Condensation of nitriles with amides promoted by coordinatively unsaturated bis-nickel(II)-hydroxy complex: a new route to alkyl- and aryl-imidoylamidines†

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A pentacoordinate bis(μ-hydroxy) nickel dimer promotes formation of alkyl- and aryl-imidoylamidines from nitriles and ureas or amides under mild conditions.

Reactions of metal-coordinated nitriles with nucleophiles and electrophiles,[1] as well as radicals or their precursors,[2] are gaining popularity as mild methods of making C–N, C–O, C–S, and C–C bonds. Incorporation of additional nitrogen atoms into nitrile-derived molecules can be easily performed in metal-assisted reactions with ammonia or amines, affording amidines.[1] Reactions of nitriles with significantly less nucleophilic amides appear to be unknown, though the synthetic product is easily obtained by other means, *i.e.* the reaction of amidines with imidoyl chlorides.[3] On the other hand, activation of amides and related molecules (especially urea) with biomimetic metallocomplexes has attracted much attention; the goal of understanding and mimicking catalytic hydrolysis of amides and ureas in biology has driven this field. Metal-bound hydroxide has proven efficient in many enzymes particularly urease,[4] which catalyzes the hydrolysis of urea (closely related to amides) into ammonia and carbon dioxide. Given that the partial hydrolysis product of nitriles are amides, reactions of nitriles with amides or ureas are certainly relevant to the study of self-condensation of nitriles. The complete hydrolysis of nitriles or of amides would generate ammonia, which can condense with two molecules of nitrile, generating imidoylamidines (IDAs).

Despite the well-ploughed fields of organonitrile activation chemistry,[1] amidine coordination chemistry,[5] and the acetylacetone (acac) analog nacnac,[6] the topic of metal complexation by IDAs has lacked attention, particularly aromatic IDAs, though they are attractive ligands for modification; the bridgehead nitrogen atom provides an additional potential route for tuning the electronic properties of the ligand relative to the similar acac. More versatile aromatic substituents offer several advantages for tuning the ligand environment, both sterically and electronically. Synthetic routes to aromatic IDAs have been known since 1952,[7,8] but known methods tend to require the preparation of moderately exotic precursors, such as lithiobenzamidine,[7] provide routes only to halogenated and N-substituted 1,3,5-triazapentadienes,[8] or suffer low yields.[9] A direct route to *in situ* formation of aromatic IDA metal complexes from a variety of nitrile substrates is therefore desirable.[10]

Nickel ions and compounds show promise in metal-promoted IDA syntheses,[11–13] but existing methods are limited. In 2001, we described a novel direct route to methyl IDA: the solvolysis of acetonitrile by a *tris*(2-picolyl)amine (TPA) bis(μ-hydroxo) nickel dimer.[11] The resulting *N*-(1-iminoethyl)-ethanimidamide nickel complex, formed *in situ* over a period of months at room temperature or days at 75 °C, incorporated three nitrogen atoms from CH_3CN in each bidentate ligand. Kukushin *et al*. reported a similar *in situ* formation of a series of alkyl or *p*-anisolyl IDA ligands by solvolysis of the corresponding nitriles, templated on nickel(II) perchlorate and mediated by acetoxime.[12] In 2006, McGaff *et al*. modified this procedure to generate *in situ* a series of aromatic IDA ligands, including derivatives of *p*-nitrobenzonitrile and *p*-trifluorotoluonitrile,[13] as well as derivatives of cyanopyridine substrates (a similar complex was described by Chen *et al*.[9]), formed not *via* solvolysis, but rather in methanol. *Via* this method, IDA complexes were formed without the addition of an oxime mediator or nickel-bound hydroxide, but attempts to generate IDAs from unsubstituted benzonitrile were unsuccessful.

We herein describe the results of applying our recently characterized coordinatively unsaturated $[(t\text{BuDPA})_2(\mu\text{-OH})_2\text{-Ni}_2](ClO_4)_2$ (*t*BuDPA = bis(2-pyridylmethyl)*tert*-butylamine) complex[14] (**1**), a 2Ni–2OH dimer structurally similar to the coordinatively saturated bis(μ-hydroxo) dimer supported by TPA.[11] Over a period of hours, at room temperature, this complex is converted to *t*BuDPA nickel(II) bis(imino(phenyl)-methyl)amide perchlorate (**3**), by way of a *t*BuDPA nickel(II) acetyl(imino(phenyl)methyl)amide perchlorate intermediate (**2**) (see Fig. 1).

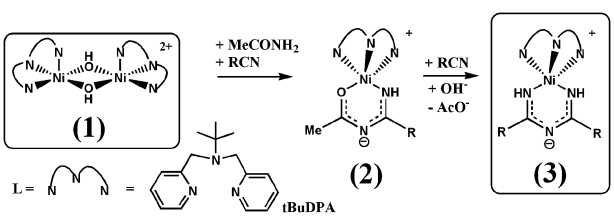

Fig. 1 Formation of **3** from **1**, nitriles, and amides. R = Me, Ph.

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† Electronic supplementary information (ESI) available: UV/Vis of **1** to **2** and **2** to **3**; CIF of **3** and crystallographic tabular materials; synthesis and characterization of **2** and **3**; ESI-MS results of ^{15}N isotopic labeling. CCDC 748549. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b919634j

The first step of condensation of nitriles with amides promoted by **1** is a clean and facile process. When **1** is dissolved in benzonitrile with one equivalent of acetamide per nickel in an argon atmosphere, the green solution turns purple within an hour at room temperature; the visible absorption band of the starting material **1** at 628 nm (ε = 16 cm^{-1} M^{-1} per nickel) disappears, and new absorption bands at 558 and 773 nm grow in. Very tight isosbestic points indicate the absence of other colored species in the course of the transformation of **1** into **2** (see ESI).†

ESI-MS of the purple intermediate **2** indicates that the 2Ni–2OH nickel dimer has been disrupted, leaving in its place a 1 : 1 Ni:*t*BuDPA complex, the base peak m/z = 474 of which suggests one acetamide molecule and one benzonitrile molecule have been incorporated into the coordination sphere of the nickel (the isotopic pattern supports this formulation). This suggests condensation of the acetamide and benzonitrile, with the resulting anion coordinated in bidentate fashion to the nickel(II) center, as indicated in Fig. 1. **2** can be precipitated out of solution by addition of diethyl ether, resulting in a stable purple solid precipitate, which when redissolved and examined by UV/Vis or ESI-MS corresponds to the original solution, which decomposes over time, preventing crystallization. IR of **2** is consistent with a bound amide moiety showing the absence of the characteristic O–H stretch of **1** at 3641 cm^{-1} and the presence of the carbonyl C=O stretch at 1668 cm^{-1}.

Overnight, **2** in benzonitrile solution gives way to an orange-brown product (see Fig. S1, ESI†), *t*BuDPA nickel(II) bis(imino(phenyl)methyl)amide perchlorate (**3**). The final product **3**, similarly observed by ESI-MS, is likewise a 1 : 1 Ni:*t*BuDPA complex, the base peak m/z = 535 of which implies a second benzonitrile molecule has replaced the acetyl group, creating a bidentate anionic IDA ligand. **3** remains stable in solution at ambient conditions for weeks, and can be isolated as analytically pure dark green solid.

The X-ray structure of **3**, shown in Fig. 2,[15] confirms this proposed formulation. In agreement with literature precedence[12,13] and ESI-MS, the cationic fragment shows a 1 : 1 Ni:*t*BuDPA complex with a *N*′-benzimidoyl-benzamidine ligand occupying the remainder of the nickel's coordination sphere. The nickel cation is located in a pentacoordinate environment; the central amine of the *t*BuDPA ligand is in a distorted axial position relative to the otherwise square-planar IDA and pyridyl nitrogens, resulting in a square-pyramidal geometry with an unusually long axial amine–Ni bond length of 2.539 Å. The equatorial Ni–N bond lengths are much shorter (1.836 to 1.930 Å), on par with the 1.900 Å average Ni–N bond length for square-planar nickel complexes with four chelating nitrogen atoms,[16] and which indicates a very strong equatorial ligand field. Despite this long Ni–N distance, the association between the nickel and the amine nitrogen appears to persist in solution, as room-temperature magnetometry of solid **3** (μ = 3.2 BM) and NMR studies of its solution confirm it is paramagnetic. The carbon–nitrogen bond lengths of the 1,3,5-triazapentadienate backbone are 1.316 and 1.347 Å, indicating significant delocalization of the negative charge.

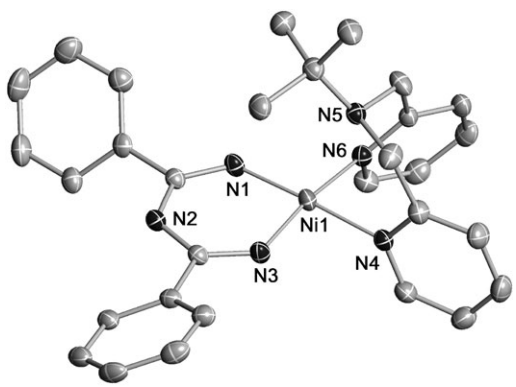

Fig. 2 The cationic fragment of **3**, with ellipsoids drawn at the 50% probability level. Hydrogens are omitted for clarity.

Mass spectrometry studies with ^{15}N-acetamide and unlabeled benzonitrile indicated that one nitrogen in each of **2** and **3** derives from acetamide (see ESI).† This overall stoichiometry corresponds to hydrolysis of the acetamide, generating a single molecule of ammonia which condenses with two molecules of nitrile. However, an assay using the indophenol method for determination of ammonia,[17] performed on a methanolic solution of **1** with two molar equivalents of acetamide, indicated no ammonia was formed. Therefore, coordinated nitriles are intimately involved in the process of ammonia abstraction from acetamide. Fig. 1 displays the starting materials, intermediates, and products we observed.

The conversion of **1** to **2** requires at least two transformations: formation of the imidoylamide intermediate species from its precursors, and breakup of the 2Ni–2OH dimer into mononuclear nickel complexes. The imidoylamide likely forms *via* nucleophilic attack on the cyano carbon of the (coordinated) nitrile by the amide nitrogen, possibly activated through partial deprotonation by bridging hydroxide in the dinickel complex. The order of these two steps, and whether they are sequential or simultaneous, is currently unknown. Aminolysis by a nickel–hydroxy dimer, resulting in elimination of water and formation of monomeric complex, has been described by López *et al.*,[18] and may play a role in the conversion of **1** to **2**. One possible pathway of formation of **3** from **2** includes hydrolysis of the imidoylamide species at the carbonyl carbon, generating acetate and a reactive amidine species which attacks a second nitrile molecule, resulting in the IDA species **3** (Fig. S5, ESI†). The mechanism of these reactions, which may include monomer–dimer equilibria, will be studied in due course.

This imidoylamidine formation reaction may be general; preliminary experiments confirm that both the nitrile and the amide reagents can be varied without loss of reactivity (Table S5, ESI†). The reaction scope in the nitrile component was tested by replacing benzonitrile (an aromatic nitrile) with the most common aliphatic nitrile, acetonitrile. An analogous reaction occurs, resulting ultimately in the formation of the same bis(acetimidoylacetamidine) nickel monomeric complex described by Kryatov[11] and others;[12,19] this has been confirmed by ESI-MS (m/z = 353) and single-crystal X-ray diffraction. Methyl analogs of **2** and **3** were observed by ESI-MS (m/z = 511 and 510, respectively), indicating the reaction proceeds through the same intermediates in both benzonitrile and acetonitrile. Mass spectrometry studies with d_3-acetonitrile

led to the analogs of **2** and **3** with molecular ion masses supporting incorporation of one and two deuterated acetonitrile molecules, respectively (m/z = 514 and 516).

Substitution of 1,1-dimethylurea for acetamide, under the same conditions, resulted in the formation of the appropriate dimethylamino derivative of **2**, and ultimately the same material **3**, observed by ESI-MS. This unusual result indicates that a combination of dinickel complex **1** and nitrile abstracts ammonia from dimethylurea and inserts a nitrogen atom in the IDA product. This is a remarkable transformation, given the high resonance stabilization of urea and substituted ureas. Although the enzyme urease readily catalyzes the hydrolysis of urea and substituted ureas, synthetic model complexes of urease rarely split urea,[20] and extant models show reactivity only at elevated temperature,[17,21] while we observe facile room-temperature transformation.

In conclusion, we have demonstrated a novel methodology for the generation of iminoamide and IDA nickel complexes from solvent acetonitrile or benzonitrile at room temperature and over a short period of time. This new reaction is promoted by a coordinatively unsaturated dinickel(II) bis-hydroxy-bridged complex tBuDPA$_2$(μ-OH)$_2$Ni$_2$(ClO$_4$)$_2$, a structural model of the active site of urease enzyme, and appears generalizable to a variety of nitriles, including aliphatic nitriles and aromatic nitriles lacking an electron-withdrawing group in the *para* position to the cyano group. Use of 1,1-dimethylurea as an alternative to acetamide indicates the reaction may be further generalizable with other amides, and even resonance-stabilized, resistant to hydrolysis ureas are activated by bis-hydroxo-bridged dinickel complex **1**. Further research on identifying the potential parameters of this chemistry, and clarifying the reaction mechanism, is underway.

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