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Catalytic Hydration of Benzonitrile and Acetonitrile using Nickel(0)

Marco G. Crestani, Alma Arévalo, Juventino J. García*

Facultad de Química, Universidad Nacional Autónoma de México, México, D.F. 04510, México
Phone: (+52)-555-622-3514, e-mail: juvent@servidor.unam.mx

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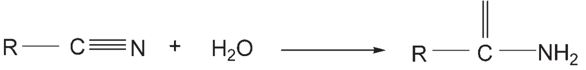
Abstract: The homogeneous catalytic hydration of benzo- and acetonitrile under thermal conditions was achieved using nickel(0) compounds of the type $[(\text{dippe})\text{Ni}(\eta^2\text{-NCR})]$ with R = phenyl or methyl (compounds **1** and **2**, respectively), as the specific starting intermediates. Alternatively, the complexes may be prepared *in situ* by direct reaction of the precursor $[(\text{dippe})\text{NiH}]_2$ (**3**) with the respective nitrile. Hydration appears to occur homogeneously, as tested by mercury drop experiments, producing benzamide and acetamide, respectively. Addition of Bu_4NI did not lead to catalysis inhibition, suggesting the prevalence of Ni(0) intermediates during catalysis. Hydration using analogous complexes of **3**, such as $[(\text{dtbpe})\text{NiH}]_2$ (**4**) and $[(\text{dcype})\text{NiH}]_2$ (**5**) was also addressed.

Keywords: amides; homogeneous catalysis; hydration; nickel; nitriles

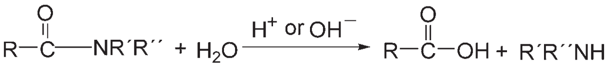
Introduction

The direct hydration (or hydrolysis, which is often used as a synonym) of nitriles to access amides [Eq. (1)] is a very important transformation both on the laboratory scale and in industry.[1]



$$R-C\equiv N + H_2O \longrightarrow R-\overset{\overset{\displaystyle O}{\|}}{C}-NH_2 \quad (1)$$

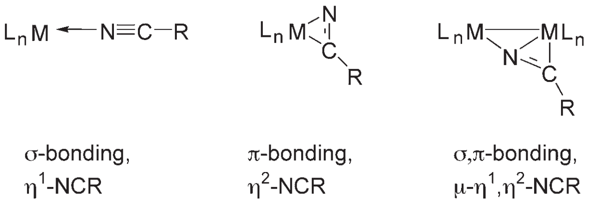
Amides exhibit a quite broad range of industrial applications (foam boosting and stabilization, emulsification, detergency, viscosity modification, lubricity, antistatic properties, corrosion inhibition, wetting, etc.),[2] and as such, the search for reagent systems that perform this conversion selectively and efficiently, under mild conditions, continues to be a challenge. Moreover, amides in general constitute excellent intermediates and raw materials for synthetic organic chemistry.[3] In particular, the lability of the amide C–N bond accounts for its fast hydrolysis under basic or acid catalysts,[4] regenerating the parent carboxylic acid and an amine, if the amide is *N*-substituted, or ammonia if it is not [Eq. (2)].[3]



$$R-\overset{\overset{\displaystyle O}{\|}}{C}-NR'R'' + H_2O \xrightarrow{H^+ \text{ or } OH^-} R-\overset{\overset{\displaystyle O}{\|}}{C}-OH + R'R''NH \quad (2)$$

R′, R′′ = alkyl, aryl or H

In fact, the fast hydrolysis of the amide function under these conditions appears as a disadvantage when the preparation of amides by direct hydration of nitriles is intended. Still, a number of procedures for stopping at the amide stage have been reported; these being, for example, the use of concentrated H_2SO_4, acetic acid and BF_3, H_2O_2 and OH^-, two equivalents of chlorotrimethylsilane followed by H_2O, heating on neutral alumina, Oxone® and the use of different metallic ions.[5] More recently, an efficient single-step, indirect, acid-catalyzed hydration of both aliphatic and aromatic nitriles, into the corresponding amides, using TFA-H_2SO_4 or AcOH-H_2SO_4 mixtures, was also published.[6] However, from the industrial point of view, the acid- or base-catalyzed reactions also suffer from the general restriction, apart from selectivity and yield, that the final neutralization of either base or acid, leads to an extensive salt formation with inconvenient product contamination and pollution effects.[1] In this context, a variety of homogeneous transition metal-based catalysts using Pd,[7] Pt,[8] Co,[4,9] Rh,[10] Ir,[11] Ru[12] and Mo,[13] as well as heterogeneous[14] and enzymatic[15] hydrolyses, among others,[16] have been reported. In all these cases, the catalytic conversions of nitriles to amides have been regarded to occur through an initial η^1-coordination of the terminal nitrogen in the nitrile function to the metal center (end-on coordination), prior to the nucleophilic attack of a hydroxide ion and further protonation of the nitrogen atom to give the respective amides.[7a,8a, e,f,13b] Similarly, in the stoichiometric cases of nitrile hydration in which amide complexes are ultimately formed, the same kind of end-on coordination is also found; in this light end-on coordination of the nitrile may appear as a general feature, ultimately leading to its hydrolysis, in aqueous media.[1] This is important considering that nitriles can interact with metal centers in two more ways, other than the terminal σ-bonded, η^1-NCR mode already mentioned, namely the π-bonded (side-on), or η^2-NCR coordination, and the bridging σ,π-bonded, μ-η^1,η^2-NCR coordination, often found in clusters (Scheme 1).[17] A relevant series of tungsten-nitrile complexes, showing either σ- or π-bonding, has been recently reported by Templeton's group.[18]



Scheme 1. σ-, π- and σ,π-modes of coordination of nitriles.[17]

In this context, our group has also published a series of reports regarding the activation of aryl, heteroaryl and alkyl cyanides using the nickel(0) fragment [(dippe)Ni], that yield π-bonded η^2-NCR complexes, such as [(dippe)Ni(η^2-NCR)] (R = phenyl or methyl; **1** and **2**), respectively.[19] In the cases of aryl and heteroaryl cyanides, oxidative addition of the C–CN bond of the nitrile to the nickel(0) proceeds with a mild warming, forming the corresponding nickel(II) complexes.[19b, c] In the case of the alkyl cyanides, such an oxidative addition is strongly dependent on the chain length and eventually can be inhibited.[19a] As part of our ongoing studies in this field, we decided to extend the chemistry of some of the nickel(0) nitrile complexes in order to investigate their reactivity towards nucleophilic substitution which, in the case of the nitrile hydration process, is accompanied by the presence of water. The fact that one starts from π-bonded η^2-NCR complexes[20] raises questions regarding the feasibility of such a hydration, considering the large number of reports that imply the necessity for η^1-NCR coordination. We report herein that hydration was achieved under catalytic conditions by a nickel(0) system, using the η^2-NCR coordination. To the best of our knowledge, only a few stoichiometric examples of the hydration process exist with this metal, all of which exhibit η^1-NCR coordination.[21] In this instance, the use of nickel-catalyzed transformations – hereby exemplified in the case of nitrile hydrations – results in added value, as nickel is inexpensive and presents environmental advantages over other metals, namely those in the same group.[22]

Results and Discussion

Catalysis of Nitrile Hydration

The catalytic hydration of benzo- and acetonitrile was selectively achieved by heating aqueous solutions of the corresponding nitriles, at temperatures ranging from 140 to 180 °C, in the presence of mononuclear nickel(0), [(dippe)Ni], moieties, which initially bind the nitrile substrates in the η^2-mode that is typical for these Ni(0) complexes.[19] Hydration catalysis for both nitrile substrates appears to occur homogeneously, as confirmed by mercury drop experiments performed for each;[23] the catalytic hydrations likely occurring through neutral intermediates, of which the [(dippe)Ni(η^2-NCR)] complex is probably the first. The prevalence of such an η^2-coordinated nitrile complex in aqueous media was verified for both **1** and **2**, by ^{31}P{^{1}H} NMR spectroscopy of these complexes in D_2O solution. The ^{31}P{^{1}H} NMR spectrum in both cases exhibits two broad asymmetric doublets, characteristic of two types of phosphorus environments, with resonances at $\delta = 79.25$ and 67.25 and $^2J_{P,P}$ coupling constants of 68 Hz in the case of **1** and resonances at $\delta = 82.18$ and 66.78 with $^2J_{P,P}$ coupling constants of 77 Hz in the case of **2**; which are consistent with the reported values for these Ni(0) complexes.[19] The results are important since they demonstrate that the oxidation state of the nickel center remains apparently unchanged in water media; a fact that was also verified during hydration catalysis of both benzo- and acetonitrile, as no inhibition of the catalytic processes was found to occur in the presence of the non-coordinating iodide salt, tetrabutylammonium iodide (Bu_4NI). Inhibition of the catalytic processes is expected to occur if the metal center is oxidized at some point of the catalytic cycle which, in these cases, would have been attributed to the formation of the nickel(II) iodide compounds derived from the poisoning of the [(dippe)Ni(η^2-NCR)] catalyst by reaction with Bu_4NI, but which did not happened. In this context, a similar experiment performed by Ghaffar and Parkins,[8a] the addition of potassium iodide to a preheated solution of the neutral [$PtH(PMe_2OH)(PMe_2O)_2H$], in a mixture of acrylonitrile, water and ethanol, has validated the existence of a cationic species responsible for the respective nitrile hydration catalysis, this being presumably [$Pt(S)(PMe_2OH)(PMe_2O)_2H$]$^+$, with S = solvating molecule. Catalysis was stopped after addition of the potassium salt, due to the poisoning of the cationic catalyst and could be restarted after further addition of silver tetrafluoroborate. In Parkins' catalysis example (see Figure 1, in ref.[8a]), the nitrile substrate is coordinated in a η^1-mode to the platinum(II) center of the catalyst, through the terminal nitrogen. The nitrile is proposed to undergo an intramolecular nucleophilic attack of the PMe_2OH hydroxy placed in an armchair position in *cis*-coordination,[24] leading to an oxo-bound, five-membered ring imide complex which, after *dihydro-oxo-biaddition of a water molecule* at the unsaturated C=N bond of the imide ligand, produces the final oxo-bound hydroxy-carbamide complex. Metathesis of the oxo substituent for hydroxy at the PMe_2 armchair ligand would be likely to assist the decoordination of the amide and the regeneration of the catalyst, completing the catalytic cycle.[8a]

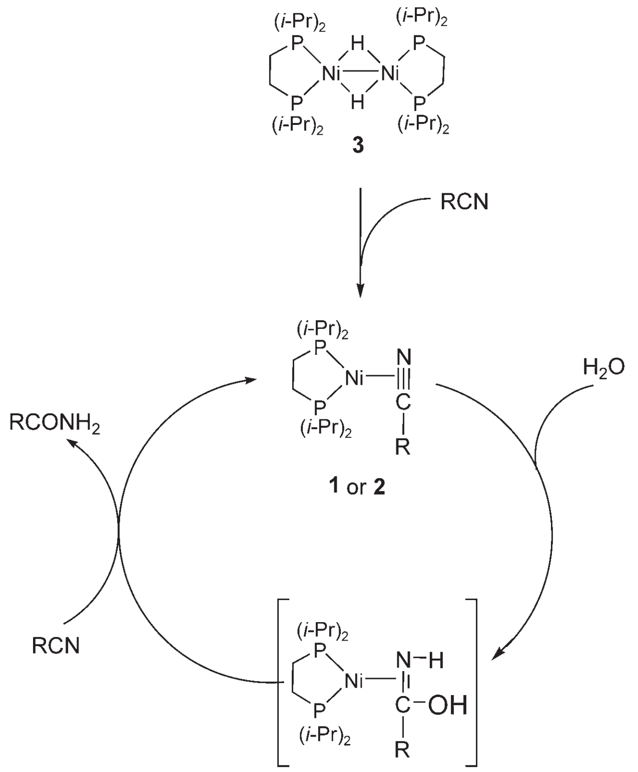
A closely related example of catalytic nitrile hydration proceeding through direct hydroxo nucleophilic attack over η^1-NCR coordinated nitrile to the molybdenum(IV) complex $[(Me\text{-}Cp)_2Mo(\eta^1\text{-}NCR)(OH)]^+$, has also been reported by Tyler's group.[13b] However, direct intramolecular nucleophilic attack of hydroxo-metal bound ligands, over η^1-coordinated nitriles does not seem to be the sole mechanism available for this process to occur. In fact, an intermolecular alternative in which a palladium(II) coordinated hydroxy ligand may interact with a water molecule from the bulk, through a general base catalysis assisting for the nitrile hydration, has also been proposed by Kaminskaia and Kostic.[7a] In this work, the kinetics for the catalytic hydration of various nitriles using palladium(II) aqua complexes were also studied. At a pK_a value of 5.1 ± 0.1 in D_2O, the aqua coordinated Pd(II) complexes may undergo deprotonation, forming the corresponding hydroxo complexes, which are somewhat better catalysts for the nitrile hydration reaction than the aqua precursors; the hydroxo ligand being a stronger nucleophile and general base than the aqua ligand. Kinetic experiments, however, could not distinguish between the aqua ligand-assisted hydration (intramolecular) and the hydroxo general base catalysis (intermolecular), therefore not ruling out either of these.[7a] A final example of nitrile hydration in basic media, reported by Jensen and Trogler in 1986, does seem to favor intermolecular nucleophilic attack of bulk hydroxide ions over platinum(II) η^1-coordinated nitriles.[8e] In all these examples, the high oxidation state of the metal centers determines the preference for η^1-coordination of the nitriles.

Contrasting with the latter information, the hydrations of acetonitrile and benzonitrile in the present work seem to occur directly over Ni(0) complexes exhibiting η^2-coordination; a conclusion that is drawn from the fact that no inhibition of the catalytic cycle of nitrile hydration was observed in the presence of Bu_4NI, as mentioned above. This result can be interpreted under the premise of the nickel center maintaining the same reduced oxidation state during catalysis and, therefore, the same nitrile coordination mode. A change in the oxidation state of the nickel center during the respective hydrations would imply a shift in the coordination mode of the nitriles, likely to acquire the η^1-mode. If so, a hydration mechanism probably proceeding through Ni(II) intermediates, either through direct aqua ligand interaction {e.g., the formation of $[(dippe)Ni(\eta^1\text{-}NCR)(H)(OH)]$, by oxidative addition of water} or through an alternative general base catalysis {for example, by *in situ* formation of square planar $[(dippe)Ni(\eta^1\text{-}NCR)(OH)]^+$ species}, by analogy to the examples by Parkins,[8a] Kostic,[7a] and Tyler[13b] would be expected. However, this is does not seem to be the case. Therefore, the amide formation is expected to occur through direct dihydro-oxo-biaddition (in this case, *N,N*-dihydro-*C*-oxo-biaddition[5a]) of a water molecule to the unsaturated CN bond of a η^2-coordinated nitrile, in a similar way as it occurs over the five-membered ring imide intermediate in Ghaffar and Parkins' mechanism, as mentioned above.[8a] Other examples of dihydro-oxo-biaddition of water to unsaturated bonds such as the triple bonds in alkynes, in the presence of mercuric ions with the corresponding production of ketones, have also been reported [Eq. (3)].[25]

$$-C\equiv C- \;+\; H_2O \xrightarrow{HgSO_4} -\overset{H}{\underset{H}{C}}-\underset{O}{\overset{\|}{C}}- \qquad (3)$$

The first step of the mechanism of alkyne hydration involves the formation of a mercuric complex $[Hg(\eta^2\text{-}C,C\text{-alkyne})]^{2+}$, which is then attacked by bulk water in an S_N2-type process to give a water-bound adduct that is rearranged into an enol. Further tautomerism of the organic function enables the final formation of the respective ketone.[25] By analogy with this mechanism, *N,N*-dihydro-*C*-oxo-biaddition[5a] of water molecules may also be expected to occur over the $[(P\text{-}P)Ni(\eta^2\text{-}N,C\text{-nitrile})]$ complexes, with the corresponding formation of the water adducts that further rearrange into *N*-protonated hydroxy imine complexes. Tautomerism of the coordinated imines would produce, in every case, saturated C–N amide bonds[26] which are likely to be readily decoordinated from the nickel(0) center, giving free amides as the overall products of catalysis and the regeneration of the starting nickel(0) catalyst species, $[(dippe)Ni(\eta^2\text{-}NCR)]$ (Scheme 2).

Several attempts were performed for the follow-up of the reaction under pseudo-order conditions at different nitrile-to-water molar proportions, temperatures ranging from 80 to 160 °C and a number of solvents (THF-d_8, toluene-d_8 and dioxane-d_8), all of which confirm the stability of the $[(dippe)Ni(\eta^2\text{-}NCR)]$ complexes in the presence of water, which had already been corroborated in D_2O. The imine intermediate, however, proved to be highly elusive and we were unable to properly establish its formation. at least on the NMR time scale, our experiments concluding with mixtures of the starting **1** or **2** complexes and the respective free organics, either reactants or products. Interestingly, when heating was performed at a less than 50 water-to-$[(dippe)Ni(\eta^2\text{-}NCR)]$ mol proportion, the formation of C–CN oxidative addition products of the type $[(dippe)Ni(R)(CN)]$,[19a] which



Scheme 2. Suggested mechanism for the hydration of nitriles by the Ni(0)-phosphine catalyst [(dippe)Ni(η^2–NCR)].

are rather unlikely to lead to the amides, was verified. This result is consistent with further observations in catalysis, which show that the turnover number and frequency of catalysis are increased when the water-to-[(dippe)Ni(η^2-NCR)] mol proportion is increased (*vide infra*); thus it proves that the presence of water acts to quench the C–CN oxidative addition reactions and therefore increases the efficiency of the nickel(0) catalyst.

Hydration Catalysis in Neutral Conditions and in the Presence of Added Base: Evaluation of Catalysis Efficiency

Since *N*,*N*-dihydro-*C*-oxo-biaddition[5] of water to the unsaturated CN bond of the coordinated nitriles is expected to occur through a concerted S_N2 mechanism, by analogy with the alkyne hydration reaction,[25] an experiment adding a source of hydroxide (NaOH solution at pH = 10) to a benzonitrile/[(dippe)NiH]$_2$ mixture was performed and the turnover frequency (TOF) of hydration compared to the respective hydration using neutral water, under otherwise the same conditions {180 °C, 0.04 mole percent of [(dippe)Ni(η^2-NCPh)] and 20% water volume}. A smaller value in the hydration TOF under excess free hydroxide would imply a rate-limiting step at the proton transfer at the imine intermediate, prior to the amide formation and, in fact, deuterium-labeling experiments performed by Jensen and Trogler have verified that rapid proton transfer from the solvent presents itself as a limiting condition for the catalytic hydration to occur.[8e] From this publication it follows that the TOF in the hydration experiment under neutral conditions would be expected to be higher, due to the equimolarity of protons and hydroxide ions: the initial and final pH of the aqueous phase in all experiments was always measured during this work and no significant variations of pH were observed in any of the experiments starting with neutral water. The TON found for the added base experiment was 354, with a TOF of 5 cycles per hour; while the TON found for the neutral pH experiment was 984, with a TOF of 14 cycles per hour; the final pH value of the aqueous phase in the added base experiment had lowered to a value of 7, thus confirming the fact that the added base had indeed been consumed during the hydration catalysis. However, the fact that the TOF value is significantly lower than the TOF under neutral conditions supports a rate-limiting proton transfer step and ,therefore, the premise of a concerted *N*,*N*-dihydro-*C*-oxo-biaddition to the nickel(0) bound CN bond is reasonable.

Catalytic Hydration of Benzonitrile using [(dtbpe)NiH]$_2$ (4) and [(dcype)NiH]$_2$ (5): Effect of Steric Hindrance of the Phosphine Ligands on the Catalysis

Alternatively to the catalytic hydration of benzonitrile using [(dippe)NiH]$_2$ (**3**), the hydration of this substrate was also attempted using [(dtbpe)NiH]$_2$ (**4**) and [(dcype)NiH]$_2$ (**5**) under the conditions found for highest efficiency and yield using complex **3** {180 °C, 0.04 mole percent of [(dippe)Ni(η^2-NCPh)] and 20% water volume under neutral conditions; TON = 984 and TOF of 14 cycles per hour}. A yield of 23% of benzamide was obtained with the use of complex **4**, with a TON of 651 and a TOF of 9 cycles per hour, calculated against the formal mole amount of the respective [(dtbpe)Ni(η^2-NCPh)] catalyst species, while complex **5** produced benzamide in 17% yield, with a TON of 467 and a TOF of 6 cycles per hour {also calculated with respect to the mole amount of [(dcype)Ni(η^2-NCPh)]}. The results in terms of TOF are illustrated in Figure 1.

The results depict a decreasing trend in the hydration rate as the alkyl substituents on the phosphine ligands become bulkier. The results are consistent with Jensen and Trogler's observation regarding the steric bulk of the substituents,[8e] since increased steric hindrance lowers the probability of effective substrate binding to the catalyst metal center and, due to their alkyl nature, these may also increase the hydrophobicity of the entire catalyst, therefore reducing the catalysis rate. The hydro-

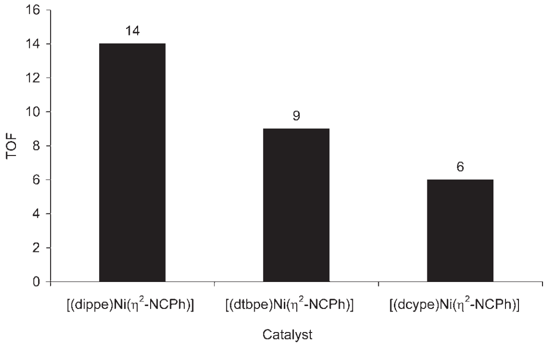


Figure 1. Activity of [(P-P)Ni(η^2-NCPh)] catalysts in cycles per hour, relative to benzonitrile hydration.

phobicity of alkyl substituents such as isopropyl and ethyl in platinum catalysts has also been commented by Yoshida's group in an early publication.[8f]

Optimization of the Hydration Catalysis using [(dippe)Ni(η^2-NCR)]

As mentioned earlier in the text, the hydration of benzo- and acetonitrile was achieved at a range of temperatures going from 140 to 180 °C; hydration attempts performed at lower temperatures were unsuccessful. The results for benzonitrile hydration on going from 140 to 180 °C are summarized in Table 1 and those of acetonitrile hydration are depicted in Table 2; the processes were optimized either in terms of activity, yield or both.

The results depicted show that at least in terms of temperature, catalysis efficiency is improved on going from 140 to 160 °C, when the catalyst percent is the same and the water volume percentage is kept constant at 90% (entries 1 and 2, Table 1, and entries 1 and 2, Table 2). Further concentrating the catalyst in the case of benzonitrile at 160 °C, however, did not give a large increase in the production of benzamide (14 to 40% yield), at the expense of a significant decrease in catalyst activity (TON = 360 to 40; entries 2 and 3, Table 1) and thus, the system was further heated to 180 °C. Yield and TON at 180 °C, at 1 mole percent both peaked with respect to former experiments at large water amounts (entry 4, Table 1); which were originally used in this work inspired from Tyler's nitrile hydration system employing a molybdenum catalyst.[13b] Decreasing both the catalyst concentration and the water volume percent were found to be useful in order to increase the catalyst efficiency (*vide infra*), which reached a TON value of 984 for benzonitrile hydration and 99 for acetonitrile; both systems using 0.04 mole percent of [(dippe)Ni(η^2-NCR)] and 20% water volume (entry 5, Table 1 and entry 3,Table 2, respectively). In the case of acetonitrile, further pressurizing the system with 100 psi of argon, to avoid acetonitrile evaporation, led to an improved catalysis of 257 turnovers (entry 4, Table 2); which is actually invariant upon additional pressure over 100 psi, since further pressurizing the autoclave to 500 psi did not produce an additional improvement (entry 5, Table 2) and therefore implying that 100 psi is already a large enough pressure.

The latter results contrast with the hydration temperatures ($T < 100$ °C) and the corresponding activities found with some palladium and platinum catalysts, which are intrinsically more nucleophilic metal centers {TON for acetonitrile hydration = 34.9 using [*trans*-PtH(H_2O)(PEt_3)$_2$][OH];[8e] 89.2 using [*trans*-PtH(H_2O)(PMe_3)$_2$][OH];[8e] 369, using [PtH(PPh_2OH)(PPh_2O)$_2$H];[8a] 405, using Pt[P(*i*-Pr)$_3$]$_3$;[8f] 520, using Pt[P(*c*-C_6H_{11})$_3$]$_2$;[8f] 4000, using $LPd_2(CH_3CONH)$ with L = a binucleating ligand;[7b] and 5700 using [PtH(PMe_2OH)(PMe_2O)$_2$H][8a]}; the respective hydrations using the nickel(0) catalyst, [(dippe)Ni(η^2-NCMe)], require

Table 1. Catalytic hydration of benzonitrile.

Entry	T [°C]	Catalyst mole percent	Water volume [%]	TON	TOF [TON/h]	Yield [%]
1	140	0.04	90	148	2	6
2	160	0.04	90	372	5	14
3	160	1.00	90	40	1	40
4	180	1.00	90	67	1	68
5	180	0.04	20	984	14	41

Table 2. Catalytic hydration of acetonitrile.

Entry	T [°C]	Catalyst mole percent	Water volume [%]	Added argon pressure [psi]	TON	TOF [TON/h]	Yield [%]
1	140	0.04	90	–	17	0.2	1
2	160	0.04	90	–	68	1	3
3	180	0.04	20	–	99	1	4
4	180	0.04	20	100	257	4	10
5	180	0.04	20	500	257	4	10

a higher temperature, a fact that is also consistent with general observations regarding the catalytic activity of first row late-transition metals with respect to their respective group members.[27] However, the overall activity for benzonitrile hydration was in fact improved to over 1000 turnovers by proper tuning of the catalytic conditions, although for acetonitrile this number is significantly smaller (TON = 250 under argon pressure). This dramatic difference in activity, on going from the aryl to the alkyl nitrile could also imply differences in the thermal behavior of the coordinated nitrile complexes **1** and **2**; the alkyl nitrile complex **2** being more likely to undergo irreversible oxidative addition to the C−CN bond.[19a] If this were to occur under the reaction conditions to some extent, then it seems likely that the catalyst half life would be significantly reduced by formation of [(dippe)Ni(CN)(Me)].

Catalysis Optimization Based on Variation of the Water Volume Percentage

As depicted in Eq. (1), the process of nitrile hydration presumes an equimolar relationship between nitrile and water, such that the addition process would consume either reactants to the same extent. Under such a basis, questions are posed regarding the eventual insolubility of the catalysts and therefore a potential drawback in the overall yield and conversion efficiency, once the system has reached a certain stage of reactant consumption. To solve this, the use of unreactive additional solvents is a reasonable alternative that presents the additional possibility of achieving milder thermal conditions for the process and, indeed, this was attempted during the course of the present work, using THF as the solvent {180 °C, 0.04 mole percent of [(dippe)Ni(η^2-NCPh)] and 20% water volume, pH = 7 and 50 mL of THF}. However, catalysis under these conditions did not take place; quantitative thermal disproportionation of the nickel(0) catalyst to metallic nickel was detected after the reaction time. The result may be explained on the basis of a lack of quenching by water of the oxidative addition reactions, due to the higher solubility of the catalyst in the organic solvent.[28] Thus, variation of the proportion of nitrile and water substrates, using them as neat solvents, was therefore explored in an attempt to determine the highest catalyst efficiency conditions. Figure 2 shows the linear correlation of catalyst activity in terms of TON, found by varying the water volume percentage from 20 to 90%, with respect of benzonitrile, maintaining the same catalyst load and the temperature of the processes at 180 °C.

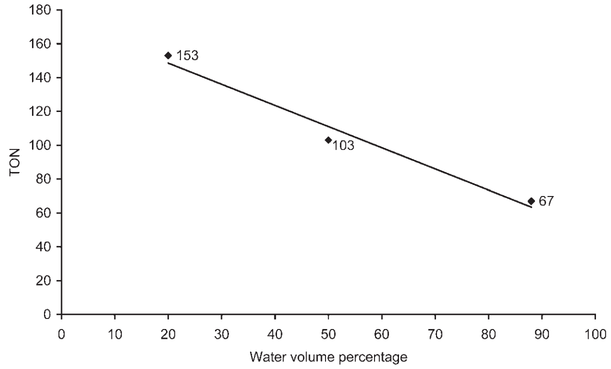


Figure 2. Activity of the [(dippe)Ni(η^2-NCPh)] catalyst towards benzonitrile hydration, with respect to water volume percentage.

As depicted, the catalyst activity drops when the amount of water is increased. From these results, it follows that hydration is best achieved at low water volume percentages. Incidentally, the lowest water volume percentage at which the catalyst exhibits the highest activity, corresponds in fact to the *equimolar benzonitrile-to-water* situation. Thus, hydration could not be further optimized in terms of substrate proportion variation, unless substoichiometric proportions were to be chosen. This, however, would require the water amount to be the limiting reactant, and since the activity of the catalyst is decreased whenever the water percentage is increased over the nitrile substrate; the use of such strategy for the optimization of the catalytic system would also lead to difficulties in maintaining the thermal stability of the [(dippe)Ni(η^2-NCPh)] catalyst at the temperature required for the process. Thus, a different alternative, employing a further diluted catalyst amount, was addressed at the low end of the water volume proportionality of 20%. In this instance, catalysis at this water volume, using the same total amount of nickel pre-catalyst [(dippe)NiH]$_2$ (80 mg), actually leads to a lower Ni(0) catalyst concentration, relative to the nitrile substrate (0.1 mole percent), *versus* that which results when the same total amount of nickel(0) is present in the 90% water volume mixture (1 mole percent). In this instance, Figure 3 shows the results on going from 0.1 mole percent [(dippe)Ni(η^2-NCPh)] to a further diluted 0.01 mole percent nickel(0) concentration.

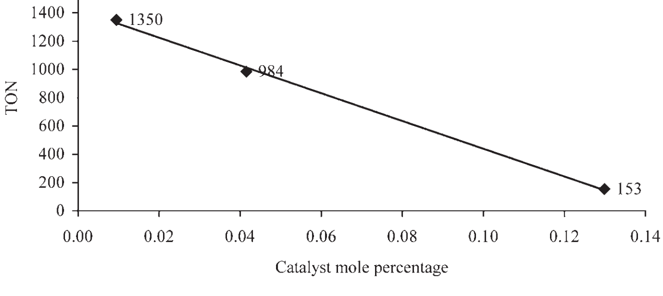


Figure 3. Activity of the [(dippe)Ni(η^2-NCPh)] catalyst towards benzonitrile hydration, with respect to catalyst mole percentage.

Figure 3 illustrates that the catalytic activity is indeed increased when the concentration of the catalyst is decreased to 0.01 mole percent, at the same water-to-nitrile volume proportionality of 20%. The yield at this situation, however, does not increase proportionally with the TON, at the same reaction time, 13% isolated yield of benzamide being obtained with the respective 0.01 catalyst mole percent, versus 41%, on using the 0.04 mole percent of the nickel(0) catalyst. As such, the 0.04 mole percent concentration of the nickel(0) catalyst was selected instead of the 0.01, this showing the best compromise between TON and yield. The low activity of the catalyst at high water concentrations or the otherwise similar conditions of high mole percent at constant water amount, concluded from these series of experiments, are useful in terms of a rationale regarding the close relationship that possibly exists between the hydrophobic nature of the catalyst and the water from the bulk, that paradoxically prevents the disproportionation of the former when the mixture is heated to 180 °C, but in excess water drastically reduces the hydration rate.

Conclusions

The catalytic hydration of benzo- and acetonitrile using nickel(0) catalysts of the type [(dippe)Ni(η^2-NCR)] was achieved under heating of the respective mixtures, optimized at 180 °C, *via* an *N*,*N*-dihydro-*C*-oxo-biaddition, using low catalyst loadings and low water content; the equimolar amount of nitrile and water being the most convenient proportion between the two substrates, at which the nickel(0) catalyst exhibits the highest efficiency for both hydration systems. Experiments are underway to further extend this chemistry to other nitriles.

Experimental Section

General Considerations

Unless otherwise noted, all manipulations were performed under an argon atmosphere in an MBraun glovebox (<1 ppm H_2O and O_2) or using standard Schlenk techniques. A 300-mL, stainless steel Parr® Series 4560 Bench Top Mini Reactor was used for all experiments of catalysis. Acetonitrile was purchased from J. T. Baker and benzonitrile was purchased from Aldrich. Both liquid substrates were reagent grade and were dried and distilled from calcium hydride (CaH_2) prior to their use;[29] the water used for all hydrations was distilled and purged with argon for at least 30 min before any experiment. All other solvents used were dried and distilled from sodium/benzophenone ketyl. Deuterated solvents for NMR experiments were purchased from Cambridge Isotope Laboratories and stored over 3 Å molecular sieves in the glovebox. The nickel(I) complex **3**, was prepared from Super-Hydride® and [(dippe)$NiCl_2$][30] suspended in hexane, similarly to the literature procedure.[31] Complexes **4** and **5**, also used in some additional hydration experiments, were prepared analogously, starting from [(dtbpe)$NiCl_2$] and [(dcype)$NiCl_2$]. All the complexes were purified by crystallization or column chromatography and their integrity was verified by the corresponding ^{1}H and ^{31}P{^{1}H} NMR spectra of all complexes, before their use. The chelating bisphosphine ligands, dippe[32] and dtbpe[33] were synthesized from 1,2-bis(dichlorophosphino)ethane (Strem) and the corresponding Grignard or lithium alkyls (Aldrich), and dcype was purchased from Strem. Neutral alumina used for the preparation of complexes **3**–**5**, was heated to 200 °C under vacuum for two days and stored in the glovebox. All other chemicals such as Bu_4NI (Aldrich) and filter aids were reagent grade and were used as received. The catalytic experiments were performed by *in situ* preparation of the nickel(0) complexes **1** or **2**, unless otherwise stated. Both complexes were prepared by reaction of [(dippe)NiH]$_2$ (**3**) with a neat solution of the corresponding nitrile, prior to the addition of water, similarly to the reported procedures.[19] The total amount of nitrile used was calculated on the basis of the mole percentage required for each experiment, relative to the corresponding nickel(0) catalyst, [(dippe)Ni(η^2-NCR)]. All catalytic mixtures were loaded in the reactor inside the glovebox. All the hydration products were recovered from the reactor washings in ethanol solution, filtered through a frit packed with alumina and dried in the vacuum line ($P<10^{-4}$ mmHg) for 4 hours, prior to their quantification or characterization; the latter of which, was made by direct comparison of the respective melting points,[34] ^{1}H and ^{13}C{^{1}H} NMR spectra with those of commercially available amides and literature reported values.[13b,35] The pH measurements were performed using a Corning® Scholar 425 pH meter. All NMR spectra of complexes and products in this work, were recorded at ambient temperature on a 300 MHz Varian Unity spectrometer. The ^{1}H, ^{31}P{^{1}H} NMR spectra of the complexes were obtained from concentrated solutions (30 mg) of the pure compounds in THF-d_8, unless otherwise stated, and all samples were handled under argon, using thin wall-0.38 mm-WILMAD® NMR tubes with J Young valves. ^{1}H and ^{13}C{^{1}H} NMR spectra of the hydration products were obtained either in $CDCl_3$ (benzamide) or $CDCl_3$ + DMSO-d_6 (acetamide). ^{1}H and ^{13}C{^{1}H} chemical shifts (δ, ppm) are reported relative to the residual proton resonance in the deuterated solvent and ^{31}P{^{1}H} NMR spectra are reported relative to external 85% H_3PO_4. Turnover numbers (TON) for the catalytic hydrations were calculated on the basis of mole of isolated product per mole of catalyst and respective turnover frequencies (TOF) are calculated as TON over reaction time, typically 72 h, unless otherwise specified. All argon used (Praxair) was supplied in high purity grade 99.998%.

Reaction of [(dippe)NiH]$_2$ (3) with Benzo- and Acetonitrile in D_2O: Stability of [(dippe)Ni(η^2-NCPh)] (1) and [(dippe)Ni(η^2-NCMe)] (2) in Aqueous Media

The stability of complex **1** and complex 2 in aqueous media was explored by addition of the respective nitrile (benzonitrile: 0.010 mL, 0.098 mmol, acetonitrile: 0.005 mL, 0.095 mmol) to a slurry of [(dippe)NiH]$_2$ (0.030 g, 0.046 mmol) in D_2O. Reactants were mixed at room temperature in the glovebox and the resulting mixture was led to react for 5 min under constant stirring with mild evolution of hydrogen gas, that was entirely vented out to the glovebox.

NMR spectra for **1** in D_2O: ^1H, $\delta = 0.87–2.22$ (dippe), 7,29–7.77 (phenyl); $^{31}P\{^1H\}$, $\delta = 79.25$ (br d, $^2J_{P,P} = 68$ Hz), 67.25 (br d, $^2J_{P,P} = 68$ Hz).

NMR spectra for **2** in D_2O: ^1H, $\delta = 1.01–1.25$ (m, 24H, CH_3), 1.5–1.65 (m, 4H, CH_2), 1.94–2.13 (m, 4H, CH), 2.42 (d, $^4J_{H,P} = 4.8$ Hz, 3H, CH_3CN); $^{31}P\{^1H\}$, $\delta = 82.18$ (br d, $^2J_{P,P} = 77$ Hz), 66.78 (br d, $^2J_{P,P} = 77$ Hz).

Similar results are obtained when **3** is dissolved in THF-d_8, toluene-d_8 or dioxane-d_8, in the presence of water and the corresponding nitrile.

Control Experiments: Attempted Nitrile Hydration in the Absence of Nickel(0) Catalysts

The reactor vessel was charged in separate runs with nitrile and water mixtures: 20 mL benzonitrile (0.20 mol) and 5 mL water (0.28 mol), or 20 mL acetonitrile (0.38 mol) and 9.5 mL water (0.53 mol), and these were heated at 180 °C under vigorous stirring for 72 h. No benzamide or acetamide was formed.

Attempted Inhibition of the Nitrile Hydration Processes in the Presence of Metallic Mercury: Proof of Homogeneity

The reactor vessel was charged in separate runs with $[(dippe)NiH]_2$ (0.026 g, 0.04 mmol), benzonitrile (20 mL, 0.20 mol) and water (5 mL, 0.28 mol) or $[(dippe)NiH]_2$ (0.05 g, 0.078 mmol), acetonitrile (20 mL, 0.38 mol) and water (5 mL, 0.28 mol) and 2 drops of elemental mercury were added to each mixture. Both mixtures were heated at 180 °C under vigorous stirring for 72 h, after which time the reactor vessel was left to cool down and opened in a hood prior to work-up. Yield of benzamide after work-up: 41% (9.7105 g, 0.080 mol), with a TON of 993 and a TOF of 14 cycles per hour. Yield of acetamide after work-up: 4% (1.0012 g, 0.017 mol), with a TON of 109 and a TOF of 2 cycles per hour. Both series of results are consistent with the values obtained in the absence of metallic mercury, at otherwise the same conditions. NMR spectra for acetamide in $CDCl_3$ + DMSO-d_6: ^1H, $\delta = 6.39$ (br s, NH), 5.8 (br s, NH), 1.76 (s, 3H, CH_3); $^{13}C\{^1H\}$, $\delta = 172.78$ (carbonyl), 22.23 (CH_3).

Catalytic Hydration of Benzonitrile using [(dippe)Ni(η^2-NCPh)] (1) Independently Prepared: Proof of Mononuclear Intermediates

The reactor vessel was charged in the glovebox with a mixture of [(dippe)Ni(η^2-NCPh)] prepared independently[19b, c] (0.1116 g, 0.26 mmol), benzonitrile (2.8 mL, 0.03 mol) and water (21 mL, 1.17 mol). The mixture was heated at 160 °C under vigorous stirring for 72 h, similarly to the procedure described above. Yield of benzamide after work-up: 39% (1.3022 g, 0.011 mol), with a TON of 41 and a TOF of 1 cycle per hour. The same result is obtained when 85 mg of $[(dippe)NiH]_2$ [0.13 mmol; yielding *in situ* 0.26 mmol of the nickel(0) catalyst] are used under the same conditions. NMR spectra for benzamide in $CDCl_3$: ^1H, $\delta = 7.8$ (d, $J = 6.89$ Hz, 2H, *o*-Ar), 7.51 (t, $J = 7.19$ Hz, 2H, *m*-Ar), 7.42 (t, $J = 7.19$ Hz, 1H, *p*-Ar), 6.13 (br s, NH), 3.13 (br s, NH); $^{13}C\{^1H\}$, $\delta = 170.28$ (carbonyl), 132.96 (ipso), 132.58 (*o*-Ar), 128.9 (*m*-Ar), 127.72 (*p*-Ar).

Attempted Inhibition of the Nitrile Hydration Processes in the Presence of Bu_4NI: Proof of Neutral intermediates

The reactor vessel was charged in separate runs with $[(dippe)NiH]_2$ (0.026 g, 0.04 mmol), benzonitrile (20 mL, 0.20 mol), water (5 mL, 0.28 mol) and Bu_4NI (0.0612 g, 0.165 mmol), or with $[(dippe)NiH]_2$ (0.0498 g, 0.077 mmol), acetonitrile (20 mL, 0.38 mol), water (5 mL, 0.28 mol) and Bu_4NI (0.1172 g, 0.32 mmol). Either mixture was heated at 180 °C for 72 h, as described for previous experiments. Yield of benzamide after work-up: 41% (9.7846 g, 0.081 mol), with a TON of 1000 and a TOF of 14 cycles per hour. Yield of acetamide after work-up: 4% (0.9142 g, 0.015 mol), with a TON of 100 and a TOF of 1 cycle per hour. Both series of results are consistent values with those obtained in the absence of Bu_4NI, under otherwise the same conditions.

Evaluation of the Effect of Basic Media on the Catalytic Hydration of Benzonitrile

The reactor vessel was charged with $[(dippe)NiH]_2$ (0.0264 g, 0.04 mmol), benzonitrile (20 mL, 0.20 mol), and 5 mL of an untampered aqueous solution of NaOH at pH = 10. The mixture was then heated at 180 °C for 72 h as described for previous experiments. Yield of benzamide after work-up: 15% (3.5133 g, 0.029 mol), with a TON of 354 and a TOF of 5 cycles per hour. The pH of remaining aqueous phase after reaction was 7.

Hydration Process Optimization at Large Water Content (90% Water Volume) upon Temperature Variation

The reactor vessel was charged in separate runs with a constant loading of $[(dippe)NiH]_2$ (0.0058 g, 0.009 mmol), benzonitrile (5 mL, 0.05 mol) and water (37.5 mL, 2.08 mol), or $[(dippe)NiH]_2$ (0.004 g, 0.006 mmol), acetonitrile (1.5 mL, 0.03 mol) and water (11 mL, 0.61 mol). Each resulting mixture (implying 0.04 mole percent of the catalyst) was then heated at a different temperature (140 or 160 °C) during 72 h. Benzonitrile hydration: yield of the benzamide produced at 140 °C, after work-up: 6% (0.3342 g, 0.003 mol), with a TON of 148 and a TOF of 2 cycles per hour. Yield of benzamide produced at 160 °C, after work-up: 14% (0.8393 g, 0.007 mol), with a TON of 372 and TOF of 5 cycles per hour. Acetonitrile hydration: yield of acetamide produced at 140 °C: 1% (0.0122 g, 0.0002 mol), with a TON of 17 and a TOF of 0.2 cycle per hour. Yield of acetamide produced at 160 °C, after work-up: 3% (0.05 g, 0.0008 mol), with a TON of 68 and a TOF of 1 cycle per hour.

Hydration Process Optimization at Large Water Content (90% Water Volume): Assessment of the Effect of Increased Catalyst Concentration (1.0 Mole Percent), on going from 160 to 180 °C

The reactor vessel was charged in separate runs with $[(dippe)NiH]_2$ (0.080 g, 0.11 mmol), benzonitrile (2.5 mL, 0.02 mol) and water (20 mL, 1.11 mol). The resulting mixtures both produce 1.0 mole percent of nickel(0) catalyst loading, and as such were tested at 160 and 180 °C for 72 h, as described in the previous experiments. Yield of benzamide produced at 160 °C after work-up: 40% (1.3423 g, 0.011 mol), with a TON of 40 and a TOF of 1 cycle per hour. Yield of benzamide produced at 180 °C after work-up: 68% (2.0222 g, 0.017 mol), with a TON of 67 and TOF of 1 cycle per hour.

Benzonitrile Hydration Process Optimization at 180 °C upon Water Volume Percent Variation

The reactor vessel was charged in separate runs with a constant loading of $[(\mathrm{dippe})\mathrm{NiH}]_2$ (0.0800 g, 0.12 mmol), while varying the volume proportions of substrates so as to achieve mixtures of 50 or 20 water volume percent, respectively: 10 mL of benzonitrile (0.1 mol) and 10 mL of water (0.56 mol) or 20 mL of benzonitrile (0.2 mol) and 5 mL of water (0.28 mol). The catalyst loading that results in each mixture corresponds to 0.25 mole percent and 0.1 mole percent, respectively. Each mixture was heated to 180 °C for 72 h, as described for previous experiments. Yield of benzamide produced on using 50% water volume, after work-up: 26% (3.099 g, 0.026 mol), with a TON of 103 and a TOF of 1 cycle per hour. Yield of benzamide produced on using 20% water volume, after work-up: 19% (4.5905 g, 0.038 mol), with a TON of 153 and TOF of 2 cycles per hour.

Benzonitrile Hydration Process Optimization at Low Water Content (20% Water Volume), upon Catalyst Mole Percent Variation at 180 °C

The reactor vessel was charged in separate runs with constant loadings of benzonitrile (20 mL, 0.20 mol) and water (5 mL, 0.28 mol), while varying the amount of starting nickel dimer $[(\mathrm{dippe})\mathrm{NiH}]_2$, so as to achieve low nickel(0) catalyst concentrations of 0.04 and 0.01 mole percent, respectively. The amounts used were 0.0262 g (0.04 mmol) and 0.006 g (0.009 mmol). Each mixture was heated at 180 °C during 72 h. Yield of benzamide produced on using 0.04 mole percent of nickel(0) catalyst after work-up: 41% (9.6902 g, 0.080 mol), with a TON of 984 and a TOF of 14 cycles per hour. Yield of benzamide produced on using 0.01 mole percent of nickel(0) catalyst: 13% (3.0471 g, 0.025 mol), with a TON of 1350 and TOF of 19 cycles per hour.

Catalytic Acetonitrile Hydration at 180 °C, 0.04 Mole Percent of Nickel(0) Catalyst and Low Water Content (20% Water Volume)

The reactor vessel was charged in separate runs with constant loadings of $[(\mathrm{dippe})\mathrm{NiH}]_2$ (0.050 g, 0.078 mmol), acetonitrile (20 mL, 0.38 mol) and water (5 mL, 0.28 mol).The resulting mixtures provide 0.04 mole percent of the corresponding nickel(0) catalyst loading, and as such, were heated at 180 °C for 72 h, in the absence and presence of additional argon pressure (100 and 500 psi). Yield of acetamide produced without added argon pressure after work-up: 4% (0.909 g, 0.015 mol), with a TON of 99 and a TOF of 1 cycle per hour. 38 mol) and water (5 mL, 0.28 mol). Yield of acetamide produced both at 100 and 500 psi of additional argon pressure after work-up: 10% (2.35 g, 0.04 mol), with a TON of 257 and a TOF of 4 cycles per hour.

Benzonitrile Hydration using Different Catalysts: Assessment of the Hydrophobic Effect of the Ligands on Catalyst Efficiency

The reactor vessel was charged in separate runs with $[(\mathrm{dtbpe})\mathrm{NiH}]_2$, **4**, (0.0262 g, 0.035 mmol), benzonitrile (20 mL, 0.20 mol) and water (5 mL, 0.28 mol), or $[(\mathrm{dcype})\mathrm{NiH}]_2$, **5**, (0.035 g, 0.036 mmol), benzonitrile (20 mL, 0.20 mol) and water (5 mL, 0.28 mol). The catalyst loading that results in each mixture is 0.04 mole percent, similar to the conditions described for the nickel(0) catalyst using dippe, described above. Both mixtures were heated at 180 °C for 72 h. Yield of benzamide on using **4** after work-up: 23% (5.4621 g, 0.045 mol), with a TON of 651 and a TOF of 9 cycles per hour. Yield of benzamide on using **5** after workup: 17% (4.1079 g, 0.034 mol), with a TON of 467 and a TOF of 6 cycles per hour.

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