Unraveling the Reaction Mechanism on Nitrile Hydration Catalyzed by [Pd(OH$_2$)$_4$]$^{2+}$: Insights from Theory

Elkin Tílvez, María I. Menéndez, and Ramón López*

Departamento de Química Física y Analítica, Facultad de Química, Universidad de Oviedo, C/Julián Clavería 8, 33006 Oviedo, Principado de Asturias, Spain

S *Supporting Information*

ABSTRACT: Density functional theory methodologies combined with continuum and discrete-continuum descriptions of solvent effects were used to investigate the [Pd(OH$_2$)$_4$]$^{2+}$-catalyzed acrylonitrile hydration to yield acrylamide. According to our results, the intramolecular hydroxide attack mechanism and the external addition mechanism of a water molecule with rate-determining Gibbs energy barriers in water solution of 27.6 and 28.3 kcal/mol, respectively, are the most favored. The experimental kinetic constants of the hydration started by hydroxide, k(OH), and water, k(H$_2$O), attacks for the *cis*-[Pd(en)(OH$_2$)$_2$]$^{2+}$-catalyzed dichloroacetonitrile hydration rendered Gibbs energy barriers whose energy difference, 0.7 kcal/mol, is the same as that obtained in the present study. Our investigation reveals the nonexistence of the internal attack of a water ligand for Pd-catalyzed nitrile hydration. At the low pHs used experimentally, the equilibrium between [Pd(OH$_2$)$_3$(nitrile)]$^{2+}$ and [Pd(OH$_2$)$_2$(OH)(nitrile)]$^+$ is completely displaced to [Pd(OH$_2$)$_3$(nitrile)]$^{2+}$. Experimental studies in these conditions stated that water acts as a nucleophile, but they could not distinguish whether it was a water ligand, an external water molecule, or a combination of both possibilities. Our theoretical explorations clearly indicate that the external water mechanism becomes the only operative one at low pHs. On the basis of this mechanistic proposal it is also possible to ascribe an ^{1}H NMR signal experimentally detected to the presence of a unidentate iminol intermediate and to explain the influence of nitrile concentration reported experimentally for nitriles other than acrylonitrile in the presence of aqua−Pd(II) complexes. Therefore, our theoretical point of view on the mechanism of nitrile hydration catalyzed by aqua−Pd(II) complexes can shed light on these relevant processes at a molecular level as well as afford valuable information that can help in designing new catalysts in milder and more efficient conditions.
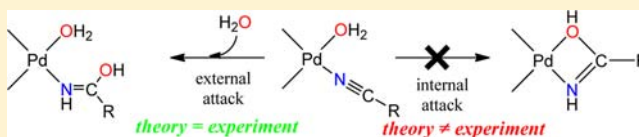
INTRODUCTION

The formation of amides from the hydration reaction of nitriles (see eq 1) is of great importance because of the utility of amides as chemical intermediates in organic synthesis[1,2] as well as in many industrial[3−6] and pharmaceutical[7,8] applications. Much effort has been directed toward the development of catalysts for nitrile hydration because of the well-known slow speed of this reaction. Acids and bases,[1,9] enzymes,[6,10−12] and transition metals[13−17] have been used to achieve that task. The use of transition metals for catalyzing nitrile hydration reactions has become the most active alternative in recent years[18−40] because almost all transition metals can form organometallic compounds, which provide a wide variety of structures and reactivities of potential use for hydrating nitriles. In addition, the coordination of these molecules to metal cations in organometallic compounds favors their susceptibility to nucleophilic attack, thus improving the rate of nitrile hydration. Other important advantages of this catalytic methodology over the above-mentioned ones are the use of milder (and/or more eco-friendly, in some cases) reaction conditions and the selective formation of amides without the formation of carboxylic acid.

$$R-C \equiv N + H_2O \rightarrow R-CONH_2 \qquad (1)$$

A broad spectrum of transition metal complexes including cobalt,[41−44] gold,[39] indium,[29] iridium,[22,45] molybdenum,[18,46,47] nickel,[23,48,49] osmium,[19,20,47,50−52] palladium,[28,53−59] platinum,[17,18,60−66] rhodium,[24,27,33,67] ruthenium,[19,21,25,26,30,31,34−36,38,68−74] silver,[37,40] and zinc[32] has been found to be effective at promoting nitrile hydration. Of particular interest are those that are water-soluble because of the potential environmental and economic benefits of replacing organic solvents with water. Among others, several aqua−palladium(II) complexes have been reported to catalyze nitrile hydration.[53,54,75] With regard to its reaction mechanism (see Scheme 1), it has been proposed that the process begins with the replacement of a water ligand by a nitrile molecule at the Pd catalyst (**A**) to give the corresponding complex (**B**), which is followed by a water attack to the nitrile ligand.[54] This can occur either internally via a water ligand to give a bidentate iminol complex (**C**^{int}) or externally through a solvent water to afford a unidentate iminol complex (**C**^{ext}). In the next step, along these two reaction pathways, the formation of a carboxamide ligand (**D**^{int} and **D**^{ext}) takes place, which is then expelled because of the entry of either another water molecule to recover **A** or

Scheme 1. Experimental Proposed Mechanisms for Nitrile Hydration Catalyzed by Pd(II)−Aqua Complexes
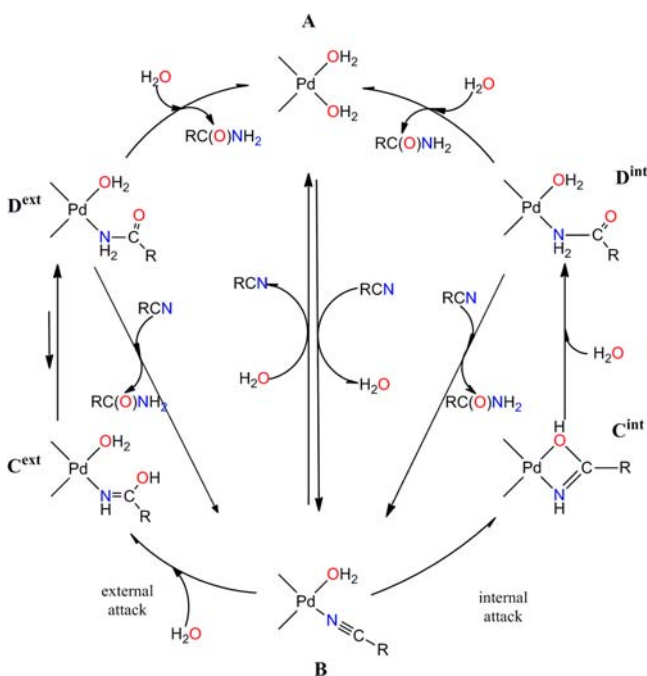
another nitrile molecule to afford **B**. Experimental kinetics could not distinguish whether nucleophilic water is one of the Pd ligands or an external one. ^{1}H NMR experiments have corroborated the presence of an iminol-type intermediate.[54] In addition, the mechanistic possibility of the hydroxide ligand acting as a nucleophile (see **1** in Scheme 2), commonly invoked

Scheme 2. Plausible Mechanisms for Metal-Catalyzed Nitrile Hydration
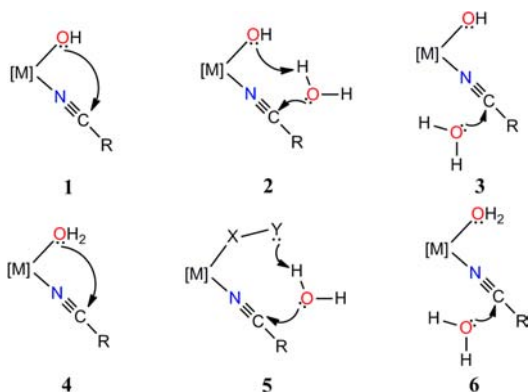
in most aqueous homogeneous nitrile hydration catalyzed by metals, has been ruled out in the Pd case because the aqua ligands cannot be deprotonated to any significant extent at the low pH conditions ($2.0 < pH < 3.0$) experimentally used.[54]

Two major questions, however, could be raised from the experimental suggestion implying the participation of the nucleophile water. First, the reaction pathway based on the attack of a water ligand to the nitrile carbon atom to give the four-membered metallocycle **C**[int] seems unlikely. Apart from the fact that the nucleophilicity of the attacking water is clearly decreased by its linkage to the metal center, a recent theoretical study on the $[Cp_2Mo(OH)(OH_2)]^+$-catalyzed acrylonitrile hydration has shown the nonexistence of a mechanistic route

for the attack of the hydroxide ligand (a stronger nucleophile than the water ligand) to the metal-coordinated N≡C unit with simultaneous transfer of the hydroxide hydrogen atom to the nitrile nitrogen atom to directly give a metallocycle analogous to **C**[int]. However, such a species has been found via an alternative stepwise mechanism but presents a very high Gibbs energy barrier.[76] Second, although both hydroxide and water are typically invoked as potential nucleophiles for hydration of nitriles (see **1**−**6** in Scheme 2), the nucleophilic action of an external water was confirmed in only two recent theoretical investigations on the catalytic hydration of acetonitrile and cyanohydrins to their corresponding amides by Rh(I)[24] and Ru(II)[31] complexes, respectively. Interestingly, in both cases, a solvent water attacks the nitrile ligand through a hydrogen-bonding interaction with a functionalized ligand of the complex (see **5** in Scheme 2), demonstrating that water has to be activated to act as a nucleophile in these metal-catalyzed reactions.

Understanding in detail the mechanisms of nitrile hydration catalyzed by metal complexes is an important issue that can explain phenomena that are not well-understood as well as give valuable information than can help in designing milder and more efficient reactions. In recent years, theoretical approaches in chemistry are proving to be useful for providing insights into the mechanisms of metal-catalyzed processes.[77,78] Despite the importance of the conversion of nitriles into amides catalyzed by metal complexes, only a few theoretical investigations have recently focused on its reaction mechanism,[18,24,28,35,76,79] but none of them involved aqua−palladium(II) complexes. This prompted us to examine the $[Pd(OH_2)_4]^{2+}$-catalyzed acrylonitrile hydration to acrylamide from a theoretical point of view. On the basis of the reaction mechanism found, we will rationalize the available experimental findings for such a reactive process.[54]

■ COMPUTATIONAL DETAILS

The molecular geometries and energies in aqueous solution of the reactants, intermediates, transition states, and products involved in the $[Pd(OH_2)_4]^{2+}$-catalyzed acrylonitrile hydration to acrylamide were computed using a density functional theory (DFT) level of theory, PCM-B3LYP/BSI. The polarizable continuum solvent (PCM) model of Tomasi et al.[80−82] with the Bondi radii[83] was employed to take into account bulk solvation effects on molecular geometries and energies from the outset. A dielectric constant of 78.39 was set in the PCM computations to simulate water, the solvent medium in the experiments.[54] Because some of the steps studied here involve a hydrogen migration or a water attack, the PCM method was combined with the inclusion of explicit water molecules in order to obtain a more realistic description of solvent effects on the energy barriers for such rearrangements. B3LYP is the popular hybrid DFT functional, which combines the Becke three-parameter nonlocal hybrid exchange potential with the nonlocal correlation functional of Lee, Yang, and Parr.[84−86] BSI means aug-cc-PVDZ[87,88] for the nonmetal atoms, a consistent correlation double-ζ basis set augmented by diffuse functions, plus aug-cc-pVDZ-PP[89] for Pd, in which the valence electrons are represented explicitly by the consistent correlation double-ζ basis set cc-pVDZ augmented by diffuse functions while the core electrons are modeled by the corresponding double-ζ Stuttgart−Koln energy consistent relativistic pseudopotential.

To obtain more accurate relative energies of the stationary points, PCM-B3LYP/BSII single-point energy calculations on the PCM-B3LYP/BSI optimized geometries were done and identified in the text as PCM-B3LYP/BSII//PCM-B3LYP/BSI computations. BSII denotes aug-cc-PVTZ[87,88] for the nonmetal atoms, a consistent correlation basis set of triple-ζ quality augmented by diffuse functions, plus aug-cc-pVTZ-PP[89] for Pd, in which the valence electrons are described

explicitly by the consistent correlation basis set of triple-ζ quality cc-pVTZ augmented by diffuse functions while the core electrons are modeled by the corresponding triple-ζ Stuttgart–Koln energy-consistent relativistic pseudopotential.

The adequacy of the PCM-B3LYP/BSII computational level for obtaining molecular geometries and energies has successfully been demonstrated on different types of Pd(II) complexes.[90] The size of the species involving explicit water solvent molecules prevented the use of such a level of theory for optimizing these molecular systems, but we reoptimized structures without explicit waters at the PCM-B3LYP/BSII level and compared the results obtained with the analogous ones at the PCM-B3LYP/BSII//PCM-B3LYP/BSI level. As it could be expected,[90] only slight discrepancies both in geometry and in energy were found (see Figure S1, Table S3, and comments in the Supporting Information) so we decided to use the same theory level for all of the structures to facilitate comparisons.

All the geometry optimizations were performed without constraints using Schlegel's algorithm.[91] The character of all first-order saddle points and local minima on the potential energy surface (PES) was confirmed by means of analytical calculations of harmonic vibrational frequencies. Intrinsic reaction coordinate (IRC) computations with the Hessian-based predictor–corrector integrator method were performed to verify the expected connections between the first saddle points and local minima on the PES.[92–94]

Thermal free-energy corrections in water solution (G^{therm}) were computed at the PCM-B3LYP/BSI level of theory within the ideal gas, rigid rotor, and harmonic oscillator approximations.[95] A pressure of 1 atm and a temperature of 298.15 K were assumed in the calculations to compare with experiment.[54] The Gibbs energy in aqueous solution was estimated by adding the G^{therm} correction to the PCM-B3LYP/BSII//PCM-B3LYP/BSI Gibbs energy (which includes the electrostatic and nonelectrostatic solute–solvent interactions).

A significant step in this work is the deprotonation of the intermediate complex $[\text{Pd}(\text{OH}_2)_3(\text{N}{\equiv}\text{CCH}{=}\text{CH}_2)]^{2+}$, which involves the release of a proton to the aqueous media. We determined the Gibbs energy of such a proton in aqueous solution ($G_{\text{sol}}(\text{H}^+)$) by adjusting this energy at the PCM-B3LYP/BSII//PCM-B3LYP/BSI level to reproduce the experimental pK_a value of 3.0[96] for the proton dissociation of the $[\text{Pd}(\text{OH}_2)_4]^{2+}$ complex. The combination of $G_{\text{sol}}(\text{H}^+)$ with the gas-phase Gibbs energy of a proton ($G_{\text{gas}}(\text{H}^+) = 5/2RT - TS_{\text{gas}} = 1.48 - 7.76 = -6.28$ kcal/mol at 298.15 K and 1 atm) permits the calculation of the corresponding solvation Gibbs energy ($\Delta G_{\text{solv}}(\text{H}^+)$). The resulting $\Delta G_{\text{solv}}(\text{H}^+)$ value, -255.6 kcal/mol, is in consonance with the reported data in the literature at 298.15 K ranging from -252.6 to -262.5 kcal/mol.[97–101]

All computations were done with the Gaussian 09 suite of programs.[102]

■ RESULTS AND DISCUSSION

The calculations for the acrylonitrile hydration reaction catalyzed by $[\text{Pd}(\text{OH}_2)_4]^{2+}$ in an aqueous medium modeled by a continuum solvent model are discussed first. Afterward, we consider a combined discrete-continuum solvent model through the inclusion of explicit water molecules in some key steps of the previously presented reaction mechanisms to obtain more realistic energy barriers in water solution. Finally, we compare our results with experiments. Unless otherwise cited, we discuss in the text PCM-B3LYP/BSII//PCM-B3LYP/BSI Gibbs energies in water solution referred to the separate reactants.

Reaction Mechanism Using a Continuum Solvent Model. Figures 1–3 display all the species involved in the reaction pathways located for the $[\text{Pd}(\text{OH}_2)_4]^{2+}$-catalyzed acrylonitrile hydration in water solution. More detailed geometrical and energetic data are collected in the Supporting Information. We considered the reaction mechanisms typically

invoked for homogeneous metal-catalyzed nitrile hydration (see Scheme 2).

All the resulting reaction pathways start with the replacement of a water ligand by acrylonitrile at the $[\text{Pd}(\text{OH}_2)_4]^{2+}$ complex to give the corresponding intermediate **I1** (-6.3 kcal/mol, **B** in Scheme 1). The catalyst $[\text{Pd}(\text{OH}_2)_4]^{2+}$ presents a square-planar conformation in the line of experimental and theoretical studies previously reported.[103–108] The Pd–OH$_2$ distance found by us (2.039 Å) agrees well with that obtained (2.04 Å) for the four first-shell water molecules at $[\text{Pd}(\text{OH}_2)_4]^{2+}$ from recent empirical potential structure refinement simulations.[105] As seen in Figure 1, the substitution process can occur in a
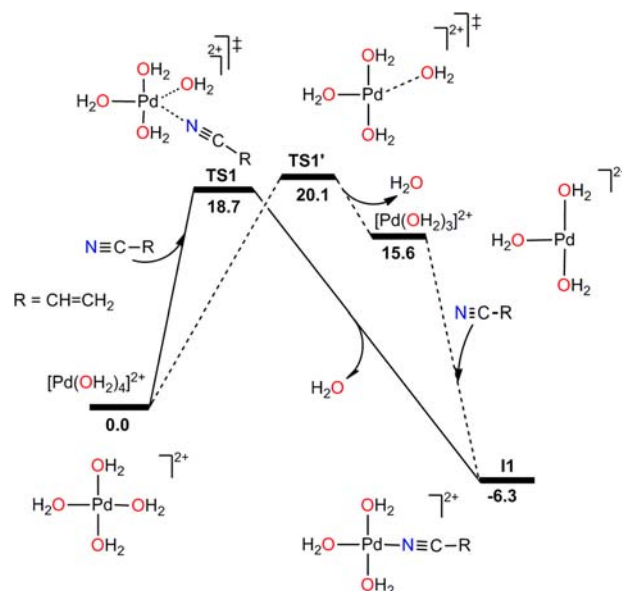

Figure 1. Alternative ways for the substitution of a water ligand at $[\text{Pd}(\text{OH}_2)_4]^{2+}$ with acrylonitrile. Relative Gibbs energies in water solution are given in kilocalories per mole at the PCM-B3LYP/BSII//PCM-B3LYP/BSI level of theory.

concerted way via the transition state (TS) **TS1** (18.7 kcal/mol) or in a two-step process through a water ligand elimination via the TS **TS1′** (20.1 kcal/mol) to give the unstable complex $[\text{Pd}(\text{OH}_2)_3]^{2+}$ (15.6 kcal/mol), followed then by the acrylonitrile addition to the metal center without any TS. In the most favored way, **TS1** presents a distorted trigonal bipyramidal geometry with two shortened bonds (axial water molecules, $d_{(\text{Pd–O})} = 2.016$ and 2.019 Å) and three elongated bonds (equatorial water molecule, $d_{(\text{Pd–O})} = 2.118$ Å; equatorial leaving water molecule, $d_{(\text{Pd–O})} = 2.339$ Å; equatorial entering nitrile molecule, $d_{(\text{Pd–N})} = 2.356$ Å when compared to the analogous bonds in $[\text{Pd}(\text{OH}_2)_4]^{2+}$ ($d_{(\text{Pd–O})} = 2.039$ Å) and **I1** ($d_{(\text{Pd–N})} = 1.955$ Å). This five-coordinated structure resembles that found for the water exchange process on planar d^8 Pd–aqua complexes in water solution.[106,107]

I1 is a bifurcation point because one of its water ligands can or cannot undergo its deprotonation. Therefore, we divided the reaction pathways into two groups: those involving hydroxide complexes, routes R1a–c in Figure 2, and those proceeding via complexes without the hydroxide ligand, routes R2 in Figure 3.

On one hand, as collected in Figure 2, **I1** (-6.3 kcal/mol) can undergo the deprotonation of a water ligand to render the intermediate **I2-R1** (-4.1 kcal/mol) without any TS. Along R1a, **I2-R1** proceeds through the attack of O$_{\text{hydroxide}}$ to C$_{\text{nitrile}}$ via
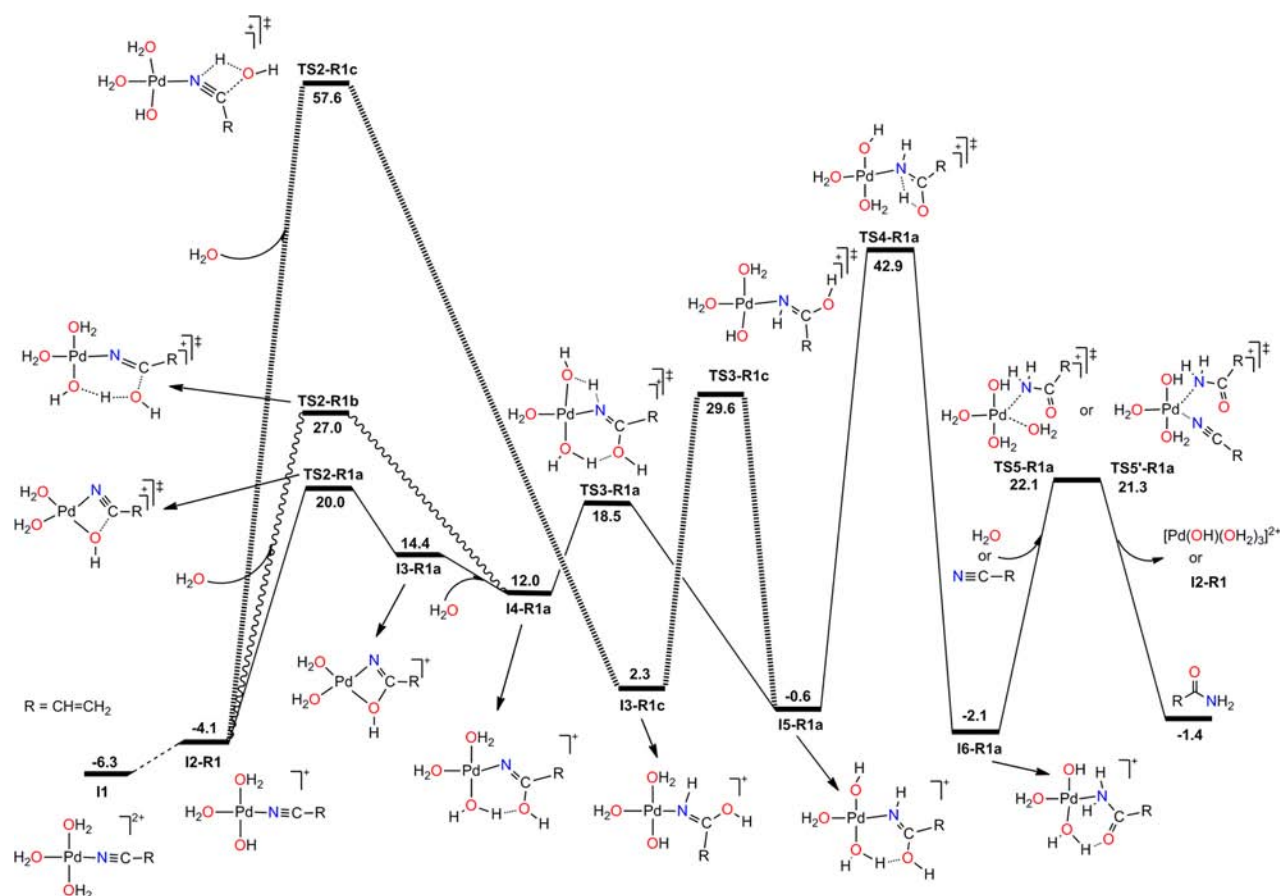
Figure 2. Reaction pathways for the $[Pd(OH_2)_4]^{2+}$-catalyzed acrylonitrile hydration to acrylamide via the participation of the hydroxide ligand starting from the complex $[Pd(OH_2)_3(N{\equiv}C\text{-}R)]^{2+}$ (**I1**). Relative Gibbs energies in water solution are given in kilocalories per mole at the PCM-B3LYP/BSII//PCM-B3LYP/BSI level of theory.

the TS **TS2-R1a** (20.0 kcal/mol) to give the four-membered metallocycle intermediate **I3-R1a** (14.4 kcal/mol). In the next step, however, the addition of an external water molecule cleaves the Pd−OH bond of the metallocyclic moiety at **I3-R1a** without any TS to give the intermediate **I4-R1a** (12.0 kcal/mol). **I3-R1a** shows a significant elongation of the Pd−OH bond (2.133 Å) compared to the same bond at **I2-R1** (1.945 Å). This fact together with the notable separation of the natural charges in the Pd−OH bond at **I3-R1a** (Pd (+0.74 *e*) and O (−0.73 *e*)) facilitates its breakage by a properly oriented external water molecule without any TS. **I4-R1a** presents a hydrogen bond interaction between the initial $O_{hydroxide}$ and a hydrogen atom of the incoming water molecule at a distance of 1.724 Å, thus favoring the formation a six-membered metallocycle less strained than that at **I3-R1a**. These electronic and geometrical rearrangements could explain the gain of stability of **I4-R1a** compared to **I3-R1a**. **I4-R1a** undergoes a hydrogen transfer to the nitrile nitrogen atom ($N_{nitrile}$) from the water ligand closest to it via the TS **TS3-R1a** (18.5 kcal/mol) to form the iminol-type intermediate **I5-R1a** (−0.6 kcal/mol). Then, another hydrogen migration takes place from the initial $O_{hydroxide}$ to $N_{nitrile}$ to afford the intermediate **I6-R1a** (−2.1 kcal/mol) in which the acrylamide ligand is present, via the TS **TS4-R1a** (42.9 kcal/mol). Finally, the acrylamide ligand can be expelled by the entry of either another water molecule via the TS **TS5-R1a** (22.1 kcal/mol) to give $[Pd(OH)(OH_2)_3]^+$ and acrylamide (−1.4 kcal/mol) or another nitrile molecule via the TS **TS5′-R1a** (21.3 kcal/mol) to recover the intermediate **I2-**

R1. This intermediate would come back to reproduce the R1a route.

Along R1b, **I2-R1** connects to **I4-R1a** via the TS **TS2-R1b** (27.0 kcal/mol) for the addition of an external water molecule between $C_{nitrile}$ and $O_{hydroxide}$. At **TS2-R1b**, the distance between the incoming water oxygen atom and $C_{nitrile}$ is 1.772 Å while a hydrogen atom of the same water molecule is interacting with $O_{hydroxide}$ at a distance of 1.413 Å. For R1c, **I2-R1** undergoes the addition of an external water molecule to the nitrile C≡N bond, without any contact with Pd or other ligands, through the TS **TS2-R1c** (57.6 kcal/mol) to give another iminol-type intermediate, **I3-R1c** (2.3 kcal/mol), which in turn evolves to the intermediate **I5-R1a** (−0.6 kcal/mol) via the TS **TS3-R1c** (29.6 kcal/mol) for a rotation around the $C_{nitrile}$−$N_{nitrile}$ bond axis. From both **I4-R1a** and **I5-R1a**, the system evolves to the formation of acrylamide as previously described for R1a.

On the other hand, along the nondeprotonated water ligand routes, R2 in Figure 3, an external water molecule is added to the nitrile C≡N bond to give the iminol-type intermediate **I2-R2** (−8.0 kcal/mol) via a highly unstable TS, **TS2-R2** (46.5 kcal/mol). **I2-R2** tautomerizes to another iminol intermediate **I3-R2** (−10.6 kcal/mol) via the TS **TS3-R2** (18.4 kcal/mol). Afterward, a hydrogen migration takes place from the $C_{nitrile}$-linked hydroxyl group to $N_{nitrile}$ via the TS **TS4-R2** (37.2 kcal/mol), thus resulting in the intermediate **I4-R2** (−7.4 kcal/mol) wherein the acrylamide ligand is already formed. Alternatively, **I2-R2** can undergo the rotation of the hydroxyl bond axis with
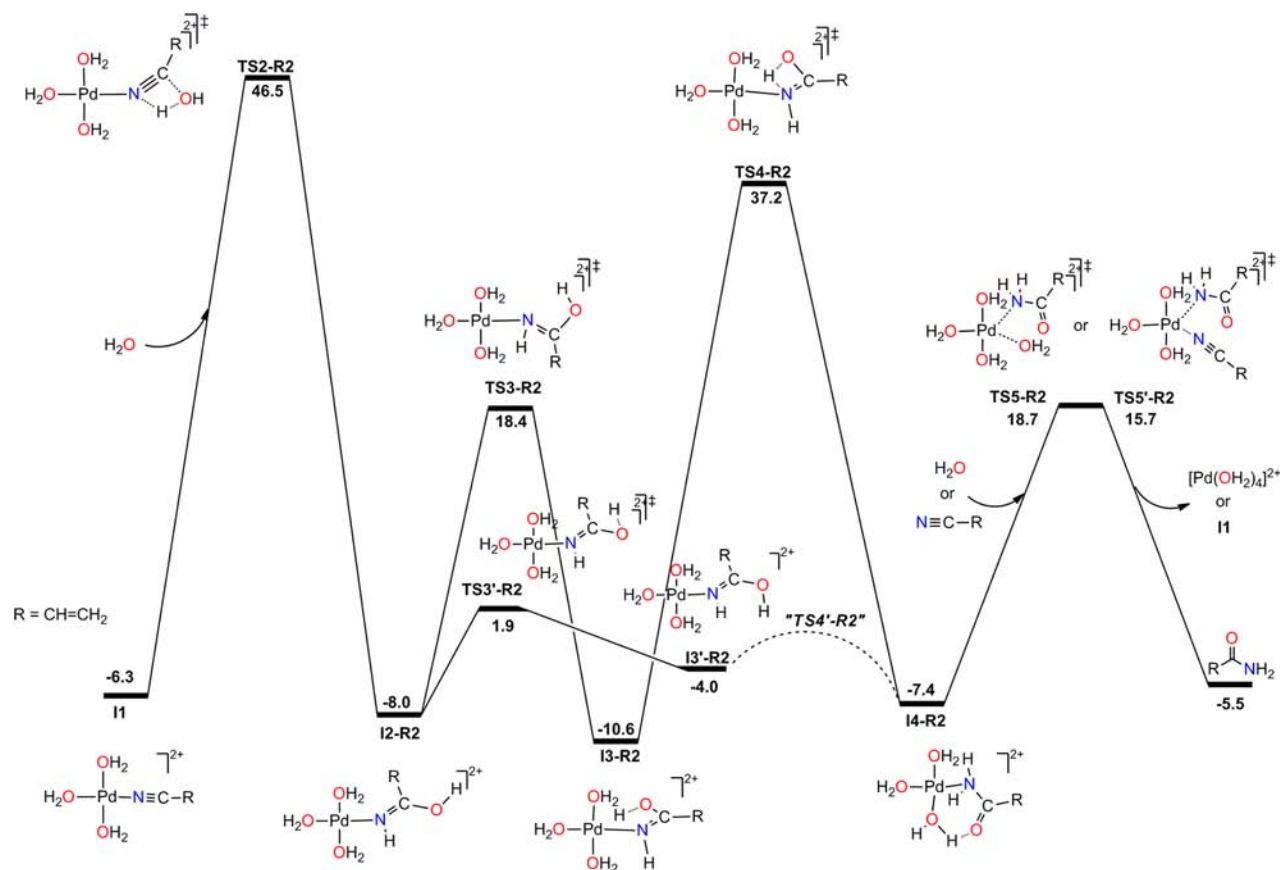
Figure 3. Reaction pathways found for the $[Pd(OH_2)_4]^{2+}$-catalyzed acrylonitrile hydration to acrylamide in the absence of the hydroxide ligand starting from the complex $[Pd(OH_2)_3(N\equiv C\text{-}R)]^{2+}$ (**I1**). Relative Gibbs energies in water solution are given in kilocalories per mole at the PCM-B3LYP/BSII//PCM-B3LYP/BSI level of theory.

respect to the $C_{nitrile}-O_{hydroxide}$ bond axis via the TS **TS3′-R2** (1.9 kcal/mol), rendering the intermediate **I3′-R2** (−4.0 kcal/mol). At this species, the hydroxide hydrogen atom is in the same side as the H−$N_{nitrile}$ bond, while a different trend is present at **I3-R2**. As happened before in similar situations, the next step would imply the formation of the acrylamide ligand through a hydrogen migration from $O_{hydroxide}$ to $N_{nitrile}$. Although we could not find the corresponding TS after an extensive search, such a rearrangement could be confirmed by the inclusion of explicit water molecules of solvent in the computations that revealed the connection between **I3′-R2** and **I4-R2** (see below). Accordingly, we named the hypothetical TS in the absence of explicit water molecules **TS4′-R2**. As happened for routes R1a−c, **I4-R2** can undergo the displacement of the acrylamide ligand through the addition of either a water molecule via the TS **TS5-R2** (18.7 kcal/mol) to give $[Pd(OH_2)_4]^{2+}$ and acrylamide (−5.5 kcal/mol) or another nitrile molecule via the TS **TS5′-R2** (15.7 kcal/mol) to afford **I1** and acrylamide. As for **I2-R1** in R1 routes, **I1** could react with another external water molecule and proceed through R2 again.

We also explored the mechanistic possibility suggested by experimentalists[54] concerning the internal attack of a water ligand to $C_{nitrile}$ at the intermediate complex $[Pd(OH_2)_3(nitrile)]^{2+}$ (see **4** in Scheme 2), but all attempts to find any significant TS failed after an extensive search. This is in accordance with the well-known fact that the nucleophilic character of water is lowered because of its linkage to the metal center. The same negative result was reached after investigating

the attack on $C_{nitrile}$ at $[Pd(OH_2)_3(nitrile)]^{2+}$ by an external water molecule interacting with a water ligand of the Pd complex.

According to the results obtained using only a continuum solvent model, R1a and R1b are the most favored mechanistic routes with a rate-determining Gibbs energy barrier in water solution of 49.2 kcal/mol (**TS4-R1a**), measured from the most stable previous intermediate (**I1**),[109] which involves the hydrogen migration from $O_{hydroxide}$ to $N_{nitrile}$. For routes R1c and R2, the water addition to the nitrile ligand is the rate-determining step with Gibbs energy barriers of 63.9 (**TS2-R1c**) and 52.8 (**TS2-R2**) kcal/mol measured from **I1**, respectively. Such high barriers are not compatible with experimental facts, so they indicate the need to improve our theoretical model.

Adding Explicit Water Molecules To Improve the Estimate of Energy Barriers. Several steps in the reaction mechanisms found for the $[Pd(OH_2)_4]^{2+}$-acrylonitrile hydration involve a hydrogen migration (**I5-R1a** → **TS4-R1a** → **I6-R1a**, **I3-R2** → **TS4-R2** → **I4-R2**, and **I3′-R2** → **TS4′-R2** → **I4-R2**) or a water nucleophilic attack (**I2-R1** → **TS2-R1c** → **I3-R1c** and **I1** → **TS2-R2** → **I2-R2**). In an aqueous medium, these molecular rearrangements are not well-modeled using a continuum solvation model because the specific solute−solvent interactions are not well-described and the possible role of solvent as bifunctional catalyst cannot be modeled.[110−114] These drawbacks can be overcome by adding explicit water molecules to the corresponding solute species immersed in the continuum solvent. The consideration of one explicit water molecule reduces the Gibbs energy barriers of the hydrogen
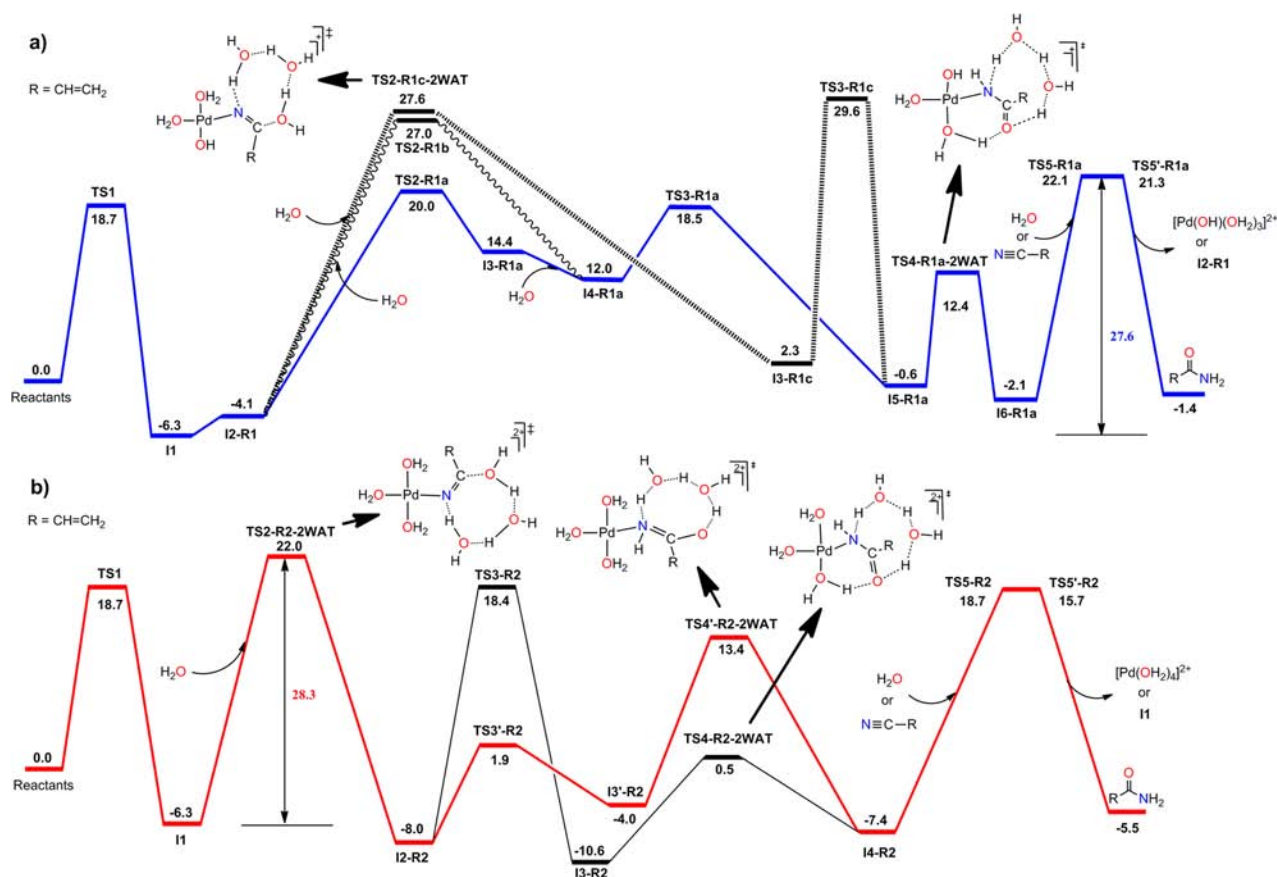
Figure 4. Resultant Gibbs energy profiles in water solution after the inclusion of two explicit water molecules (in kilocalories per mole) for routes R1a−c (a) and R2 (b) at the PCM-B3LYP/BSII//PCM-B3LYP/BSI level of theory.

migration TSs (measured from the corresponding previous intermediate) in the range of 19.0−28.1 kcal/mol (see Figure S2 in the Supporting Information). The inclusion of two explicit water molecules allows the formation of looser TSs where both water molecules directly connect with both reacting sites at the solute molecule, thus collecting the main solute−solvent specific interactions. As no charge separation is derived from the hydrogen transfers here analyzed, we assume that two explicit water molecules are enough to properly reproduce solute−solvent interactions in the real system and that the presence of a larger number would hardly modify the obtained energy barriers.[110,112−114] As a matter of fact, accurate results have been obtained considering two explicit water molecules in conjunction with a continuum solvent for previous theoretical studies on the acrylonitrile hydration and carbon monoxide oxidation catalyzed by $[Cp_2Mo(OH)(OH_2)]^+$.[76,115]

Taking a general overview, we conclude that R1a could be the most favored mechanism at the experimental conditions, allowing the deprotonation of a water ligand of the Pd complex. This route presents a rate-determining Gibbs energy barrier in water solution of 27.6 kcal/mol (measured from the most stable previous intermediate $[Pd(OH_2)_3(nitrile)]^{2+}$, **I1**),[109] corresponding to the acrylamide formation step via the entry of a nitrile molecule (**TS5′-R1a**, see blue line in Figure 4a). This energy barrier competes with those obtained for the intramolecular hydroxide attack step (**TS2-R1a**, 26.3 kcal/mol) and the acrylamide formation via the entry of a water molecule (**TS5-R1a**, 28.4 kcal/mol). The attack of an external water molecule to the nitrile C≡N bond at the nondeprotonated intermediate **I1** is the rate-determining step along the R2

mechanisms, the second most preferred, with a Gibbs energy barrier of 28.3 kcal/mol (see red line in Figure 4b). We also note that route R2 evolving through **I3′-R2** is more favorable than that proceeding through **I3-R2** because of the cost of the isomerizations preceding each of them. Once again, the acrylamide release via the entry of a nitrile molecule (**TS5′-R2**) is more favorable than that of a water molecule (**TS5-R2**) by 3.0 kcal/mol. Routes R1b and R1c are more energy-demanding than those mentioned above (see black lines in Figure 4a). R1b presents a rate-determining Gibbs energy barrier in solution of 33.3 kcal/mol (**TS2-R1b**) ascribed to the water attack on the nitrile carbon atom at the deprotonated intermediate $[Pd(OH_2)_2(OH)(nitrile)]^+$, **I2-R1**, while a value of 35.9 kcal/mol (**TS3-R1c**) was obtained for R1c.

Discussion and Comparison with Experiment. On the basis of our results for the $[Pd(OH_2)_4]^{2+}$-catalyzed acrylonitrile hydration displayed in Figure 4, the intramolecular hydroxide attack (R1a; Gibbs energy barrier of 27.6 kcal/mol) and the external water attack on the non-deprotonated complex $[Pd(OH_2)_3(nitrile)]^{2+}$ (R2; Gibbs energy barrier of 28.3 kcal/mol) are the most favored mechanisms. The small difference between the rate-determining Gibbs energy barriers of R2 and R1a (0.7 kcal/mol) is the same as that derived from the experimental rate constants $k(H_2O)$ and $k(OH)$ reported for the cis-$[Pd(en)(OH_2)_2]^{2+}$-catalyzed dichloroacetonitrile hydration[54] using the thermodynamic formulation of transition state theory (TST). $k(H_2O)$ and $k(OH)$ denote the rate constants measured for the mechanisms involving the participation of water and hydroxide as nucleophiles, respectively. After an extensive search, our results also indicate the nonexistence of

any TS for the internal attack of a water ligand on the nitrile ligand at the complex $[Pd(OH_2)_3(nitrile)]^{2+}$ (**I1**), thus discarding the mechanism suggested by experimentalists involving an aqua ligand attacking internally (see Scheme 1).

Experimental results have shown that the reaction rate for the *cis*-$[Pd(en)(OH_2)_2]^{2+}$-catalyzed dichloroacetonitrile hydration depends on the pH because of the acid−base equilibrium involving the deprotonation of a water ligand at the intermediate complex $[Pd(OH_2)_3(nitrile)]^{2+}$ (**I1**).[54] Our results reflect that **I1** is only 2.2 kcal/mol more stable than the deprotonated species $[Pd(OH_2)_2(OH)(nitrile)]^+$ (**I2-R1**), thus corroborating the equilibrium between **I1** and **I2-R1** experimentally proposed. Low pH values are required to avoid both the subsequent hydrolysis of the carboxamide product and the formation of inactive polynuclear aqua−Pd complexes.[54] In strongly acidic solutions, therefore, we argue that the equilibrium **I1** → **I2-R1** + H⁺ will be completely displaced to **I1**. Consequently, R1 routes are inaccessible, and route R2 will become the operative mechanism. This fact, in conjunction with the computationally proven absence of an internal attack of a water ligand, clarifies the experimental mechanistic proposal. Experimentally, it had been indicated that internal attack on the nitrile ligand by the aqua ligand and external attack on the nitrile ligand by solvent water occur at similar rates.[54] However, our calculations indicate that at low pHs an external water molecule is the only one involved in the reaction. The rate-determining Gibbs energy barrier in water solution obtained by us for R2 (28.3 kcal/mol) compares well with that derived from the experimental rate constant measured at 40 °C for the $[Pd(OH_2)_4]^{2+}$-catalyzed acetonitrile hydration[54] using the TST equation (27.5 kcal/mol). Besides this, the relatively stable intermediate **I2-R2** (−8.0 kcal/mol) found along R2 supports the assignment of the resonance at δ 6.68, observed in ¹H NMR experiments for the $[Pd(OH_2)_4]^{2+}$-catalyzed dichloroacetonitrile hydration,[54] to the presence of a unidentate iminol. In neutral and basic solutions, the equilibrium **I1** → **I2-R1** + H⁺ will be displaced to **I2-R1**. This, along with the fact that R1a is slightly more favored than R2, will favor the carboxamide formation via complexes involving the hydroxide ligand.

In addition, along the operative mechanism at low pHs, our results show that the Gibbs energy barriers for the release of acrylamide determined by **TS5-R2** (26.7 kcal/mol) and **TS5′-R2** (23.7 kcal/mol) are close to that obtained for the nucleophilic water attack (**TS2-R2**, 28.3 kcal/mol), the rate-determining step of the overall process at low pHs. This could explain why both steps were found to be competitive in most of the hydration reactions of nitriles catalyzed by aqua−Pd(II) complexes.[54] It is also possible to rationalize the effect of the nitrile concentration on the formation of the carboxamide product on the basis of the Gibbs energy barriers determined by **TS5-R2** and **TS5′-R2**. In effect, as both energy barriers are less unfavorable than the rate-determining one, at a relatively low nitrile concentration the acrylamide formation will take place mainly via the entry of a water molecule determined by **TS5-R2**. At a high nitrile concentration, the addition of a nitrile molecule determined by **TS5′-R2** instead of a water molecule will displace the acrylamide ligand, and the reactive cycle will resume from **I1**.

CONCLUSIONS

The reaction mechanism of $[Pd(OH_2)_4]^{2+}$-catalyzed acrylonitrile hydration was investigated using a DFT methodology in conjunction with continuum and discrete-continuum solvent models. At the more realistic description of solute−solvent interactions, the inclusion of two explicit water molecules reveals that the intramolecular nucleophilic hydroxide attack is the most favorable mechanism with a rate-determining Gibbs energy barrier in water solution of 27.6 kcal/mol, corresponding to the acrylamide formation via the entry of a nitrile molecule. The second most favorable mechanism corresponds to the attack on the nitrile ligand by an external water molecule with a rate-determining Gibbs energy barrier of 28.3 kcal/mol. The difference between the two above-mentioned Gibbs energy barriers is the same as that obtained from experimental rate constants measured for the *cis*-$[Pd(en)(OH_2)_2]^{2+}$-catalyzed dichloroacetonitrile hydration. At low pHs, the external water attack becomes the only operative mechanism as the process $[Pd(OH_2)_3(N\equiv C-CH=CH_2)]^{2+}$ → $[Pd(OH)(OH_2)_2(N\equiv C-CH=CH_2)]^+$ + H⁺ is strongly penalized, thus preventing the evolution via intermediate complexes involving the hydroxide ligand. This agrees with the experimental suggestion about a solvent water attacking externally for Pd(II)-catalyzed nitrile hydration. Conversely, our results allow us to rule out, after an extensive search, the other experimental mechanistic proposal concerning the internal attack of a water ligand to the Pd-coordinated nitrile on the basis of the nonexistence of a chemically significant species for such a molecular rearrangement. Besides, it was also possible to clarify the structure of a unidentate iminol suggested experimentally in the conversion of nitriles into carboxamides and rationalize the formation of the carboxamide product depending on the concentration of nitrile. Therefore, we believe that our study not only can shed light on the mechanism of nitrile hydration catalyzed by metal complexes but also can afford valuable information that can aid in designing new catalysts in milder and more efficient conditions.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Optimized geometries and energy data of the species involved in the $[Pd(OH_2)_4]^{2+}$-catalyzed acrylonitrile hydration (Figure S1 and Tables S1−S3), comments on Figure S1 and Table S3, and influence of the inclusion of one and two explicit water molecules in the steps involving hydrogen migrations and water attack (Figures S2−S4). This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
*E-mail: rlopez@uniovi.es.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

REFERENCES

(1) Greenberg, A.; Breneman, C. M.; Liebman, J. F. *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Material Science*; Wiley: New York, 2000.

(2) Zabicky, J. *The Chemistry of Amides*; Wiley Interscience: New York, 1970.

(3) Haberman, C. E. Amides. In *Encyclopedia of Chemical Technology*; Krosshwitz, J. I., Howe-Grand, M., Eds.; John Wiley & Sons: New York, 1991; Vol. *1*, p 251.

(4) Johansson, I. *Kirk-Othmer Encyclopedia of Chemical Technology*, 5th ed.; Wiley: New York, 2004; Vol. *2*, pp 442−463.

(5) Opsahl, R. Amides. In *Encyclopedia of Chemical Technology*; Krosshwitz, J. I., Howe-Grand, M., Eds.; John Wiley & Sons: New York, 1991; Vol. *1*, pp 346−356.

(6) Yamada, H.; Kobayashi, M. *Biosci., Biotechnol., Biochem.* **1996**, *60*, 1391−1400.

(7) Bhattacharya, A.; Scott, B. P.; Nasser, N.; Ao, H.; Maher, M. P.; Dubin, A. E.; Swanson, D. M.; Shankley, M. P.; Wickenden, A. D.; Chaplan, S. R. *J. Pharmacol. Exp. Ther.* **2007**, *323*, 665−674.

(8) Rivara, S.; Lodola, A.; Mor, M.; Bedini, A.; Spadoni, G.; Lucini, V.; Pannacci, M.; Fraschini, F.; Scaglione, F.; Ochoa-Sánchez, R.; Gobbi, G.; Tarzia, G. *J. Med. Chem.* **2007**, *50*, 6618−6626.

(9) Bailey, P. D.; Mills, T. J.; Pettecrew, R.; Price, R. A. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2005; Vol. *5*, pp 201−294.

(10) Kovacs, J. A. *Chem. Rev.* **2004**, *104*, 825−848.

(11) Li, B.; Su, J.; Tao, J. *Org. Process Res. Dev.* **2011**, *15*, 291−293.

(12) Sanchez, S.; Demain, A. L. *Org. Process Res. Dev.* **2011**, *15*, 224−230.

(13) Ahmed, T. J.; Knapp, S. M. M.; Tyler, D. R. *Coord. Chem. Rev.* **2011**, *255*, 949−974.

(14) García-Álvarez, R.; Crochet, P.; Cadierno, V. *Green Chem.* **2013**, *15*, 46−66.

(15) Kukushkin, V. Y.; Pombeiro, A. J. L. *Chem. Rev.* **2002**, *102*, 1771−1802.

(16) Kukushkin, V. Y.; Pombeiro, A. J. L. *Inorg. Chim. Acta* **2005**, *358*, 1−21.

(17) Parkins, A. W. *Platinum Met. Rev.* **1996**, *40*, 169−174.

(18) Ahmed, T. J.; Fox, B. R.; Knapp, S. M. M.; Yelle, R. B.; Juliette, J. J.; Tyler, D. R. *Inorg. Chem.* **2009**, *48*, 7828−7837.

(19) Ashraf, S. M.; Kandioller, W.; Mendoza-Ferri, M. G.; Nazarov, A. A.; Hartinger, C. G.; Keppler, B. K. *Chem. Biodiversity* **2008**, *27*, 2030−2035.

(20) Buil, M. L.; Cadierno, V.; Esteruelas, M. A.; Gimeno, J.; Herrero, J.; Izquierdo, S.; Enrique Oñate, E. *Organometallics* **2012**, *31*, 6861−6867.

(21) Cadierno, V.; Francos, J.; Gimeno, J. *Chem.—Eur. J.* **2008**, *14*, 6601−6605.

(22) Crestani, M. G.; Steffen, A.; Kenwright, A. M.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Organometallics* **2009**, *28*, 2904−2914.

(23) Crisóstomo, C.; Crestani, M. G.; García, J. J. *Inorg. Chim. Acta* **2010**, *363*, 1092−1096.

(24) Daw, P.; Sinha, A.; Wahidur-Rahaman, S. M.; Dinda, S.; Bera, J. K. *Organometallics* **2012**, *31*, 3790−3797.

(25) García-Álvarez, R.; Díez, J.; Crochet, P.; Cadierno, V. *Organometallics* **2011**, *30*, 5442−5451.

(26) García-Álvarez, R.; García-Garrido, S. E.; Díez, J.; Crochet, P.; Cadierno, V. *Eur. J. Inorg. Chem.* **2012**, 4218−4230.

(27) Goto, A.; Endo, K.; Saitao, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3607−3609.

(28) Hirano, T.; Uehara, K.; Kamata, K.; Mizuno, N. *J. Am. Chem. Soc.* **2012**, *134*, 6425−6433.

(29) Kim, E. S.; Lee, H. S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2010**, *51*, 1589−1591.

(30) Knapp, S. M. M.; Sherbow, T. J.; Juliette, J. J.; Tyler, D. R. *Organometallics* **2012**, *31*, 2941−2944.

(31) Knapp, S. M. M.; Sherbow, T. J.; Yelle, R. B.; Zakharov, L. N.; Juliette, J. J.; Tyler, D. R. *Organometallics* **2013**, *32*, 824−834.

(32) Kopylovich, M. N.; Kukushkin, V. Y.; Haukka, M.; Fraústo da Silva, J. J. R.; Pombeiro, A. J. L. *Inorg. Chem.* **2002**, *41*, 4798−4804.

(33) Lee, J.; Kim, M.; Chang, S.; Lee, H. Y. *Org. Lett.* **2009**, *11*, 5598−5601.

(34) Lee, W.; Frost, B. J. *Green Chem.* **2012**, *14*, 62−66.

(35) Leung, C. W.; Zheng, W.; Zhou, Z.; Lin, Z.; Lau, C. P. *Organometallics* **2008**, *27*, 4957−4969.

(36) Martin, M.; Horvath, H.; Sola, E.; Katho, A.; Joo, F. *Organometallics* **2009**, *28*, 561−566.

(37) Mitsudome, T.; Mikami, Y.; Mori, H.; Arita, S.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Chem. Commun.* **2009**, 3258−3260.

(38) Nasir-Baig, R. B.; Varma, R. S. *Chem. Commun.* **2012**, *48*, 6220−6222.

(39) Ramón, R. S.; Marion, N.; Nolan, S. P. *Chem.—Eur. J.* **2009**, *15*, 8695−8697.

(40) Shimizu, K.; Imaiida, N.; Sawabe, K.; Satsuma, A. *Appl. Catal., A* **2012**, *421−422*, 114−120.

(41) Chin, J.; Kim, J. H. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 523−525.

(42) Heinrich, L.; Mary-Verla, A.; Li, Y.; Vaissermann, J.; Chottard, J. C. *Eur. J. Inorg. Chem.* **2001**, 2203−2206.

(43) Kim, J. H.; Britten, J.; Chin, J. J. *J. Am. Chem. Soc.* **1993**, *115*, 3618−3622.

(44) Tyler, L. A.; Noveron, J. C.; Olmstead, M. M.; Mascharak, P. K. *Inorg. Chem.* **2003**, *42*, 5751−5761.

(45) Chin, C. S.; Kim, S. Y.; Joo, K.-S.; Won, G.; Chong, D. *Bull. Korean Chem. Soc.* **1999**, *20*, 535−538.

(46) Breno, K. L.; Pluth, M. D.; Tyler, D. R. *Organometallics* **2003**, *22*, 1203−1211.

(47) Breno, K. L.; Pluth, M. D.; Landorf, C. W.; Tyler, D. R. *Organometallics* **2004**, *23*, 1738−1746.

(48) Crestani, M. G.; Arévalo, A.; García, J. J. *Adv. Synth. Catal.* **2006**, *348*, 732−742.

(49) Crisóstomo, C.; Crestani, M. G.; García, J. J. *J. Mol. Catal. A: Chem.* **2007**, *266*, 139−148.

(50) Breno, K. L.; Ahmed, T. J.; Pluth, M. D.; Balzarek, C.; Tyler, D. R. *Coord. Chem. Rev.* **2006**, *250*, 1141−1151.

(51) Cavarzan, A.; Scarso, A.; Strukul, G. *Green Chem.* **2010**, *12*, 790−794.

(52) Stepanenko, I. N.; Cebrian-Losantos, B.; Arion, V. B.; Krukhin, A. A.; Nazarov, A. A.; Keppler, B. K. *Eur. J. Inorg. Chem.* **2007**, 400−411.

(53) Kaminskaia, N. V.; Guzei, I. A.; Kostic, N. M. *J. Chem. Soc., Dalton Trans.* **1998**, 3879−3885.

(54) Kaminskaia, N. V.; Kostic, N. M. *J. Chem. Soc., Dalton Trans.* **1996**, 3677−3686.

(55) Kim, E. S.; Kim, H. S.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 2973−2975.

(56) Kim, E. S.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 6286−6289.

(57) Villain, G.; Constant, G.; Gaset, A.; Kalck, P. J. *J. Mol. Catal.* **1980**, *7*, 355−364.

(58) Villain, G.; Gaset, A.; Kalck, P. J. *J. Mol. Catal.* **1981**, *12*, 103−111.

(59) Villain, G.; Kalck, P.; Gaset, A. *Tetrahedron Lett.* **1980**, *21*, 2901−2904.

(60) Arnold, D. P.; Bennett, M. A. J. *Organomet. Chem.* **1980**, *199*, 119−135.

(61) Ghaffar, T.; Parkins, A. W. *Tetrahedron Lett.* **1995**, *36*, 8657−8660.

(62) Ghaffar, T.; Parkins, A. W. J. *J. Mol. Catal. A: Chem.* **2000**, *160*, 249−261.

(63) Jensen, C. M.; Trogler, W. C. J. *J. Am. Chem. Soc.* **1986**, *108*, 723−729.

(64) Jiang, X. B.; Minnaard, A. J.; Feringa, B. L.; De Vries, J. G. J. *J. Org. Chem.* **2004**, *69*, 2327−2331.

(65) North, M.; Parkins, A. W.; Shariff, A. N. *Tetrahedron Lett.* **2004**, *45*, 7625−7627.

(66) Yoshida, T.; Matsuda, T.; Okano, T.; Kitani, T.; Otsuka, S. J. *J. Am. Chem. Soc.* **1979**, *101*, 2027−2038.

(67) Djoman, M. C. K. B.; Ajjou, A. N. *Tetrahedron Lett.* **2000**, *41*, 4845−4849.

(68) Fung, W. K.; Huang, X.; Man, M. L.; Ng, S. M.; Hung, M. Y.; Lin, Z.; Lau, C. P. J. *J. Am. Chem. Soc.* **2003**, *125*, 11539−11544.

(69) García-Álvarez, R.; Díez, J.; Crochet, P.; Cadierno, V. *Organometallics* **2010**, *29*, 3955−3965.

(70) Murahashi, S.; Sasao, S.; Saito, E.; Naota, T. *J. Org. Chem.* **1992**, *57*, 2521−2523.

(71) Oshiki, T.; Yamashita, H.; Sawada, K.; Utsunomiya, M.; Takahashi, K.; Takai, K. *Organometallics* **2005**, *24*, 6287−6290.

(72) Van Dijk, A. J. M.; Heyligen, T.; Duchateau, R.; Meuldijk, J.; Koning, C. E. *Chem.—Eur. J.* **2007**, *13*, 7664−7672.

(73) Yamaguchi, K.; Matsushita, M.; Mizuno, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1576−1580.

(74) Yi, C. S.; Zeczycki, T. N.; Lindeman, S. V. *Organometallics* **2008**, *27*, 2030−2035.

(75) Vicente, J.; Arcas, A. *Coord. Chem. Rev.* **2005**, *249*, 1135−1154.

(76) Tílvez, E.; Menéndez, M. I.; López, R. *Organometallics* **2012**, *31*, 1618−1626.

(77) Houk, K. N.; Cheong, P. H. *Nature* **2008**, *455*, 309−313.

(78) Kirchner, B.; Wennmohs, F.; Ye, S.; Neese, F. *Curr. Opin. Chem. Biol.* **2007**, *11*, 134−141.

(79) Barbosa, L. A. M. M.; van Santen, R. A. *J. Mol. Catal. A: Chem.* **2001**, 101−121.

(80) Tomasi, J.; Cammi, R. *J. Comput. Chem.* **1995**, *16*, 1449−1458.

(81) Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999−3093.

(82) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027−2094.

(83) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441−451.

(84) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098−3100.

(85) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.

(86) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.

(87) Dunning, T. H., Jr. *J. Chem. Phys.* **1989**, *90*, 1007−1013.

(88) Kendall, R. A.; Dunning, T. H., Jr.; Harrison, R. J. *J. Chem. Phys.* **1992**, *96*, 6796−6802.

(89) Peterson, K. A.; Figgen, D.; Dolg, M.; Stoll, H. *J. Chem. Phys.* **2007**, *126*, 124101-1−124101-12.

(90) Tílvez, E.; Díaz, N.; Menéndez, M. I.; Suárez, D.; López, R. *Theor. Chem. Acc.* **2011**, *128*, 465−475.

(91) Schlegel, H. B. *J. Comput. Chem.* **1982**, *3*, 214−218.

(92) Hratchian, H. P.; Schlegel, H. B. *J. Chem. Phys.* **2004**, *120*, 9918−9924.

(93) Hratchian, H. P.; Schlegel, H. B. In *Theory and Applications of Computational Chemistry: The First 40 Years*; Dykstra, C. E., Frenking, G., Kim, K. S., Scuseria, G., Eds.; Elsevier: Amsterdam, 2005; pp 195−249.

(94) Hratchian, H. P.; Schlegel, H. B. *J. Chem. Theory & Comput.* **2005**, *1*, 61−69.

(95) McQuarrie, D. A.; Simon, J. D. *Molecular Thermodynamics*; University Science Books: Sausalito, CA, 1999.

(96) Elding, L. I. *Inorg. Chim. Acta* **1976**, *20*, 65−69.

(97) Conway, B. E. *J. Solution Chem.* **1978**, *7*, 721−770.

(98) Gomer, R.; Tryson, G. *J. Chem. Phys.* **1977**, *66*, 4413−4424.

(99) Klots, C. E. *J. Phys. Chem.* **1981**, *85*, 3585−3592.

(100) Tawa, G. J.; Topol, I. A.; Burt, S. K.; Caldwell, R. A.; Rashin, A. A. *J. Chem. Phys.* **1998**, *109*, 4852−4863.

(101) Tissandier, M. D.; Cowen, K. A.; Feng, W. Y.; Gundlach, E.; Cohen, M. H.; Earhart, A. D.; Coen, J. V.; Tuttle, T. R. *J. Phys. Chem. A* **1998**, *102*, 7787−7794.

(102) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, revision A.1; Gaussian, Inc.: Wallingford, CT, 2009.

(103) Beret, E. C.; Martínez, J. M.; Pappalardo, R. R.; Sánchez-Marcos, E.; Doltsinis, N. L.; Marx, D. *J. Chem. Theory & Comput.* **2008**, *4*, 2108−2121.

(104) Beret, E. C.; Pappalardo, R. R.; Doltsinis, N. L.; Marx, D.; Sánchez-Marcos, E. *ChemPhysChem* **2008**, *9*, 237−240.

(105) Bowron, D. T.; Beret, E. C.; Martín-Zamora, E.; Soper, A. K.; Sánchez-Marcos, E. *J. Am. Chem. Soc.* **2012**, *134*, 962−967.

(106) Deeth, R. J.; Elding, L. I. *Inorg. Chem.* **1996**, *35*, 5019−5026.

(107) Helm, L.; Merbach, A. E. *Coord. Chem. Rev.* **1999**, *187*, 151−181.

(108) Martínez, J. M.; Torrico, F.; Pappalardo, R. R.; Sánchez-Marcos, E. *J. Phys. Chem. B* **2004**, *108*, 15851−15855.

(109) Kozuch, S.; Shaik, S. *Acc. Chem. Res.* **2011**, *44*, 101−110.

(110) Jaramillo, P.; Coutinho, K.; Canuto, S. *J. Phys. Chem. A* **2009**, *113*, 12485−12495.

(111) Karton, A.; O'Reilly, R. J.; Radom, L. *J. Phys. Chem. A* **2012**, *116*, 4211−4221.

(112) Maeda, S.; Matsuda, Y.; Mizutani, S.; Fujii, A.; Ohno, K. *J. Phys. Chem. A* **2010**, *114*, 11896−11899.

(113) Sambrano, J. R.; Andrés, J.; Gracia, L.; Safont, V. S.; Beltrán, A. *Chem. Phys. Lett.* **2004**, *384*, 56−62.

(114) Tortonda, F. R.; Silla, E.; Tuñón, I.; Rinaldi, D.; Ruiz-López, M. F. *Theor. Chem. Acc.* **2000**, *104*, 89−95.

(115) Tílvez, E.; Menéndez, M. I.; López, R. *Eur. J. Inorg. Chem.* **2012**, 4445−4453.