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Investigation of the Reactivity of Pt Phosphinito and Molybdocene Nitrile Hydration Catalysts With Cyanohydrins

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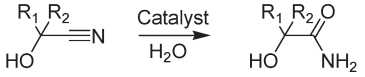
Aldehyde- and ketone-derived cyanohydrins were reacted with the nitrile hydration catalysts [PtCl(PR_2OH)-{($PR_2O)_2H$}] (**1**) and $Cp_2Mo(OH)(OH_2)^+$ (**2**) under a variety of hydration reaction conditions. In general, the cyanohydrins were hydrated to the amides rather slowly using these catalysts, but no subsequent hydrolysis of the amide products occurred. Catalyst **2** was much less reactive than catalyst **1**, showing at best trace amounts of amide product. Product inhibition-, substrate inhibition-, and cyanide poisoning-tests demonstrated that coordination of cyanide, generated by dehydrocyanation of the cyanohydrins, is responsible for the generally low catalytic activity of **1** and **2** with cyanohydrin substrates. Addition of KCN to reaction mixtures of acetonitrile and **1** gave a linear plot of rate versus cyanide concentration, indicating that binding of cyanide to the catalysts is irreversible. Density functional theory (DFT) calculations showed that, for the hydration reaction catalyzed by **2**, the formation of most intermediates and the overall reaction itself are energetically more favorable for lactonitrile (a cyanohydrin) than for 3-hydroxypropionitrile (not a cyanohydrin). From this result, it is concluded that, from an electronic standpoint, there is no intrinsic reason for the lack of reactivity observed for cyanohydrins, a result consistent with the finding that the slow hydration reactivity is caused by cyanide poisoning. In addition, DFT calculations showed that, for nitriles in general (not necessarily cyanohydrins), product inhibition occurs because coordination of the amide product to the metal center is stabilized by isomerization to the more strongly bonded iminol tautomer.

Introduction

The catalytic hydration of cyanohydrins (eq 1) is an important transformation in many chemical and pharmaceutical processes because it provides an atom economical route to high-value α-hydroxyamides, α-hydroxycarboxylic acids, and α-hydroxycarboxylic esters.[1,2]



(1)

Classical methods of using concentrated acid to promote the hydration of cyanohydrins present several disadvantages. For example, when sulfuric acid is used, the amide sulfate salt is generated as opposed to the α-hydroxyamide. Although the amide sulfate salt can be hydrolyzed or esterified to afford value-added carboxylic acids and esters in high yield (>92%), the reaction also produces undesired sulfonates, oligomers, polymers, and ammonium bisulfate.[1] The production of byproduct ammonium bisulfate is a major economic and environmental drawback of a large-scale sulfuric acid mediated process because its disposal is typically not permitted and its recycle to virgin sulfuric acid requires additional high-energy processing steps. Anhydrous HCl can also be used to hydrate cyanohydrins, but stoichiometric quantities of undesirable alkyl chloride byproduct are generated. For these reasons, our goal is to develop an acid-free process for the hydration of cyanohydrins using a low-cost homogeneous, transition metal catalyst that will allow direct access to the α-hydroxyamide product.[3] In principle, the electronic and structural environment of such a catalytic system could be tailored to afford a general synthetic route by which a range of chiral and achiral α-hydroxyamides, α-hydroxycarboxylic acids, and α-hydroxycarbocylic esters could be accessed.

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(3) Several noteworthy acid-free synthetic methods for the hydration of cyanohydrins utilizing boron, metal oxides, and nitrile hydratase enzymes as mediators have been disclosed in patents and in the literature. These methods are summarized in the Supporting Information.

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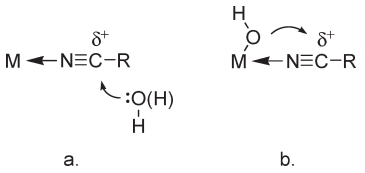

Figure 1. Intermolecular (a) and intramolecular (b) pathways for the metal-catalyzed hydration of nitriles.

A host of organometallic and coordination complexes of early and late transition metals have been shown to catalyze the conversion of nitriles to amides.[4] In general, these activate the nitrile by removing electron density from the nitrile carbon, making it more susceptible to intramolecular or intermolecular nucleophilic attack by water or hydroxide (Figure 1). In doing so, the metal center lowers the activation barrier to hydration of the nitrile relative to hydrolysis of the amide, and in many cases further hydrolysis of the amide functionality is not observed. However, none of these catalytic systems have been applied to cyanohydrins. Of the transition metal complexes reported in the literature, the Pt phosphinito complexes, $[PtX(PR_2OH)\{(PR_2O)_2H\}]$ where X = Cl or H, first developed by Parkins and co-workers,[5−7] are the most reactive and versatile in hydrolytic nitrile conversions. For example, acrylonitrile is hydrated regioselectively to acrylamide in refluxing aqueous ethanol at a turnover frequency of 0.5 s^{-1} using only 0.015 mol % of $[PtCl(PMe_2OH)\{(PMe_2O)_2H\}]$.[6] In related work, Cobley et al. demonstrated that the Pt complexes are also effective in the hydrolytic amidation of nitriles to N-substituted amides using alkylamines.[8] Further work by Jiang et al. demonstrated that the Pt phosphinito complexes are also efficient in the hydration of bulky nitriles and in nitriles containing acid- or base-sensitive functionalities (i.e., ether and carbohydrate functionalities),[9] which typically show very low reactivity and selectivity with other nitrile hydration catalysts.

The broad applicability and high activity of the Pt phosphinito complexes toward nitrile substrates makes them excellent candidates for catalytic conversions of cyanohydrins. In this report, the reactivity of the $[PtCl(PMe_2OH)\{(PMe_2O)_2H\}]$ (**1**) complex toward variously substituted cyanohydrins is described. In addition, the catalytic reactivity of $Cp_2Mo(OH)(OH)_2^+$ (**2**) with cyanohydrins is reported. In prior work, our laboratory demonstrated the utility of molybdocene complexes, such as (**2**),[10−12] in the hydration of nitrile substrates. Like the Pt phosphinito complexes, the molybdocenes are slightly water-soluble, effective toward the regioselective hydration of acrylonitrile (TOF = 3.8×10^{-4} s^{-1} using 1.4% $(\eta^5\text{-}C_5H_4Me)_2Mo(OH)(OH_2)^+$ in D_2O at 75 °C),[10] and reactive with bulky nitriles. Furthermore, although molybdocenes are much less reactive than the Pt phosphinito complexes, they show improved reactivity with nitriles containing electron-withdrawing substituents, which bodes well for cyanohydrin substrates.

1 **2**

Experimental Section

General Considerations. Experiments were performed using standard air-free techniques in an atmosphere of N_2 unless otherwise stated. The complexes $[PtCl(PMe_2OH)\{(PMe_2O)_2H\}]$ (**1**),[6] $[Cp_2Mo(\mu\text{−}OH)]_2[OTs]_2$ (**2**),[13] 2-methoxypriopionitrile,[14] and 2-methoxyisobutyronitrile[14] were synthesized according to procedures previously reported in the literature. Reagent grade nitriles (>97% purity) were purchased from Sigma-Aldrich. Cyanohydrins were distilled before use, except cyclohexanone cyanohydrin (a solid) and glycolonitrile (purchased as a 55% solution in water). Glycolamide was obtained from Sigma-Aldrich, and 2-hydroxyisobutyramide was obtained from TCI Japan Organic Chemicals. All hydrolysis and hydration reaction samples were prepared in a glovebox under an atmosphere of N_2 in Wilmad 9 in. precision NMR tubes or Wilmad J-Young screw cap NMR tubes, except where noted. Reactions carried out in the Wilmad 9 in. NMR tubes were flame-sealed while frozen. Reaction tubes were heated in an oil bath. ^1H NMR spectra were obtained using a Varian Inova 500 MHz (500.104 MHz for ^1H and 125.764 MHz for ^{13}C) or 600 MHz NMR spectrometer (599.982 MHz for ^1H and 150.879 MHz for ^{13}C). Cyanohydrin hydration reactions were performed using a plethora of reaction conditions. Representative procedures that yielded the best results are given below.

Preparation of Stock Solutions of 1. Stock solutions of **1** were prepared by adding **1** and thallium triflate to 10 mL of D_2O and heating to 80 °C. After 8 h, the solutions were allowed to cool to room temperature and filtered using 0.22 μm filters to remove gray or white precipitate. The concentration of $[PtX(PMe_2OH)\{(PMe_2O)_2H\}]$ and degraded Pt was determined using a known amount of tetrabutylphosphonium bromide as an internal standard. (The identity of X in $[PtX(PMe_2OH)\{(PMe_2O)_2H\}]$ is discussed in the last section of the Results and Discussion section.)

General Procedures for the Hydration of Cyanohydrins Catalyzed by 1. Note that the procedures using catalyst **2** were identical to the procedures described below; however, no Tl salt was added.

Glycolonitrile. Catalyst **1** (0.0054 g, 0.012 mmol) and TlOTf (0.0036 g, 0.010 mmol) were added to a solution of 55% glyconitrile (3.55 mmol) in H_2O and allowed to react at 25 °C. After 3 days, the ^1H NMR spectrum showed a mixture of glycolonitrile at 4.50 ppm (s, 2H, $(HO)CH_2CN$) and glycolamide at 4.30 ppm (s, 2H, $(HO)CH_2C(O)NH_2$).

Lactonitrile. Lactonitrile (250 μL, 3.49 mmol), catalyst **1** (0.0102 g, 0.0220 mmol), and TlOTf (0.0110 g, 0.0311 mmol) were added to 250 μL of D_2O. The mixture was allowed to react at 25 °C for 13 days, over which time 69.0% of lactonitrile was hydrated to 2-hydroxypropionamide. In the ^1H NMR spectrum, resonances (D_2O) for lactonitrile were observed at 4.66 ppm (q, J = 6.5 Hz, 1H, $(HO)(CH_3)CHCN$) and 1.48 ppm (d, J =

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6.5 Hz, 3H, (HO)(CH_3)CHCN), and resonances for 2-hydroxypropionamide were observed at 4.22 ppm (m, 1H, (HO)(CH$_3$)CHC(O)ND$_2$) and 1.29 ppm (d, J = 7.0 Hz, 3H, (HO)(CH$_3$)CHC(O)ND$_2$). The generation of 2-hydroxypropionamide was also observed in the ^{13}C NMR spectrum at 183.5 ppm (s, (HO)(CH$_3$)CHC(O)ND$_2$), 70.3 ppm (s, (HO)(CH$_3$)CHC(O)ND$_2$), 22.4 ppm (s, (HO)(CH$_3$)CHC(O)ND$_2$). Less intense resonances for acetaldehyde were observed at 9.61 ppm.

2-Hydroxybutyronitrile. A solution containing catalyst **1** (0.0165 g, 0.0356 mmol), TlOTf (0.0150 g, 0.0424 mmol), 2-hydroxybutyronitrile (250 μL, 2.83 mmol), 50 μL of H_2O, and 200 μL of methanol was prepared. Over 5 days at 25 °C, ^{1}H NMR resonances for 2-hydroxybutyronitrile at 4.57 ppm (t, J = 6.9 Hz, 1H, CH$_3$(HO)(CH$_2$)CHCN), 1.91 ppm (quintet, J = 7.0 Hz, 2H, CH$_3$(HO)(CH$_2$)CHCN), and 1.14 ppm (t, J = 7.2 Hz, 3H, CH_3(HO)(CH$_2$)CHCN) disappeared, and the appearance of 2-hydroxybutyramide at 7.52 ppm (s, 1H, CH$_3$(HO)(CH$_2$)CHCONH_2), 7.11 ppm (s, 1H, CH$_3$(HO)(CH$_2$)CHCONH_2), 4.12 ppm (m, 1H, CH$_3$(HO)(CH$_2$)CHCONH$_2$), 1.74 ppm (m, 2H, CH$_3$(HO)(CH_2)CHCONH$_2$), and 1.06 ppm (t, J = 7.0 Hz, 3H, CH_3(HO)(CH$_2$)CHCONH$_2$) was observed. 2-Hydroxybutyramide was also observable in the ^{13}C NMR spectrum at 182.1 ppm (s, CH$_3$(HO)(CH$_2$)CHCONH$_2$), 75.4 ppm (2, CH$_3$(HO)(CH$_2$)CHCONH$_2$), 30.2 ppm (s, CH$_3$(HO)(CH$_2$)CHCONH$_2$), and 11.6 ppm (s, CH$_3$(HO)(CH$_2$)CHCONH$_2$).

Mandelonitrile. A solution containing catalyst **1** (0.0183 g, 0.0395 mmol), TlOTf (0.0170 g, 0.0481 mmol), mandelonitrile (250 μL, 2.10 mmol), 50 μL of H_2O, and 200 μL of methanol was prepared. Initially, ^{1}H NMR resonances for mandelonitrile appeared at 7.46 ppm (m, 2H, C$_5H_5$(HO)CHCN), 7.32 ppm (m, 3H, C$_5H_5$(HO)CHCN), and 5.59 ppm (s, 1H, C$_5$H$_5$(HO)CHCN). After 3 days at 25 °C, benzaldehyde signals were noted at 9.77 ppm (s, 1H, C$_5$H$_5$(HO)CHC(O)H) in the ^{1}H NMR spectrum and 197.1 ppm in the ^{13}C spectrum (s, C$_5$H$_5$(HO)CHC(O)H). A signal attributable to mandelamide was detected in the ^{13}C NMR spectrum at 180.2 ppm (s, C$_5$H$_5$(HO)CHC(O)NH$_2$).

Cyclohexanone Cyanohydrin. Cyclohexanone cyanohydrin (0.0901 g, 0.720 mmol), catalyst **1** (0.0162 g, 0.0349 mmol), TlOTf (0.0150 g, 0.0424 mmol) were added to a mixture of 50 μL of H_2O and 450 μL of methanol. After 3 days at 25 °C, amide protons were apparent at 7.59 ppm and 7.01 ppm in the ^{1}H NMR spectrum. 2-hydroxy-2-cyclohexanoic acid amide was also observed in the ^{13}C NMR spectrum at 185.3 ppm (C$_6$H$_{10}$CHC(O)ND$_2$), 77.6 ppm (C$_6$H$_{10}$$C$C(O)ND$_2$), 36.6 ppm ($C_6H_{10}$CC(O)ND$_2$), 27.9 ppm ($C_6H_{10}$C(O)ND$_2$), and 23.7 ppm ($C_6H_{10}$C(O)ND$_2$).

Acetone Cyanohydrin. A solution containing catalyst **1** (0.0232 g, 0.0500 mmol), TlOTf (0.0200 g, 0.0566 mmol), acetone cyanohydrin (500 μL, 5.48 mmol), and 500 μL of D_2O was prepared. The mixture was allowed to react for 7 days at 25 °C. During this time, the acetone cyanohydrin was hydrated to 2-hydroxyisobutyramide (2.73% yield) and dissociated to give 0.93% of acetone. ^{1}H NMR resonances for the acetone cyanohydrin appeared at 1.51 ppm (s, 6H, HO(CH_3)$_2$CCN) and 2-hydroxyisobutyramide was observed at 1.44 ppm (s, 6H, HO(CH_3)$_2$CCOND$_2$). A less intense resonance was observed for acetone at 2.01 ppm (s, 6H, (CH$_3$)$_2$CO. The presence of 2-hydroxyisobutyramide was confirmed in the ^{13}C spectrum at 182.3 ppm (s, 6H, HO(CH$_3$)$_2$$C$COND$_2$), 73.1 ppm (s, 6H, HO(CH$_3$)$_2$$C$COND$_2$), 28.6 ppm (s, 6H, HO($CH_3$)$_2$CCOND$_2$). The amide deuterium atoms were observable in the ^{2}H spectrum at 7.46 ppm and 6.76 ppm.

Hydration of Other Nitriles Catalyzed by 1. 3-Hydroxypropionitrile. 3-Hydroxypropionitrile (16 μL, 0.24 mmol) was added to 0.60 mL of catalyst solution (0.24 μmol) and 0.10 mL of PBu$_4$Br (0.32 μmol). Over 10 h at 43 °C, ^{1}H NMR resonances (D_2O) for the 3-hydroxypropionitrile at 3.78 ppm (t, J = 6.0 Hz, 2H, HOCH_2CH$_2$CN) and 2.67 ppm (t, J = 6.0 Hz, 2H, HOCH$_2$CH_2CN) disappeared, and the appearance of 3-hydroxypropionamide at 3.76 ppm (t, J = 6.0 Hz), 2H, HOCH$_2$CH_2CONH$_2$) and 2.45 ppm (t, J = 6.0 Hz), 2H, HOCH_2CH$_2$CONH$_2$) was observed.

2-Methoxypropionitrile. Catalyst stock solution (0.60 mL, 0.24 μmol), PBu$_4$Br (0.10 mL, 0.32 μmol), and 2-methoxypropionitrile (22 μL, 0.24 mmol) were added to a 9 in. NMR tube. The ^{1}H NMR resonances (D_2O) before heating appeared at 4.39 ppm (q, J = 6.8 Hz, 1H, (CH$_3$O)(CH$_3$)CHCN), 3.44 ppm (s, 3H, (CH_3O)(CH$_3$)CHCN), and 1.49 (d, J = 6.8 Hz, 3H, (CH$_3$O)(CH_3)CHCN). Over 15 h at 43 °C, the ^{1}H NMR resonances corresponding to 2-methoxypropionitrile decreased in intensity, and resonances for 2-methoxypropionamide increased at 3.82 ppm (q, J = 6.8 Hz, 1H, (CH$_3$O)(CH$_3$)CHC(O)ND$_2$), 3.33 ppm (s, 3H, (CH_3O)(CH$_3$)CHC(O)ND$_2$), and 1.29 (d, J = 6.8 Hz, 3H, (CH$_3$O)(CH_3)CHC(O)ND$_2$).

2-Bromopropionitrile. 2-Bromopropionitrile (21 μL, 0.24 mmol) was added to a mixture of catalyst stock solution (0.60 mL, 0.24 μmol) and PBu$_4$Br (0.10 mL, 0.32 μmol). 2-Bromopropionitrile was sparingly soluble in D_2O and formed a white layer at the bottom of the NMR tube. The sample was heated at 43 °C for 24 h. During this time, all of the 2-bromoproionitrile dissolved and the ^{1}H NMR resonances (D_2O) for the 2-bromopropionitrile at 4.69 ppm (q, J = 7.2 Hz, 1H, (Br)(CH$_3$)CHCN) and 1.90 ppm (d, J = 7.1 Hz, 3H, (Br)(CH_3)CHCN) were replaced by resonances for 2-bromopropionamide at 4.49 ppm (q, J = 6.9 Hz, 1H, (Br)(CH$_3$)HC(O)ND$_2$) and 1.71 ppm (d, J = 6.9 Hz, 3H, (Br)(CH_3)CHC(O)ND$_2$). Less intense resonances attributed to 2-hydroxypropionamide were also observed at 4.37 ppm and 1.33 pppm.

Acetonitrile. Acetonitrile (12.5 μL, 0.24 mmol) was added to a mixture of catalyst stock solution (0.60 mL, 0.24 μmol) and PBu$_4$Br (0.10 mL, 0.32 μmol). The resulting mixture was heated at 43 °C for 45 h. During this time, acetonitrile was converted to acetamide. The production of acetamide was monitored in the ^{1}H NMR spectrum (D_2O) by disappearance of the acetonitrile protons at 2.01 (s, CH_3CN) and the appearance of acetamide at 1.93 ppm (s, CH_3C(O)ND$_2$).

Propionitrile. Catalyst stock solution (0.60 mL, 0.24 μmol), PBu$_4$Br (0.10 mL, 0.32 μmol), and propionitrile (17 μL, 0.24 mmol) were added to a 9 in. NMR tube. Over 3 days at 43 °C, ^{1}H NMR resonances (D_2O) for the propionitrile at 2.38 ppm (q, J = 7.6 Hz, 2H, CH$_3$CH_2CN) and 1.18 ppm (t, J = 7.6 Hz, 3H, CH_3CH$_2$CN) disappeared, and the appearance of propionamide at 2.21 ppm (q, J = 7.6 Hz), 2H, CH$_3$CH_2C(O)ND$_2$) and 1.05 ppm (t, J = 7.7 Hz), 3H, CH_3CH$_2$C(O)ND$_2$) was observed.

Isobutyronitrile. Catalyst stock solution (0.60 mL, 0.24 μmol), PBu$_4$Br (0.10 mL, 0.32 μmol), and isobutyronitrile (22 μL, 0.24 mmol) were added to a 9 in. NMR tube. ^{1}H NMR resonances (D_2O) were observed at 2.81 ppm (heptet, J = 7.0 Hz, 1H, (CH$_3$)$_2$CHCN) and 1.26 ppm (d, J = 7.0 Hz, 6H, (CH$_3$)$_2$CHCN) before heating. Over 3 weeks at 43 °C, the ^{1}H NMR resonances corresponding to isobutyronitrile decreased in intensity, and resonances for 2- isobutyroamide appeared at 2.49 ppm (heptet, J = 7.0 Hz, 1H, (CH$_3$)$_2$CHC(O)ND$_2$) and 1.07 ppm (d, J = 7.0 Hz, 6H, (CH$_3$)$_2$CHC(O)ND$_2$).

Trimethylacetonitrile. Catalyst stock solution (0.60 mL, 0.24 μmol), PBu$_4$Br (0.10 mL, 0.32 μmol), and 2-methoxypropionitrile (26 μL, 0.24 mmol) were added to a 9 in. NMR tube. The resulting mixture was heated on an oil bath at 80 °C 2 days. During this time, trimethylacetonitrile was converted to trimethylacetamide. The production of trimethylacetamide was monitered by ^{1}H NMR (D_2O) by the disappearance of the trimethylacetonitrile protons at 1.31 (s, (CH_3)$_3$CN) and the appearance of trimethylacetamide at 1.35 ppm (s, (CH_3)$_3$C(O)ND$_2$).

2-Methoxyisobutyronitrile. 2-Methoxyisobutyronitrile (35 μL, 0.34 mmol), **1** (0.0010 g, 2.2 μmol), and excess NaBPh$_4$ in D_2O were added to a 9 in. NMR tube. The solution was heated to 60 °C

for 14 h, during which time the 2-methoxyisobutyronitrile was hydrated. The hydration was monitored by the disappearance of ^{1}H NMR resonances (D_2O) at 3.36 ppm (s, 3H, (CH_3O)(CH_3)$_2$CCN) and 1.51 ppm (s, 6H, (CH_3O)(CH_3)$_2$CCN) and by the appearance of resonances at 3.18 (s, 3H, (CH_3O)(CH_3)$_2$CC(O)ND_2) and 1.28 ppm (s, 6H, (CH_3O)(CH_3)$_2$CC(O)ND_2).

Control Experiment for the H/D Exchange Reaction. A 7.00 μL portion of acetone cyanohydrin (77.0 μmol) was added to 0.800 mL of D_2O containing NBu_4BF_4 (6.96 μmol) and CD_3SO_3D (1.13 μmol) as internal standards (pH 3.5). The disappearance of ACH was monitored at 1.62 ppm (s, 6H, HO(CH_3)$_2$CCN), and the appearance of acetone and HCN were monitored at 2.23 ppm (s, 6H, (CH_3)$_2$CO) and 5.29 ppm (*H*CN) in the ^{1}H NMR spectrum. The appearance of deuterated ACH, acetone, and hydrocyanic acid were monitored in the ^{2}H NMR spectra at 1.62 ppm (DO(CD_3)$_2$CCN), 2.25 ppm ((CD_3)$_2$CO), and 5.28 ppm (*D*CN). After 25 days, 90.5% of the ACH was fully deuterated, and a total of 43.3% of the ACH was dissociated to acetone and HCN.

Tests for Substrate Inhibition. PBu_4Br (100 μL, 0.398 μmol), an aliquot of stock solution of **1** (400 μL, 0.195 μmol), and 3-hydroxyproponitrile (17.0 μL, 0.250 mmol) were added to each of three 9 in. NMR tubes. After 50 min of reaction, one reaction mixture was spiked with lactonitrile (18.0 μL, 0.250 mmol), and acetone cyanohydrin (23.0 μL, 0.250 mmol) was added to a second. The reaction solutions spiked with lactonitrile and ACH showed an abrupt halt in reactivity.

Tests for Product Inhibition. Acetonitrile (28.0 mL, 0.536 mmol), 2-hydroxyisobutryonitrile (0.0135 g, 0.184 μmol), and PBu_4Br (100 μL, 0.44 μmol) were added to 400 μL of **1** (0.24 μmol) in D_2O and heated to 35 °C in oil bath and monitored for 3 days. In a separate trial, acetonitrile (12.5 μL, 0.239 mmol), glycolamide (0.0244 g, 0.325 mmol), and PBu_4Br (100 μL, 0.32 μmol) were added to 600 μL of **1** (0.24 μmol) in D_2O and heated to 35 °C in oil bath and monitored for 3 days. In both cases, the acetonitrile hydration was monitored by ^{1}H NMR spectroscopy as noted above. The rate of acetamide production was identical to that observed for the control reactions performed using identical concentrations of reactants (and internal standard) and no added amide.

Titration with KCN. Aliquots of KCN dissolved in D_2O (2−60 μL; 8.91 μmol−0.913 mmol) were added to reaction mixtures containing 28.0 μL acetonitrile (0.536 mmol), 400 μL of **1** (0.205 μmol), and 100 μL of PBu_4Br (0.398 μmol) in 9 in. NMR tubes. The mixtures were heated at 35 °C in an oil bath for 3 days, over which time the production of acetamide was monitored as noted above. Complete cessation of catalytic reactivity was observed above 3.5 equiv. The rate of acetonitrile hydration was calculated from the percent conversion at 22 h of reaction and plotted as a function of KCN equivalents with respect to dissolved Pt. The resulting linear plot was described by $y = -0.012x + 0.033$.

Hg poisoning test. 1 (13 mg, 0.028 mmol) was added to a stirred mixture of acetonitrile (6.5 mL, 0.12 mol) and H_2O (4.0 mL, 0.22 mol). $AgBF_4$ (7.4 mg, 0.038 mmol) was added to the reaction mixture, and the mixture was refluxed at 85 °C for 3 h. Hg^0 (3 drops) was added to the reaction mixture, and the reaction was stirred under reflux for another 21 h. Aliquots (0.25 mL) of the reaction were taken at 3, 4, 5, 6, and 23 h, being careful not to remove any Hg^0. Aliquots were added to an internal standard (3.32 mM [NMe_4][PF_6] in D_2O, 0.25 mL) in an NMR tube, and quantitated by ^{1}H NMR.

Computational Methods. To compare the reactivities of cyanohydrins with other nitriles toward catalytic hydration, density functional theory (DFT) calculations were performed on various reaction intermediates of the isomeric compounds lactonitrile and 3-hydroxypropionitrile (3-HPN). The molybdocene catalyst **2** was used in the calculations, and the intermediates are based on the mechanism proposed by Breno (Figure 8).[10] The building and modeling of $Cp_2Mo(OH)NCR$ and all related intermediates were performed using the program Ecce v3.2.4.[15,16] Each intermediate has a +1 charge. Calculations were performed on singlet states of each intermediate. All DFT calculations were performed using NWChem version 5.0.[17,18]

Geometry optimizations were performed on all structures, and frequency and single-point energy calculations were performed on the optimized structures. All structures yielded zero imaginary frequencies. For some structures, a fine grid and tighter convergence criteria were needed to obtain a minimum energy structure. For all atoms except molybdenum, the 6-31G* basis set[19] was used for the geometry optimizations and frequency calculations, and the 6-311G** basis set[20] was used for the final energy calculations. For molybdenum, a triple-ζ valence basis set and effective core potential developed by Andrae et al.,[21] augmented with one diffuse f function (ζ = 0.338) determined by Martin and Sundermann[22] resulting in a (8s7p6d1f)/[6s5p3d1f] contraction, was used for both the optimizations and single-point energy calculations. Final energies include solvation energies, as well as thermal and entropic corrections. All calculations employed the B3LYP functional.[23−26]

Solvation contributions were approximated by employing the COSMO reaction field[27] on the gas-phase optimized structures. Solvent effects were not incorporated into geometry optimizations because it was found to be very difficult to obtain converged structures with this approach. In addition, it is possible that hydrogen bonding from the solvent may participate in the reaction. Since both nitriles can utilize hydrogen bonding, it is unlikely to account for the observed differences between them, thus the effects of hydrogen bonding are not considered here. A dielectric constant of 78.4 corresponding to H_2O was used for the solvation energy calculations. The atomic radii used for the solvation energy calculations were those developed by Stefanovich and Truong,[28] except for molybdenum, where an approximate cavity radius of 2.0 Å was used. Radii for sp/sp^2-carbon atoms (1.635 Å) were used for the cyclopentadienyl- and nitrile-carbons, and radii for sp^3-carbon

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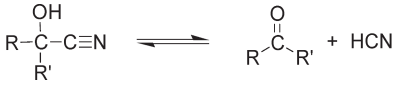
atoms (2.096 Å) were used for treating the aliphatic carbons. A solvent probe radius of 0.2 Å was used because it gave the closest agreement with experimental solvation energies of H_2O, acetonitrile, and acetamide (which are representative of the system).

Results and Discussion

Hydration Reactions of Cyanohydrins Using Catalysts 1 and 2. The cyanohydrins in Figure 2 were reacted with catalytic amounts of **1** and **2** under a variety of hydration reaction conditions. Selected reaction conditions and results illustrating the range of reactivity are listed in Table 1. In general, species **2** was a very poor catalyst for the hydration reactions, while the catalytic activity of **1** varied greatly with catalyst concentration, substrate concentration, and volume of cosolvent. With catalyst **1**, lactonitrile and 2-hydroxybutryonitrile produced the highest yields of amide product (> 50%), while glycolonitrile and cyclohexanone cyanohydrin yielded only 4% and 14% of the respective α-hydroxyamides. Of the various nitriles, acetone cyanohydrin (ACH), and mandelonitrile showed the lowest reactivity with **1**, producing only a few percent of α-hydroxyisobutyramide (< 3%) and trace amounts of α-mandelamide, respectively. Note also in Table 1 that, in many cases, dissociation of the cyanohydrin to give an equilibrium mixture of the cyanohydrin, HCN, and the parent aldehyde or ketone (eq 2) was the only reactivity observed.



(2)

Because the reaction mixtures were acidified using triflic-, methyl sulfonic-, or tosic-acid, the extent of cyanohydrin dissociation observed in the dilute reaction mixtures was surprisingly larger than expected. It was expected that acidic conditions would help to stabilize the cyanohydrin species because acid is produced upon its dissociation (eq 2). However, even at pH 1, extensive dissociation (> 80%) was observed in dilute reaction mixtures of ACH. In fact, note in Table 1 that aldehyde or ketone from the dissociation of cyanohydrin was always observed by ^{1}H NMR spectroscopy in all of the reaction mixtures. A control experiment showed that the dissociation is not metal mediated. Thus, cyanohydrin dissociation occurred without **1** or **2** present (in water with or without cosolvents; see Table 1), even under acidic conditions. For example, at pH 3 and 23 °C, 76.1% dissociation of ACH was observed in 5 days without either catalyst present.

Although the metal complex does not appear to mediate degradation, it does influence the position of the cyanohydrin-HCN equilibrium. As shown in Table 1, a higher percentage of degradation was observed when a higher concentration of catalyst was used but with all other conditions identical (i.e., solvent composition, reaction temperature, and substrate concentration). Over time, the percent degradation always approached or exceeded the percent catalyst. The experimental consequences of the cyanohydrin dissociation are discussed later.

In several of the ACH reaction mixtures where no reactivity was observed, scrambling of the ketone and cyanohydrin protons with solvent deuterium occcurred,

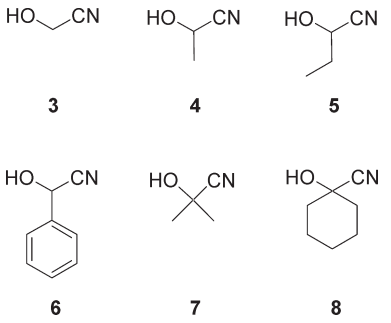


Figure 2. Structures of glycolonitrile (**3**); lactonitrile (**4**); 2-hydroxybutyronitrile (**5**); mandelonitrile (**6**); acetone cyanohydrin, ACH (**7**); and cyclohexanone cyanohydrin (**8**).

as indicated in the ^{1}H NMR spectrum by the appearance of triplet and quintet resonances on the shoulder of the parent resonance (Figure 3). The presence of the deuterated species was also confirmed in the ^{2}H spectrum of the ACH, which showed resonances at 1.62 ppm ($DO(CD_3)_2CCN$), 2.25 ppm ($(CD_3)_2CO$), and 5.28 ppm (DCN). The mechanism of H/D exchange is not metal mediated because H/D exchange was also observed in a control reaction performed at pH 3 without **1** present.[29] It is suggested that H/D exchange proceeds by the keto−enol tautomerism of the acetone under acidic conditions (Scheme 1). At high ACH concentration when no acid was added to the reaction mixture, no deuterated acetone or cyanohydrin was observed, a result consistent with the proposed acid catalyzed mechanism. Note that the HCN present in the reaction mixture is not acidic enough to protonate the acetone.

Comparison of Cyanohydrins to Other Nitriles. The α-hydroxy substituent in cyanohydrins was expected to increase the reactivity of the nitrile group by increasing the partial positive charge on the nitrile carbon. This expectation was based on prior work that showed molybdocene catalysts were most reactive toward nitriles containing electron-withdrawing substituents.[10] (An increase in the reaction rate with increasing electron withdrawing ability of the substrate is expected for a mechanism involving nucleophilic attack of the hydroxo ligand on the coordinated substrate.) Interestingly, lactonitrile (an α-hydroxynitrile) is essentially unreactive with catalyst **2**, whereas a prior study found that the hydration of 3-hydroxypropionitrile (3-HPN; a β-hydroxynitrile) was the fastest molybdocene-catalyzed nitrile hydration of the nitriles studied.[10] To explain this result, it was initially hypothesized that the nitrile carbon of cyanohydrins may be more electron rich (i.e., have more cyanide-like character) than other nitrile substrates. Such an electron-rich carbon center would be much less susceptible to nucleophilic attack and would, therefore, be less reactive by typical metal-mediated nitrile hydration pathways. However, comparison of the ^{13}C NMR resonance frequencies of selected nitriles shows that the nitrile carbons of ACH and 2-hydroxypropionitrile resonate at a frequency similar to that of other nitriles (Table 2),

(29) Prior studies showed that H/D exchange in alcohols occurs by a mechanism involving coordination through the oxygen atom, followed by β-hydride elimination. (See Balzarek, C.; Weakley, T. J. R.; Tyler, D. R. *J. Am. Chem. Soc.* **2000**, *122*, 9427.) However, beta-hydride elimination is not possible from coordinated ACH because it is a tertiary alcohol.

Table 1. Summary of Selected Cyanohydrin Hydration Results Using $PtCl(PMe_2OH)\{(PMe_2O)_2H\}$ (1) and $Cp_2Mo(OH)(OH_2)^+$ (2) Nitrile Hydration Catalysts

cyanohydrin	catalyst	cosolvent	mL of cyano-hydrin	mL of water	mL of other cosolvent	[cyanohydrin] (M)	% catalyst	reaction temp (°C)	% dissociation	% hydration	rxn time (h)
glycolonitrile	1	H_2O	0.275	0.225	0.000	8.68	0.06%	25	1.00%	3.98%	52.6
lactonitrile	1	D_2O	0.025	1.000	0.000	0.34	0.29%	80	1.07%	68.00%	1896.0
lactonitrile	1	D_2O	0.250	0.250	0.000	6.97	0.63%	25	0.25%	68.95%	143.8
lactonitrile	2	H_2O	0.250	0.25	0.000	6.97	1.04%	25	0.21%	0.82%	74.8
2-hydroxybutyronitrile	1	D_2O	0.500	0.100	0.000	9.42	0.20%	50	$<0.5\%$	0.00%	24.0
2-hydroxybutyronitrile	1	H_2O, CH_3OH	0.250	0.050	0.200	5.65	1.26%	25	$<0.5\%$	51.35%	99.5
mandelonitrile	1	D_2O	0.500	0.100	0.000	7.01	0.20%	50	2.86%	0.00%	24.0
mandelonitrile	1	H_2O, CH_3OH	0.200	0.050	0.250	3.36	2.35%	25	2.86%	Trace	74.4
cyclohexanone cyanohydrin	1	D_2O	0.030 g	0.500	0.000	0.40	0.20%	50		0.00%	24.0
cyclohexanone cyanohydrin	1	H_2O, CH_3OH	0.0901	0.450	0.050	1.26	4.71%	25		14.00%	74.4
acetone cyanohydrin	1	D_2O	0.032	1.000	0.000	0.34	0.33%	25	5.30%	0.00%	24.2
acetone cyanohydrin	1	D_2O, $(CH_3)_2CO_2H$	1.000	0.426	1.000	4.51	0.05%	80	47.85%	0.00%	24.0
acetone cyanohydrin	1	D_2O, $(CH_3)_2CO$	0.640	0.426	0.815	3.73	0.08%	80	68.60%	0.00%	24.0
acetone cyanohydrin	1	D_2O	0.500	0.100	0.000	9.13	0.20%	50	25.00%	0.00%	328.2
acetone cyanohydrin	1	CH_3OH	0.500	0.000	0.100	9.13	0.19%	50	1.57%	0.00%	328.6
acetone cyanohydrin	1	IPA	0.500	0.000	0.100	9.13	0.10%	50	0.90%	0.00%	328.5
acetone cyanohydrin	1	D_2O	0.900	0.100	0.000	9.86	0.02%	25	0.32%	0.00%	170.7
acetone cyanohydrin	1	D_2O	0.500	0.500	0.000	5.48	0.04%	25	0.60%	0.00%	170.7
acetone cyanohydrin	1	D_2O	0.100	0.900	0.000	1.10	0.20%	25	2.98%	0.00%	170.7
acetone cyanohydrin	1	D_2O	0.500	0.500	0.000	5.48	0.91%	25	0.93%	2.72%	144.8
acetone cyanohydrin	1	H_2O, CH_3OH	0.250	0.050	0.200	5.48	1.34%	25	0.90%	2.00%	163.9
acetone cyanohydrin	1	H_2O, CH_3OH	0.250	0.250	0.000	5.48	1.34%	25	1.27%	1.06%	163.9
acetone cyanohydrin	2	D_2O, Acetic Acid	0.500	0.200	0.500	4.56	0.19%	80	80.00%	0.52%	38.6
acetone cyanohydrin	2	H_2O	0.250	0.250	0.000	5.48	1.76%	25	6.42%	1.00%	75.0

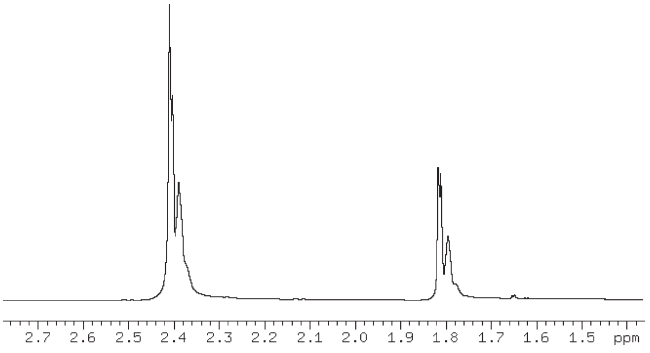


Figure 3. ^1H NMR spectrum of ACH reaction mixture showing appearance of deuterated acetone and ACH.

which suggests that the electronic charge on the nitrile carbon in cyanohydrins is not unusual.

To gain insight into the sluggish reactivity of the cyanhydrins and the electronic and steric influences of the α-hydroxy group on the rate, an investigation of variously substituted nitriles (Figure 4) was conducted using the more reactive catalyst **1**. A summary of the results appears in Table 3.[30,31] An interesting point, not

(30) The rates shown in the table were calculated for the nitrile substrates based on the percent conversion after 2 h of reaction. No carboxylic acid product was observed in the reaction mixtures of these systems, even after prolonged heating. Note that all of the reactions proceeded to completion and displayed first- or zero-order dependence on the substrate and eventually proceeded to completion.[31]

Scheme 1. Proposed Mechanism of H/D Exchange for Cyanohydrins under Acidic Reaction Conditions

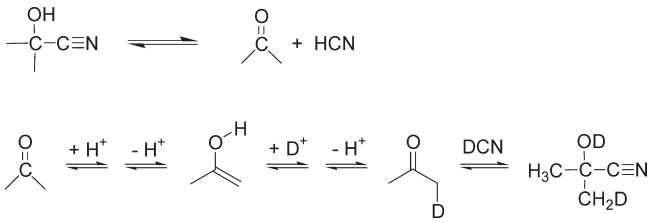


Table 2. Comparison of Nitrile ^{13}C NMR Resonate Frequencies for Selected Nitriles

nitrile	δ (NCR)
acetonitirile	118.1
3-hydroxypropionitrile	120.7
2-hydroxypropionitrile	121.5
acetone cyanohydrin	123.3
propionitrile	123.7

shown in the table, is that the rate of lactonitrile hydration declined rapidly from an initial rate of 0.062 M/h[32] to 1.9×10^{-4} M/h within 9 h of reaction (Figure 5). This behavior is typical of product inhibition. Interestingly, the substrates 2-methoxypropionitrile and 2-methoxyisobutyronitrile,[33] which are electronically similar to lactonitrile and acetone cyanohydrin (σ_m = 0.10 and 0.13 for MeO and OH, respectively) but more sterically encumbered, reacted rapidly in excellent yield and showed no signs of inhibition. On the basis of the results in Table 3, it is clear that (a) electron-withdrawing substituents facilitate the hydration reaction, and (b) cyanohydrins are initially as reactive to hydration by catalyst **1** as the other nitriles tested. The lack of long-term rapid reactivity noted for the cyanohydrins is apparently due to some type of inhibition, which among the nitriles is unique to the cyanohydrins. The possible causes of inhibition are discussed in the following section.

Catalyst Inhibition Tests. Although the α-hydroxy group of cyanohydrins is electronically similar to an α-methoxy substituent, the substrates differ in that the cyanohydrins can be deprotonated. The consequences of cyanohydrin deprotonation are formation of an alkoxide species, which is a better ligand than a nitrile, and dissociation of the cyanohydrinate to form HCN and the parent aldehyde or ketone. On the basis of this possible reactivity, three hypotheses were formulated to explain the inhibition of catalytic activity observed with cyanohydrin substrates: (1) Following nucleophilic attack of water or hydroxide on the nitrile carbon, catalysis may be inhibited by irreversible formation of an inert iminol or iminolate species, which is perhaps chelated (Figure 6). In support of this hypothesis, it is known that molybdocene-catalyzed nitrile hydration is inhibited by irreversible coordination of amides[10] and that

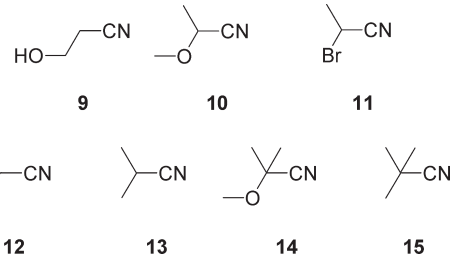


Figure 4. Structures of 3-hydroxypropionitrile (3-HPN; **9**); 2-methoxypropionitrile (**10**); 2-bromopropionitrile (**11**); propionitrile (**12**); isobutryonitrile (**13**); 2-methoxyisobutyronitrile (**14**); and trimethylacetonitrile (**15**).

coordination of amides to transition metals stabilizes the iminol tautomer.[4] Once the iminol tautomer is formed, the α-hydroxy group could coordinate, resulting in the formation of a more stable five-membered ring species that may be even more inert. (This mechanism was explored by DFT calculations. See the Supporting Information.) (2) The cyanohydrin preferentially binds through the alcohol functionality leading to formation of an alkoxide ligand. Binding of the cyanohydrin through the oxygen may lead to inadequate activation of the nitrile carbon and decreased reactivity. Furthermore, if the resulting alkoxide ligand is relatively inert, the formation of the metal-alkoxide complex will be a thermodynamic sink, resulting in acute substrate inhibition. (3) The HCN produced in the dissociation of the cyanohydrin may poison the catalyst by coordination of cyanide to the metal center.

Experimental tests of hypotheses 1 and 2 were negative and are reported in the Supporting Information. Hypothesis 3 suggests that free cyanide generated from dissociation of the cyanohydrin may bind irreversibly to the Pt center and deactivate the catalyst. Indeed, the addition of excess KCN to 3-HPN prevented hydration of the nitrile (see details in the Supporting Information). Instead of hydration, substitution of the hydroxy group in the 3-HPN occurred to give succinonitrile. To determine the efficiency of cyanide poisoning, sub-stoichiometric aliquots of potassium cyanide were added to reaction mixtures containing acetonitrile substrate (Figure 7). Catalytic activity did not cease until the $[CN^-]/[Pt]_{total}$ ratio reached 3:1.[34] The identity of the resulting Pt cyanide complex(es) was not determined; however, it is apparent that three cyanide ligands are required to deactivate the catalyst. Furthermore, the rate of acetonitrile hydration versus cyanide equivalents gives a linear relationship, which indicates that cyanide binding is irreversible.

Hypothesis 3 is also consistent with the results summarized in Table 1. As noted previously, at least trace amounts of ketone or aldehyde were detected in the ^1H NMR spectra of all of the reaction mixtures, indicating equivalent levels of HCN. In addition, the highest yields of hydration were observed using lactonitrile and 2-hydroxybutyronitrile, which are more robust to dissociation than acetone cyanohydrin and mandelonitrile. These latter two substrates showed little reactivity.[35]

(31) For the reactions carried out at 43 °C, nitriles containing electron-withdrawing groups displayed pseudo-first order kinetics. In contrast, pseudo-zero-order kinetics were observed for electron-donating nitriles, indicating a change in the rate-determining step. This inconsistency precluded generation of a Hammett plot. Kinetic traces for each substrate are available in the Supporting Information.

(32) This value was the rate after 30 min of reaction.

(33) Unfortunately, rate data could not be obtained for the 2-methoxyisobutyronitrile. However, the reaction of ~0.50 M 2-methoxyisobutyronitrile did proceed to completion.

(34) Note that the concentration of **1** does not account for all of the Pt in solution, as some free ligand is observed in solution due to degradation of the Pt complex. The aqueous behavior of $[PtCl(PMe_2OH)\{(PMe_2O)_2H\}]$ is described in more detail in a following section.

(35) Schlesinger, G.; Miller, S. L. *J. Am. Chem. Soc.* **1973**, *95*, 3729.

Table 3. Rate Data for Hydration of Various Nitriles Catalyzed by **1**

substrate	[substrate] (M)	% catalyst	rxn temp. (°C)	rate (M/h)	% conversion
3-hydroxypropionitrile[a]	0.34	0.10	43	9.4×10^{-2}	100
2-methyoxypropionitrile[a]	0.34	0.10	43	5.5×10^{-2}	100
2-bromopropionitrile[a]	0.34	0.10	43	2.5×10^{-2}	90
lactonitrile[a]	0.34	0.10	43	2.2×10^{-2}	12
acetonitrile[a]	0.34	0.10	43	1.3×10^{-2}	100
propionitrile[a]	0.34	0.10	43	8.0×10^{-3}	100
isobutyronitrile[a]	0.34	0.10	43	2.2×10^{-3}	100
trimethylacetonitrile	0.34	0.25	80	1.1×10^{-1}	100

[a] Reaction mixtures also contained 0.45 mM PBu_4Br as an internal standard.

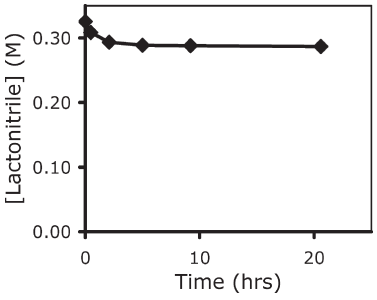


Figure 5. Plot of [Lactonitrile] versus time for the hydration of lactonitrile (0.34 M) catalyzed by **1**.

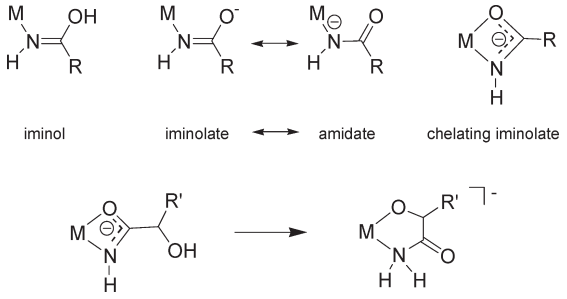


Figure 6. Stabilization of iminol and iminolate (amidate) ligands by metal coordination. Rearrangement of the chelating iminolate would result in a more stable species with a five-membered ring.

Close scrutiny of Table 1 shows that hydration was only observed when the percent dissociation was less than the percent of catalyst in solution, except in the cases of lactonitrile and glycolonitrile. This result may be rationalized after considering that the equilibrium between cyanohydrins and HCN/aldehyde(ketone) in solution occurs at different rates. The apparent inconsistency in the cases of glycolonitrile and lactontrile is most likely due to slower dissociation of these more robust substrates, which leads to slower catalyst poisoning. In general, note that lower yields (or no yield in the case of ACH) were observed at higher reaction temperatures, consistent with faster cyanohydrin dissociation at higher temperatures and concomitant faster catalyst poisoning.

It is interesting that 3 equiv of HCN were not required to inhibit hydration of the cyanohydrins, as was the case in acetonitrile hydration. The relative acuteness of cyanide poisoning in the cyanohydrin reaction mixtures may be due to the inferiority of the cyanohydrins as ligands in comparison to acetonitrile. That is, acetonitrile is sterically less hindered and more electron-donating relative to the α-hydroxynitriles. As such, the acetonitrile substrate

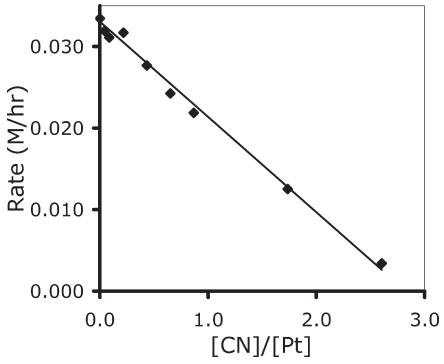


Figure 7. Plot of acetonitrile hydration rate versus $[CN^-]/[Pt]$ showing the effect of CN^- on the catalytic activity of the $[PtCl(PMe_2OH)\{(PMe_2O)_2H\}]$ ($y = -0.012x + 0.033$).

will be more competitive versus cyanide for Pt binding than the cyanohydrins. The high oxidation state molybdocene catalyst (**2**) is even more susceptible to cyanide poisoning because it is a much stronger Lewis acid than the Pt catalyst (**1**).[12]

DFT Analysis of Molybdocene Catalyzed Nitrile Hydration. The calculated reaction profiles for the molybdocene-catalyzed hydration of lactonitrile (LN) and 3-hydroxyproprionitrile (3-HPN) are shown in Figure 8. The intermediates in these profiles are based on the mechanism for nitrile hydration reported in a previous paper.[10] In the first step, energy comparisons show that binding of either LN or 3-HPN to the molybdenum center is reversible. In the next step, attack of the hydroxo ligand on the substrates occurs to form the iminolate complexes. This step is slightly more favorable for LN (by 2 kcal/mol). Optimizations of the next step (H_2O coordination to the metallocycle; step 3) resulted in a proton transfer to the carbonyl oxygen in both cases, yielding the iminol form of the ligand. Step 3 is slightly endergonic for both LN and 3-HPN (+1 and +4 kcal/mol, respectively); note it is more favorable by 3 kcal/mol for LN. The net reactions of the iminol intermediates to give the final products are slightly favorable (−1 kcal/mol) for both nitriles, but the calculation suggests that this reaction may not proceed by way of the coordinated amide species because of the high barrier to reach the amides (+9 kcal/mol for LN, +11 kcal/mol for 3-HPN). (Note that the molybdocene stabilizes the iminol over the amide. However, should the amides form, the dissociation of the amide is favorable for both cases (−10 kcal/mol for LN, −12 kcal/mol for 3-HPN).) Overall the free energies of hydration are calculated to be −15 kcal/mol for LN and −9 kcal/mol for 3-HPN.

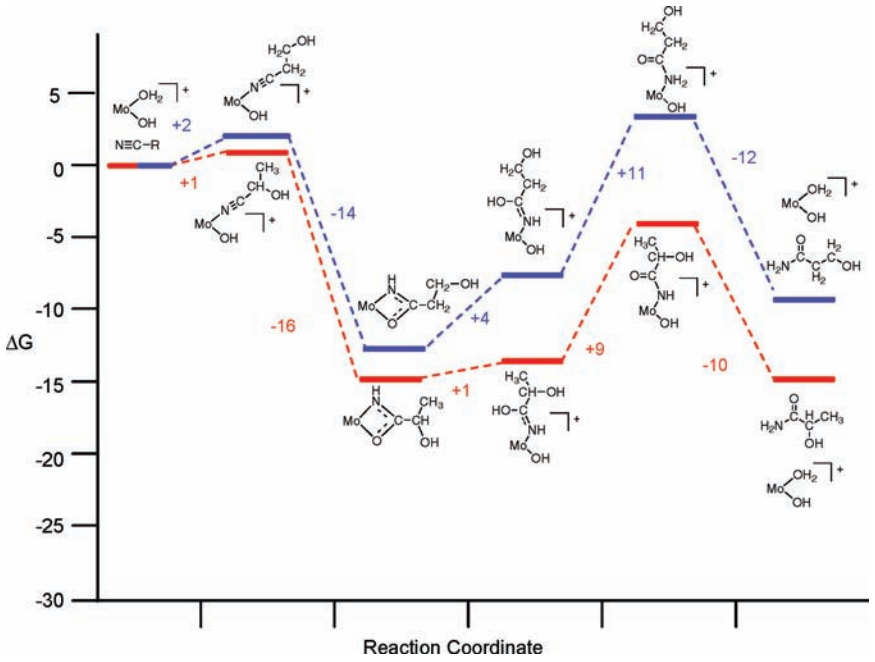


Figure 8. Reaction profiles for proposed catalytic cycle of molybdocene-catalyzed lactonitrile and 3-hydroxypropionitrile hydration. Free energies are in kcal/mol. The Cp_2Mo fragment is abbreviated as Mo.

The first important point to come from the calculations is that the formation of most intermediates and the overall reaction itself are more favorable for LN than for 3-HPN. Thus, from an electronic standpoint, there appears to be no reason for the lack of reactivity observed for lactonitriles. These findings corroborate the experimental finding that the initial rates of the metal-mediated hydration reactions of cyanohydrins are comparable to the rates of the other nitriles. The second important point concerns inhibition of the hydration reaction. In previous studies, it was shown that the rate of molybdocene-catalyzed nitrile hydration decreased with increasing substrate concentration or with the intentional addition of amide product.[10] It was proposed that the amide binds irreversibly to the molybdocene catalyst and deactivates it. Amides in general are not strongly bonding ligands, but according to the computational analysis presented here, amide inhibition occurs because coordination is stabilized by isomerization to the iminol tautomer.

Additional DFT calculations computationally tested the three hypothesis described above in the section on catalyst inhibition. The results support hypothesis 3, namely, that cyanide poisoning is responsible for the low amide yields in the case of molybdocene catalyzed hydration of cyanohydrin. The results and further discussion of these calculations are found in the Supporting Information.

Aqueous Behavior of $[PtCl(PMe_2OH)\{(PMe_2O)_2H\}]$. Previous studies prepared the active catalyst from complex **1** by abstracting the chloride ligand in aqueous solution.[6] In the present study, however, partial to complete degradation of the $[PtCl(PMe_2OH)\{(PMe_2O)_2H\}]$ complex (because of dissociation of the dimethyl phosphinito ligands) was always observed when **1** was treated with Ag^+, Tl^+, or Na^+ salts. For example, upon treatment of complex **1** with one of the aforementioned salts, the resonances in the ^{31}P NMR spectrum sharpened (δ 96 (d, 2 P) and δ 58 (t, 1 P)) and new resonances appeared at δ 35 (t) and δ 53 (s), due to free ligand and dimethylphosphinic acid, respectively. Note that dimethylphosphinic acid is generated by disproportionation (eq 3) of dimethylphosphine oxide (the tautomer of the dimethylphosphinito ligand).

$$2P(O)(CH_3)_2H \rightarrow P(O)(CH_3)_2(OH)+P(CH_3)_2H \quad (3)$$

The gaseous dimethylphosphine byproduct is typically not observed; however, spiking with an authentic sample decisively identified the dimethylphosphinic acid. (The resonance for dimethyl phosphinic acid was observed at δ 53 but no additional resonances.) Little or no dimethylphosphinic acid was observed when oxygen was excluded from the reaction vessel.

Degradation of the catalyst is more extensive at high temperatures or when using Ag^+ salts. In fact, no resonances due to **1** were detectable by ^{31}P NMR spectroscopy after 12 h of reflux in water solution in the presence of AgOTf or $AgBF_4$. Quantification of the resulting phosphine oxide and/or dimethylphosphinic acid accounted for only 67% of **1**; however, analysis of the remaining solid indicated undissolved **1**. Note that stock solutions of catalyst prepared using Ag^+ salts were less reactive toward nitriles in general, especially the bulky 2° and 3° nitriles. Furthermore, in some cases, the reaction mixtures changed colors after several hours of reaction time. The color changes were inconsistent and appeared blue, pink, purple, red, yellow, and amber in different trials, and several reaction mixtures continued to change in color from colorless to blue to pink if left on the heat source. In many of the experiments where the solid formed upon treatment with Ag^+ was removed prior to addition of the nitrile (the solid was presumed to be AgCl), an abrupt halt in the hydration of the substrate accompanied this color change. The reaction rates were

also inconsistent when Ag^+ salts were used to abstract the chloride from **1**, which is suggestive of heterogeneous catalysis. However, no evidence was collected in support of heterogeneous catalysis. For example, addition of mercury to the acetonitrile hydration reaction catalyzed by **1** did not affect the rate of the reaction. (Rate data for the Hg poisoning experiment are found in the Supporting Information.)

It was not possible to determine the identity of the catalyst that formed when [PtCl(PMe_2OH){($PMe_2O)_2H$}] was treated with chloride abstraction reagents. Repeated attempts to crystallize the catalyst from stock solutions after treatment with a chloride abstraction agent merely resulted in crystallization of [PtCl(PMe_2OH){($PMe_2O)_2H$}]·$0.5H_2O$.

Summary and Key Insights

Comparison of the hydration reactivity of cyanohydrins to that of other nitriles demonstrated that the low reactivity of the α-hydroxynitrile substrates is not due to the steric or electronic consequences of the hydroxy group on the α carbon. In fact, the cyanohydrin lactonitrile exhibits initial rates that are comparable to those of other nitriles containing electron-withdrawing substituents, demonstrating that the electronic character of the nitrile carbon in cyanohydrins is not unusual in comparion with other nitriles. The low reactivity of cyanohydrins is instead due to liberation of HCN from the cyanohydrin substrate, the coordination of which leads to deactivation of the catalyst. Unfortunately, because water is necessary for the hydration reaction, generation of some small equilibrium amount of HCN is inevitable. No evidence of metal-mediated dehydrocyanation was observed; however, coordination of the free cyanide to the transition metal encourages greater dehydrocyanation by removing HCN from the equilibrium. Irreversible binding of cyanide ensures complete catalyst poisoning. Deactivation due to cyanide poisoning occurred for both catalysts **1** and **2**, and such deactivation may explain the lack of cyanohydrin hydration noted for other transition metal nitrile hydration catalysts. Overall, this work provides a more thorough understanding of the challenges associated with transition metal catalyzed nitrile hydration. Furthermore, the results obtained using the α-methoxy-substituted nitriles indicated that protected cyanohydrins provide a viable route to access α-hydroxyamides. This knowledge is being used to develop new cyanohydrin hydration catalysts that are less susceptible to cyanide poisoning.

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Supporting Information Available: Additional information as noted in the text. This material is available free of charge via the Internet at http://pubs.acs.org.