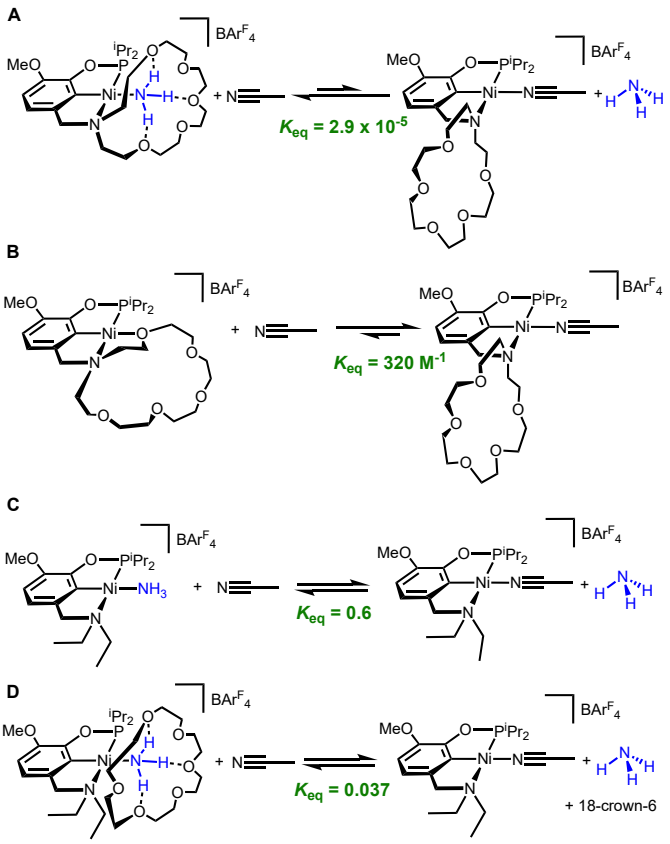
The ability of **^{18c6}NiNH$_3$** to capture ammonia in solution through the use of a chemical stimulus is noteworthy; here, the crown ether enhances ammonia's binding affinity to the nickel complex by H-bonding. These results demonstrate *cation-switchable ligand substitution* controlled by H-bonding networks with the pendent crown ether, providing an analogy to how some enzymes use H-bonding networks and ion cofactors to gate substrate access **(Figure 1A** above).

To better understand the origin of the cation-switchable ligand substitution, exchange equilibria were studied with several different complexes of varying structure. The switchable pincer-crown ether complex featuring ammonia H-bonding, **^{18c6}NiNH$_3$**, is noteworthy for resisting acetonitrile coordination. An equilibrium constant (K_{eq} in **Scheme 3A**) could only be quantified in conditions approaching neat acetonitrile solvent.

A complex without NH_3 present, the κ^4-bound complex **^{18c6}Ni**, was examined next. This complex lacks a H-bonding network and instead has a weak Ni–O bond with one of the crown ether oxygen atoms. Titration of acetonitrile to **^{18c6}Ni** led to broadening and shifting of the chemical shifts, consistent with a rapid exchange process attributed to competitive binding between the acetonitrile and the crown ether oxygen ligands (K_{eq} = 320 M^{-1}, **Scheme 3B** and **SI Figures 61-62**).[31] This occurs without any Na^+ added, showing that the crown ether alone is not sufficient to regulate nitrile coordination to the metal center; the ammine ligand is an essential component for controlled nitrile binding.

A complex that retains the ammonia ligand, but that lacks a pendent crown ether, was examined next. In the absence of any interactions with a crown ether, substitution of ammonia by acetonitrile is facile. Addition of acetonitrile to **^{Et}NiNH$_3$** resulted in partial conversion to the cationic nickel acetonitrile complex, $[(\kappa^3\text{-}^{Et}NCOP)Ni(NCCH_3)]^+$ (**^{Et}NiMeCN**) (**Scheme 3C**). These two species are in slow exchange, with relative integration indicating a K_{eq} of 0.6 for substitution of ammonia to form **^{Et}NiMeCN**. Thus, ammonia alone cannot prevent nitrile binding and the pendent crown is essential for switchable reactivity.

Scheme 3.

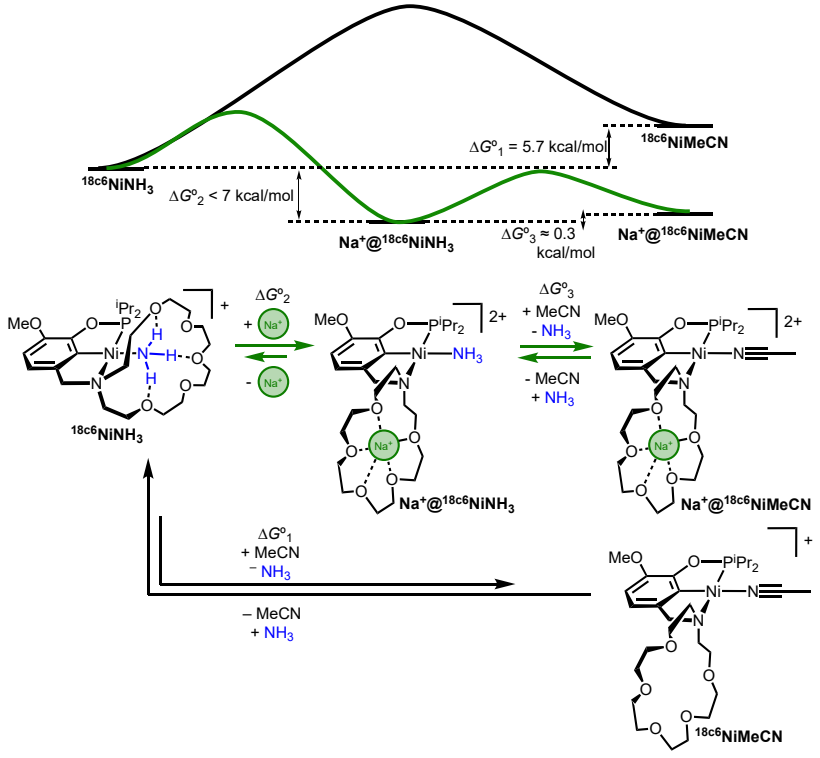


Finally, the importance of intramolecular H-bonding with a pendent crown ether was probed by comparisons to an intermolecular adduct with free crown ethers. In an attempt to form an intermolecular crown ether adduct, 1 equiv of free 18-crown-6-ether was added to **^{Et}NiNH$_3$** in dichloromethane solvent. This crown ether, which has the same total macrocycle size as the pincer-crown ether ligand but one more oxygen donor available for H-bonding, reacted to form a new species assigned as [(κ^3-^{Et}NCOP)Ni(NH$_3$)•18c6]$^+$ (**^{Et}NiNH$_3$•18c6**) based on mass spectrometry and NMR spectroscopy (SI Figures 50-52). Notably, the NH$_3$ proton resonances shift downfield by 0.53 ppm and additional shifts are observed for the aromatic resonances. This adduct is similar to previously reported 1:1 adducts of transition metal ammine complexes.[38] Subsequent addition of MeCN resulted in formation of substantial amounts of **^{Et}NiMeCN** (**Scheme 3D**). The equilibrium constant, K_{eq} = 0.037, suggests that the intermolecular crown adduct would not prevent

nitrile binding under catalytically relevant conditions (e.g., 50 equivalents of nitrile-containing substrate), in contrast to the excellent protection from nitrile binding afforded by the intramolecular interactions of the pincer-crown ether complex. The reactivity of ^{Et}**NiNH$_3$** with the smaller 15-crown-5 ether, which matches the O-donor count in ^{18c6}**NiNH$_3$**, is very similar (SI Figure 48-49).

The various equilibrium constants can be combined to provide a comprehensive thermodynamic view of the interactions relevant to switchable catalysis. **Scheme 4** illustrates a free energy landscape for switchable acetonitrile/ammonia ligand substitution. Without cations present, ligand substitution to bind acetonitrile is unfavorable (ΔG^{o}_{1} = 5.7 kcal) (**Scheme 4**, black trace). Given that the NH_3 in ^{Et}**NiNH$_3$**, which lacks any H-bonding network, is readily displaced by MeCN, the unfavorable substitution of NH_3 in ^{18c6}**NiNH$_3$** can be largely ascribed to an energetically stabilizing effect of the intramolecular H-bonding network. The H-bonding strength (i.e. the free energy required to break all of the H-bonds) is estimated to be ca. 5.4 kcal/mol (see the SI for a detailed thermodynamic analysis).

Scheme 4. Free energy landscape describing switchable ligand substitution. $\triangle G^{\circ}_{3}$ is estimated based on **Scheme 3C**.



When Na^+ is added, substitution of NH_3 by MeCN becomes possible with only a slight excess of nitrile (**Scheme 4**, green trace). The switch in reactivity is attributed to an alteration in crown ether bonding, from H-bonding to cation-dipole interactions. The cation-crown interactions (ΔG^o_2) were directly probed by NMR spectroscopy. Changes in chemical shift were observed up to 1 equiv of $NaBAr^F_4$ added, and the addition of more than 1 equiv of $NaBAr^F_4$ to **^{18c6}NiNH$_3$** did not result in any further changes detected by NMR. Thus, the cation binding energy is beyond the upper limit of quantification by NMR spectroscopy, K_a >10^5 M^{-1} (ΔG^o_2 < –7 kcal/mol) in dichloromethane.[43,44] This behavior is strikingly distinct from the reactivity of nickel complexes lacking ammine ligands that feature direct binding of an ether oxygen to nickel, which show no measurable interaction with alkali metal cations in dichloromethane (K_a < 0.1 M^{-1}).[33] In order to achieve switchable reactivity according to the reaction profile of **Scheme 4**, the cation-crown interaction must be stronger than the H-bonding energy, as was observed.

Switchable hydroamination catalysis by nickel ammine complexes

The ability to regulate ligand binding in **^{18c6}NiNH$_3$** provides an opportunity for switchable catalysis. The hydroamination of crotononitrile was selected as a proof-of-principle test reaction involving nitrile binding to nickel as a key substrate activation step.[45–47] Alkenyl nitriles are good candidates for multi-catalyst sequences that sequentially react with the olefin and nitrile functionalities, where a switchable catalyst could address compatibility challenges, or a tunable catalyst could enable rate-matching to maximize kinetics.[48,49] The strong donor nitrile group, however, normally disrupts switchable catalysis in pincer-crown ether systems.

The hydroamination of crotononitrile by morpholine in C_6H_5Cl, catalyzed by **^{18c6}NiNH$_3$**, was monitored by ^{1}H NMR spectroscopy (**Figure 4**). In the absence of $NaBAr^F{}_4$, the yield of 3-morpholinobutanenitrile was 2.7% after 48 h. Under the same conditions but with 1 equiv of $NaBAr^F{}_4$ present, the reaction proceeded cleanly to generate 53% yield of morpholinobutanenitrile after 48 h. A control reaction with $NaBAr^F{}_4$ present but no nickel catalyst showed no reaction even after 48 hours (**SI Figure 67**). The reaction is noteworthy for being almost completely "off" in the H-bonding-protected state and having a difference of more than 50-fold in activity between the two states (**Table 1**), an ideal situation for switchable catalysis.[5]

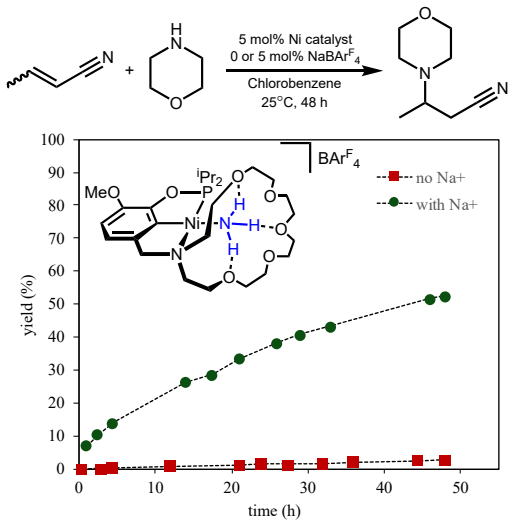


Figure 4. Hydroamination of crotononitrile with morpholine catalyzed by **^{18c6}NiNH$_3$**, with no salt additive (red squares) and with NaBAr$^F_4$ (green circles). Conditions: 6 mM Ni (5 mol%), 0 or 6 mM NaBAr$^F_4$, 120 mM morpholine, and 240 mM crotononitrile, with 10 mM hexamethyldisolaxane (HMDSO) as an internal standard, in chlorobenzene solvent at 25°C.

Switchable catalytic activity was demonstrated with **^{18c6}NiNH$_3$** by toggling between on and off states *in situ* using chemical additives (**Figure 5**). In its native state with strong H-bonding, the Ni catalyst is off (1% yield after 18 hours). Addition of Na^+ to the same flask initiated the reaction by disrupting the H-bonding, switching on reactivity to generate 13% yield of product after several hours. Addition of 15-crown-5 ether halted the reaction, reverting the catalyst back to the off state. Catalytic activity can be restored to the initial levels by adding two more equivalents of Na^+. These results highlight the reversible nature of this organometallic catalyst through the dual cofactors.

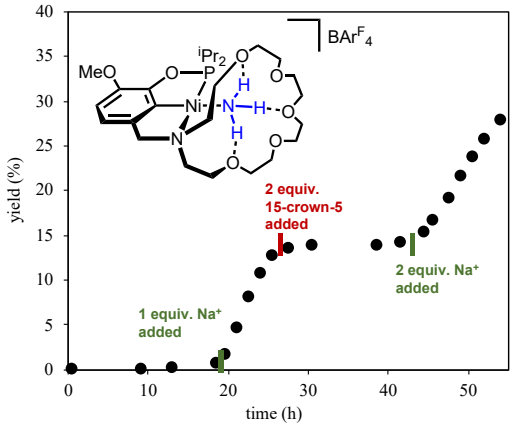


Figure 5. Cation-controlled hydroamination of crotononitrile with morpholine catalyzed by ^{18c6}**NiNH$_3$**. Conditions: 6 mM Ni (5 mol%), 120 mM morpholine, and 240 mM crotononitrile, with mesitylene as an internal standard, in chlorobenzene-d_5 at 25°C. The vertical lines mark the time at which amounts (relative to catalyst concentration) of $NaBAr^F{}_4$ or 15-crown-5 were added to start or stop the reaction.

The crown ether moiety and the dual cofactors NH_3 and Na^+ are all needed to achieve switchable catalysis of crotononitrile hydroamination. To systematically study the roles of each component, the reactivity of three other catalysts were compared: the ammine complex supported by a macrocycle-free diethylamine-based ligand, ^{Et}**NiNH$_3$**; the crown-containing aquo complex, ^{18c6}**NiOH$_2$**, an analogue of ^{18c6}**NiNH$_3$** that replaces ammonia with water as the H-bonding donor; and the complex without a monodentate ligand and only intramolecular crown ether binding to nickel, ^{18c6}**Ni**.

When diethylamino-substituted complex ^{Et}**NiNH$_3$** was subjected to the standard catalytic conditions, 3-morpholinobutanenitrile formed in 73% yield after 48 hours, even without Na^+. Under the same conditions but with 1 equiv $NaBAr^F{}_4$, the yield was effectively unchanged. Thus, there is no off state for this catalyst and it is not suitable for switchable reactivity. The comparison also provides mechanistic insight. Because the ^{Et}**NiNH$_3$** complex exhibits similar hydroamination activity to ^{18c6}**NiNH$_3$** activated with Na^+, the primary role of the Na^+ can be ascribed to disruption of the H–bonding between the crown and the ammine ligand, enabling substrate binding. This comparison also suggests that the proximal Na^+ ion does not induce significant inductive or electrostatic effects, or else the rate of ^{Et}**NiNH$_3$** with and without Na^+ would differ (**SI Figure 81-82**). Using ^{Et}**NiNH$_3$** as the catalyst in the presence of 18-crown-6 ether, which forms an intermolecular H-bonding adduct as described above, did not significantly influence the product yields. This comparison shows that the intramolecular H-bonding afforded by the pendent crown ether is essential for switchable catalysis.

Table 1. Yields (from NMR spectroscopy) of hydroamination of crotononitrile with morpholine catalyzed by nickel complexes, with and without $NaBAr^{F}{}_4$ after 48 hours. Conditions: 6 mM Ni (5 mol%), 6 mM $NaBAr^{F}{}_4$, 120 mM morpholine, and 240 mM crotononitrile, with HMDSO internal standard, in chlorobenzene at 25°C. Uncertainty is reported as the standard deviation of triplicate runs.

	^{18c6}**NiNH$_3$**	^{Et}**NiNH$_3$ (+ 18-crown-6)**	^{18c6}**Ni**	^{18c6}**NiOH$_2$**
final % yield, no Na$^+$	2.7 ± 0.2	73 ± 5 (66 ± 0.8)	67 ± 0.6	64 ± 3
final % yield, with Na$^+$	53 ± 2	68 ± 3 (70 ± 1)	88 ± 0.8[b]	84 ± 2
initial reactivity ratio[a]	59	1.0	1.7	3.8

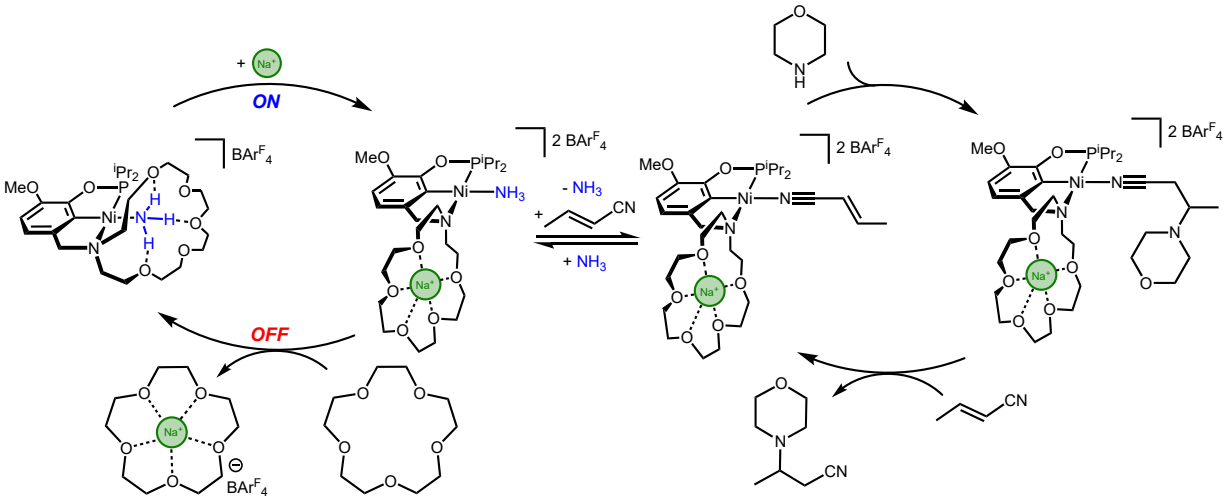
[a] ratio of the initial rate without salt and with $NaBAr^{F}{}_4$. [b] isolated yield 69%.

Comparisons were also carried out with **^{18c6}NiOH$_2$**, which features water instead of ammonia as a H-bonding cofactor. When **^{18c6}NiOH$_2$** was subjected to standard conditions in the absence of $NaBAr^{F}{}_4$, a yield of 64% for 3-morpholinobutanenitrile was obtained. The aquo ligand is therefore not a suitable secondary cofactor because it does not adequately gate access of the substrate to the active site (stoichiometric reactions with MeCN are consistent with this, SI Figures 67-68). When $NaBAr^{F}{}_4$ is present, the yield increased to 86%, but because catalysis proceeds even without the Na^+ cofactor present, switchable reactivity is not possible. We attribute this to facile aquo ligand displacement, based on our observation that **^{18c6}NiOH$_2$** reacts with 1 equiv NH_3 to give full conversion to nickel ammine **^{18c6}NiNH$_3$** (**Figure 2A**).

Similar behavior was observed for complex **^{18c6}Ni**, in which a crown ether oxygen atom is bound directly to nickel. This catalyst lacking a H-bonding network produces 3-morpholinobutanenitrile in 67% yield, increasing to 89% in the presence of $NaBAr^{F}{}_4$. This is

consistent with the model studies above that show nitriles can readily displace the crown ether oxygen, again showing that the ammonia ligand is a crucial cofactor enabling switchable catalysis. Only ^{18c6}**NiNH$_3$** demonstrates on/off switchable behavior. These results emphasize the importance of the ammonia cofactor and the macrocycle working together to produce a gate that prevents nitrile and amine binding to the active site — yet this gate can still be opened using Na^+ cofactors to give good catalytic activity.

Scheme 5. Proposed mechanism of hydroamination reactions catalyzed by ^{18c6}**NiNH$_3$**.



Scheme 5 proposes a mechanism for switchable hydroamination of crotononitrile by ^{18c6}**NiNH$_3$**. Switchable hydroamination is possible with this system because the key step in the mechanism is proposed to be substrate binding to the metal center.[30] When there is no Na^+ present, the nickel system is in the off state and minimal catalysis takes place because the nitrile substrate cannot readily access the Ni center. Addition of Na^+ turns the system on, breaking the H-bonding network to open the gate and allow for the nitrile substrate to displace the ammonia ligand to initiate catalysis. Evidence for distinct on/off states can be found in $^{31}P\{^1H\}$ NMR spectra obtained during catalysis. In the off state, only one resonance for ^{18c6}**NiNH$_3$** is observed. In contrast, both ^{18c6}**NiNH$_3$** and a new species assigned as the nickel crotononitrile adduct (on state) are observed

upon 5 mol% Na^+ addition (**SI Figure 90**). The speciation shifts to favor the substrate-bound on state when up to 20% $NaBAr^F{}_4$ is added, resulting in higher yields (ca. 65%, **SI Figure 89**). Increasing $NaBAr^F{}_4$ concentration beyond 20 mol% resulted in decreased yields, however, which we hypothesize to be the result of Na^+ binding to morpholine and dampening its nucleophilicity. The mechanism is further supported by comparative catalysis studies that establish the NH_3 cofactor, crown ether, and Na^+ salt as all being essential for switchable catalysis behavior. Access to switchable reactivity does incur a slight decrease in yield relative to the catalysts without an NH_3 ligand, which we attribute to modest inhibition of substrate binding by the ammonia ligand.

One significant challenge in switchable catalysis is the development of systems that can perform reactions with a wider range of substrates.[5] The difficulty arises from substrates that are often incompatible with reaction conditions and/or catalyst. For instance, with previous nickel pincer-crown ether systems, switchable catalysis was not possible with neutral strongly donating ligands like nitriles.[31] These substrates were able to displace the hemilabile crown-ether donors without cofactors present, leading to the breakdown of the gating mechanism, so no controlled catalysis was possible. The control of H-bonding networks using dual cofactors provides a solution to this challenge, enabling switchable activity with a greater substrate scope.

Another notable challenge is that many (though certainly not all) systems exhibit only modest differences in on and off states of catalysis.[5] In comparison to previous pincer-crown ether systems, the dual cofactor enables a high degree of difference between two states of catalytic activity (**Table 1**). Ultimately, the ability to control H-bonding networks to regulate substrate access to a transition metal active site is a promising strategy that can improve reactivity ratios and may engender new forms of reactivity. Such a switchable catalyst could facilitate catalyst recovery/recycling by switching between a high activity state and a low activity state that is

sufficiently robust to survive workup and product removal, or could enhance multi-catalyst reactions through cation-tuned rate-matching or by on/off switching to avoid catalyst incompatibility.[50]

Conclusion

Pincer-crown ether nickel complexes can be regulated by two cofactors: an ammonia molecule that enables a H-bonding network between the primary and secondary coordination sphere and Na^+ ion that is able to break the network to form cation-dipole interactions in the secondary coordination sphere. These interactions have been leveraged to design a system capable of switchable ligand substitution and catalysis. Thermodynamic studies of pincer-crown ether complexes and non-macrocyclic variants confirm the essential role of both cofactors in achieving on and off switching. The dual cofactor approach achieves an on/off system that is compatible even with substrates containing strongly donating functional groups that often interfere with gates. The structural and mechanistic insights here, with inspiration drawn from enzymatic systems that often use multiple cofactors or regulate catalytic activity through H-bonding networks, provide guidance for developing artificial catalysts with similar degrees of control.

Associated Content

Supporting information
Full experimental details, NMR spectra, derivation of thermodynamic analysis, and crystallographic details (PDF)

Accession codes
CCDC 2295751-2295755 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif., or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033

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Notes

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References

(1) Page, M.; Di Cera, E. Is Na+ a Coagulation Factor? *Thromb. Haemost.* **2006**, *95* (06), 920–921. https://doi.org/10.1160/TH06-05-0239.
(2) Hritz, J.; Žoldák, G.; Sedlák, E. Cofactor Assisted Gating Mechanism in the Active Site of NADH Oxidase from Thermus Thermophilus. *Proteins Struct. Funct. Bioinforma.* **2006**, *64* (2), 465–476. https://doi.org/10.1002/prot.20990.
(3) Nechushtai, R .; Lammert, H.; Michaeli, D.; Eisenberg-Domovich, Y.; Zuris, J. A.; Luca, M. A.; Capraro, D. T.; Fish, A.; Shimshon, O.; Roy, M.; Schug, A.; Whitford, P. C.; Livnah, O.; Onuchic, J. N.; Jennings, P. A. Allostery in the Ferredoxin Protein Motif Does Not Involve a Conformational Switch. *Proc. Natl. Acad. Sci.* **2011**, *108* (6), 2240–2245. https://doi.org/10.1073/pnas.1019502108.
(4) Li, Q.-A.; Mavrodi, D. V.; Thomashow, L. S.; Roessle, M.; Blankenfeldt, W. Ligand Binding Induces an Ammonia Channel in 2-Amino-2-Desoxyisochorismate (ADIC)

Synthase PhzE. *J. Biol. Chem.* **2011**, *286* (20), 18213–18221. https://doi.org/10.1074/jbc.M110.183418.
(5) Blanco, V.; Leigh, D. A.; Marcos, V. Artificial Switchable Catalysts. *Chem. Soc. Rev.* **2015**, *44* (15), 5341–5370. https://doi.org/10.1039/C5CS00096C.
(6) Ginovska, B.; Gutiérrez, O. Y.; Karkamkar, A.; Lee, M.-S.; Lercher, J. A.; Liu, Y.; Raugei, S.; Rousseau, R.; Shaw, W. J. Bioinspired Catalyst Design Principles: Progress in Emulating Properties of Enzymes in Synthetic Catalysts. *ACS Catal.* **2023**, 11883–11901. https://doi.org/10.1021/acscatal.3c00320.
(7) Thaggard, G. C.; Haimerl, J.; Fischer, R. A.; Park, K. C.; Shustova, N. B. Traffic Lights for Catalysis: Stimuli-Responsive Molecular and Extended Catalytic Systems. *Angew. Chem. Int. Ed.* **2023**, *62* (29), e202302859. https://doi.org/10.1002/anie.202302859.
(8) Winkler, C. K.; Schrittwieser, J. H.; Kroutil, W. Power of Biocatalysis for Organic Synthesis. *ACS Cent. Sci.* **2021**, *7* (1), 55–71. https://doi.org/10.1021/acscentsci.0c01496.
(9) Deng, S.; Jolly, B. J.; Wilkes, J. R.; Mu, Y.; Byers, J. A.; Do, L. H.; Miller, A. J. M.; Wang, D.; Liu, C.; Diaconescu, P. L. Spatiotemporal Control for Integrated Catalysis. *Nat. Rev. Methods Primer* **2023**, *3* (1), 28. https://doi.org/10.1038/s43586-023-00207-0.
(10) Wiester, M. J.; Ulmann, P. A.; Mirkin, C. A. Enzyme Mimics Based upon Supramolecular Coordination Chemistry. *Angew Chem - Int Ed* **2011**, *50*, 114.
(11) Raynal, M.; Ballester, P.; Vidal-Ferran, A.; van Leeuwen, P. W. N. M. Supramolecular Catalysis. Part 1: Non-Covalent Interactions as a Tool for Building and Modifying Homogeneous Catalysts. *Chem Soc Rev* **2014**, *43*, 1660.
(12) Raynal, M.; Ballester, P.; Vidal-Ferran, A.; van Leeuwen, P. W. N. M. Supramolecular Catalysis. Part 2: Artificial Enzyme Mimics. *Chem Soc Rev* **2014**, *43*, 1734.
(13) Vlatković, M.; Collins, B. S. L.; Feringa, B. L. Dynamic Responsive Systems for Catalytic Function. *Chem. - Eur. J.* **2016**, *22* (48), 17080–17111. https://doi.org/10.1002/chem.201602453.
(14) Ali, M. H.; Imperiali, B. Protein Oligomerization: How and Why. *Bioorg. Med. Chem.* **2005**, *13* (17), 5013–5020. https://doi.org/10.1016/j.bmc.2005.05.037.
(15) Rowlett, R. S. Structure and Catalytic Mechanism of the β-Carbonic Anhydrases. *Biochim. Biophys. Acta BBA - Proteins Proteomics* **2010**, *1804* (2), 362–373. https://doi.org/10.1016/j.bbapap.2009.08.002.
(16) Cronk, J. D.; Rowlett, R. S.; Zhang, K. Y. J.; Tu, C.; Endrizzi, J. A.; Lee, J.; Gareiss, P. C.; Preiss, J. R. Identification of a Novel Noncatalytic Bicarbonate Binding Site in Eubacterial β-Carbonic Anhydrase. *Biochemistry* **2006**, *45* (14), 4351–4361. https://doi.org/10.1021/bi052272q.
(17) Barman, S. K.; Jones, J. R.; Sun, C.; Hill, E. A.; Ziller, J. W.; Borovik, A. S. Regulating the Basicity of Metal–Oxido Complexes with a Single Hydrogen Bond and Its Effect on C–H Bond Cleavage. *J. Am. Chem. Soc.* **2019**, *141* (28), 11142–11150. https://doi.org/10.1021/jacs.9b03688.
(18) Lee, J. L.; Ross, D. L.; Barman, S. K.; Ziller, J. W.; Borovik, A. S. C–H Bond Cleavage by Bioinspired Nonheme Metal Complexes. *Inorg. Chem.* **2021**, *60* (18), 13759–13783. https://doi.org/10.1021/acs.inorgchem.1c01754.
(19) Reek, J. N. H.; De Bruin, B.; Pullen, S.; Mooibroek, T. J.; Kluwer, A. M.; Caumes, X. Transition Metal Catalysis Controlled by Hydrogen Bonding in the Second Coordination Sphere. *Chem. Rev.* **2022**, *122* (14), 12308–12369. https://doi.org/10.1021/acs.chemrev.1c00862.

(20) McGuirk, C. M.; Mendez-Arroyo, J.; Lifschitz, A. M.; Mirkin, C. A. Allosteric Regulation of Supramolecular Oligomerization and Catalytic Activity via Coordination-Based Control of Competitive Hydrogen-Bonding Events. *J. Am. Chem. Soc.* **2014**, *136* (47), 16594–16601. https://doi.org/10.1021/ja508804n.
(21) McGuirk, C. M.; Stern, C. L.; Mirkin, C. A. Small Molecule Regulation of Self-Association and Catalytic Activity in a Supramolecular Coordination Complex. *J. Am. Chem. Soc.* **2014**, *136* (12), 4689–4696. https://doi.org/10.1021/ja500214r.
(22) McGuirk, C. M.; Mendez-Arroyo, J.; d'Aquino, A. I.; Stern, C. L.; Liu, Y.; Mirkin, C. A. A Concerted Two-Prong Approach to the *in Situ* Allosteric Regulation of Bifunctional Catalysis. *Chem. Sci.* **2016**, *7* (11), 6674–6683. https://doi.org/10.1039/C6SC01454B.
(23) Beswick, J.; Blanco, V.; De Bo, G.; Leigh, D. A.; Lewandowska, U.; Lewandowski, B.; Mishiro, K. Selecting Reactions and Reactants Using a Switchable Rotaxane Organocatalyst with Two Different Active Sites. *Chem. Sci.* **2015**, *6* (1), 140–143. https://doi.org/10.1039/C4SC03279A.
(24) Green, S. A.; Montgomery, H. R.; Benton, T. R.; Chan, N. J.; Nelson, H. M. Regulating Transition-Metal Catalysis through Interference by Short RNAs. *Angew. Chem. Int. Ed.* **2019**, *58* (46), 16400–16404. https://doi.org/10.1002/anie.201905333.
(25) Pimentel, E. B.; Peters-Clarke, T. M.; Coon, J. J.; Martell, J. D. DNA-Scaffolded Synergistic Catalysis. *J. Am. Chem. Soc.* **2021**, *143* (50), 21402–21409. https://doi.org/10.1021/jacs.1c10757.
(26) Acosta-Calle, S.; Miller, A. J. M. Tunable and Switchable Catalysis Enabled by Cation-Controlled Gating with Crown Ether Ligands. *Acc. Chem. Res.* **2023**, *56* (8), 971–981. https://doi.org/10.1021/acs.accounts.3c00056.
(27) Yoo, C.; Dodge, H. M.; Miller, A. J. M. Cation-Controlled Catalysis with Crown Ether-Containing Transition Metal Complexes. *Chem. Commun.* **2019**, *55* (35), 5047–5059. https://doi.org/10.1039/C9CC00803A.
(28) Kita, M. R.; Miller, A. J. M. An Ion-Responsive Pincer-Crown Ether Catalyst System for Rapid and Switchable Olefin Isomerization. *Angew. Chem. Int. Ed.* **2017**, *56* (20), 5498–5502. https://doi.org/10.1002/anie.201701006.
(29) Camp, A. M.; Kita, M. R.; Blackburn, P. T.; Dodge, H. M.; Chen, C.-H.; Miller, A. J. M. Selecting Double Bond Positions with a Single Cation-Responsive Iridium Olefin Isomerization Catalyst. *J. Am. Chem. Soc.* **2021**, *143* (7), 2792–2800. https://doi.org/10.1021/jacs.0c11601.
(30) Farquhar, A. H.; Gardner, K. E.; Acosta-Calle, S.; Camp, A. M.; Chen, C.-H.; Miller, A. J. M. Cation-Controlled Olefin Isomerization Catalysis with Palladium Pincer Complexes. *Organometallics* **2022**, *41* (22), 3366–3372. https://doi.org/10.1021/acs.organomet.2c00315.
(31) Smith, J. B.; Miller, A. J. M. Connecting Neutral and Cationic Pathways in Nickel-Catalyzed Insertion of Benzaldehyde into a C–H Bond of Acetonitrile. *Organometallics* **2015**, *34* (19), 4669–4677. https://doi.org/10.1021/acs.organomet.5b00405.
(32) Lifschitz, A. M.; Rosen, M. S.; McGuirk, C. M.; Mirkin, C. A. Allosteric Supramolecular Coordination Constructs. *J. Am. Chem. Soc.* **2015**, *137* (23), 7252–7261. https://doi.org/10.1021/jacs.5b01054.
(33) Smith, J. B.; Kerr, S. H.; White, P. S.; Miller, A. J. M. Thermodynamic Studies of Cation–Macrocycle Interactions in Nickel Pincer–Crown Ether Complexes Enable Switchable

Ligation. *Organometallics* **2017**, *36* (16), 3094–3103. https://doi.org/10.1021/acs.organomet.7b00431.
(34) Smith, J. B.; Camp, A. M.; Farquhar, A. H.; Kerr, S. H.; Chen, C.-H.; Miller, A. J. M. Organometallic Elaboration as a Strategy for Tuning the Supramolecular Characteristics of Aza-Crown Ethers. *Organometallics* **2019**, *38* (22), 4392–4398. https://doi.org/10.1021/acs.organomet.9b00462.
(35) Arunan, E.; Desiraju, G. R.; Klein, R. A.; Sadlej, J.; Scheiner, S.; Alkorta, I.; Clary, D. C.; Crabtree, R. H.; Dannenberg, J. J.; Hobza, P.; Kjaergaard, H. G.; Legon, A. C.; Mennucci, B.; Nesbitt, D. J. Definition of the Hydrogen Bond (IUPAC Recommendations 2011). *Pure Appl. Chem.* **2011**, *83* (8), 1637–1641. https://doi.org/10.1351/PAC-REC-10-01-02.
(36) Colquhoun, H. M.; Lewis, D. F.; Stoddart, J. F.; Williams, D. J. Crown Ethers as Second-Sphere Ligands. The Interactions of Transition-Metal Ammines with 18-Crown-6 and Dibenzo-18-Crown-6. *J. Chem. Soc. Dalton Trans.* **1983**, 607–613.
(37) Colquhoun, H. M.; Stoddart, J. F.; Williams, D. J. Second-Sphere Coordination–a Novel Role for Molecular Receptors. *Angew. Chem. Int. Ed. Engl.* **1986**, *25* (6), 487–507. https://doi.org/10.1002/anie.198604873.
(38) Raymo, F. M.; Stoddart, J. F. Second-Sphere Coordination. *Chem. Ber.* **1996**, *129* (9), 981–990. https://doi.org/10.1002/cber.19961290902.
(39) Akutagawa, T.; Takamatsu, N.; Hasegawa, T.; Nakamura, T.; Inabe, T. Crystal Structure and Magnestism of [Ni(Dmit) 2] − Salts With Supramolecular Cations of M + (15-Crown-5). *Mol. Cryst. Liq. Cryst.* **2002**, *376* (1), 39–46. https://doi.org/10.1080/10587250210736.
(40) Kita, M. R.; Miller, A. J. M. Cation-Modulated Reactivity of Iridium Hydride Pincer-Crown Ether Complexes. *J. Am. Chem. Soc.* **2014**, *136* (41), 14519–14529. https://doi.org/10.1021/ja507324s.
(41) Gu, N. X.; Oyala, P. H.; Peters, J. C. Hydrazine Formation via Coupling of a Nickel(III)–NH $_2$ Radical. *Angew. Chem. Int. Ed.* **2021**, *60* (8), 4009–4013. https://doi.org/10.1002/anie.202013119.
(42) Dunn, P. L.; Cook, B. J.; Johnson, S. I.; Appel, A. M.; Bullock, R. M. Oxidation of Ammonia with Molecular Complexes. *J. Am. Chem. Soc.* **2020**, *142* (42), 17845–17858. https://doi.org/10.1021/jacs.0c08269.
(43) Fielding, L. Determination of Association Constants (Ka) from Solution NMR Data. *Tetrahedron* **2000**, *56* (34), 6151–6170. https://doi.org/10.1016/S0040-4020(00)00492-0.
(44) Thordarson, P. Determining Association Constants from Titration Experiments in Supramolecular Chemistry. *Chem Soc Rev* **2011**, *40* (3), 1305–1323. https://doi.org/10.1039/C0CS00062K.
(45) Fadini, L.; Togni, A. Asymmetric Hydroamination of Acrylonitrile Derivatives Catalyzed by Ni(II)-Complexes. *Tetrahedron Asymmetry* **2008**, *19* (22), 2555–2562. https://doi.org/10.1016/j.tetasy.2008.11.010.
(46) Mitsudo, K.; Imura, T.; Yamaguchi, T.; Tanaka, H. Preparation of a Cationic Bisoxazolinic Nickel Pincer Catalyst and Its Applications to Michael Addition and Mizoroki–Heck Reaction. *Tetrahedron Lett.* **2008**, *49* (51), 7287–7289. https://doi.org/10.1016/j.tetlet.2008.10.029.
(47) Castonguay, A.; Spasyuk, D. M.; Madern, N.; Beauchamp, A. L.; Zargarian, D. Regioselective Hydroamination of Acrylonitrile Catalyzed by Cationic Pincer Complexes of Nickel(II). *Organometallics* **2009**, *28* (7), 2134–2141. https://doi.org/10.1021/om800840u.

(48) Meng, J.; Chang, F.; Su, Y.; Liu, R.; Cheng, T.; Liu, G. Switchable Catalysts Used To Control Suzuki Cross-Coupling and Aza–Michael Addition/Asymmetric Transfer Hydrogenation Cascade Reactions. *ACS Catal.* **2019**, *9* (9), 8693–8701. https://doi.org/10.1021/acscatal.9b01593.
(49) Miao, X.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H.; Dubois, J.-L.; Couturier, J.-L. Tandem Catalytic Acrylonitrile Cross-Metathesis and Hydrogenation of Nitriles with Ruthenium Catalysts: Direct Access to Linear α,ω-Aminoesters from Renewables. *ChemSusChem* **2012**, *5* (8), 1410–1414. https://doi.org/10.1002/cssc.201200086.
(50) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. Concurrent Tandem Catalysis. *Chem. Rev.* **2005**, *105* (3), 1001–1020. https://doi.org/10.1021/cr020018n.