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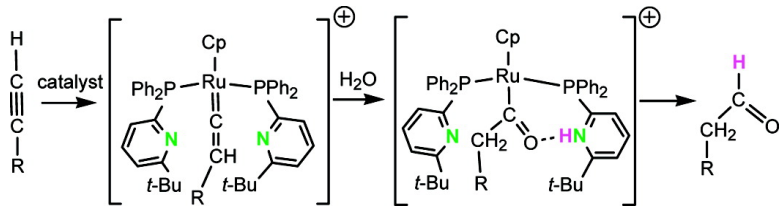

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Finding the Proton in a Key Intermediate of *anti*-Markovnikov Alkyne Hydration by a Bifunctional Catalyst

Douglas B. Grotjahn,*,† Elijah J. Kragulj,† Constantinos D. Zeinalipour-Yazdi,‡ Valentín Miranda-Soto,† Daniel A. Lev,† and Andrew L. Cooksy†

Department of Chemistry and Biochemistry, 5500 Campanile Drive, San Diego State University, San Diego, California 92182-1030, and Heterogeneous Catalysis Laboratory, Department of Chemistry, University of Cyprus, Nicosia, CY 1678 Cyprus

Received April 27, 2008; E-mail: grotjahn@chemistry.sdsu.edu

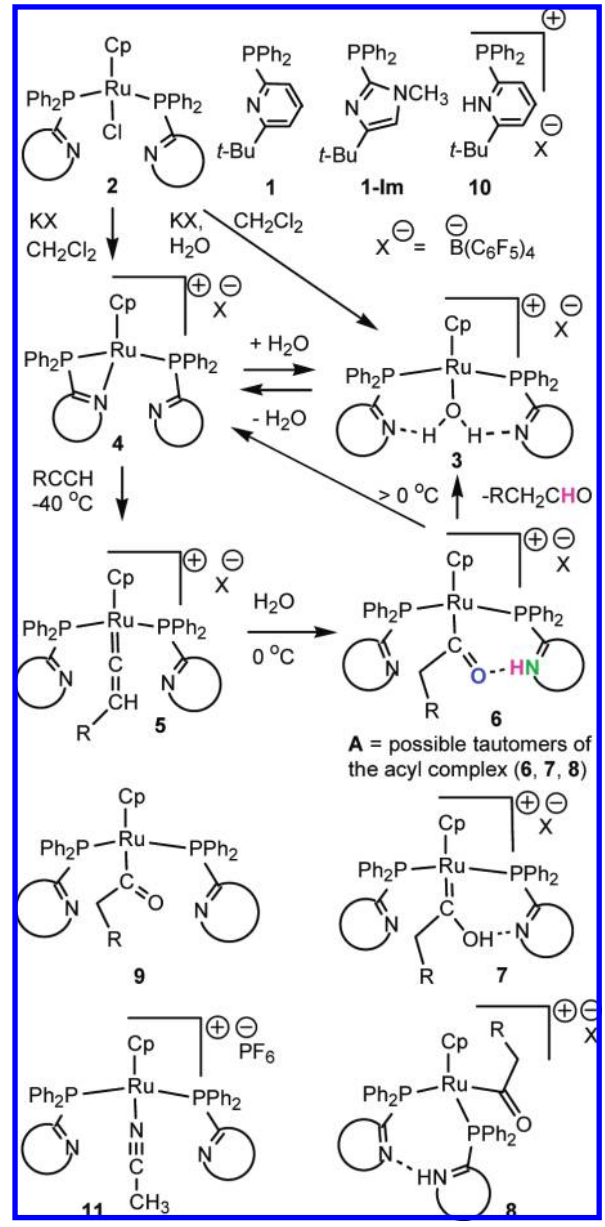
Many of Nature's metalloenzyme active sites feature a metal ion or ions and a variety of acidic or basic groups, which act in concert, allowing enzymes to achieve turnover frequencies rarely rivaled by synthetic catalysts.[1] A major contributor to enzymatic rate accelerations is secondary structure, with a network of hydrogen bond or proton donors and acceptors that lower the energy of intermediates or transition states. We are interested in the increased activity and selectivity of small-molecule bifunctional catalysts[2] and their secondary structure. Catalysts for *anti*-Markovnikov hydration of terminal alkynes to give aldehydes[3a–e] or for alkene isomerization[3f] are made 1000−10 000 times faster using bifunctional phosphine ligands. However, the same features that increase the efficiency of bifunctional catalysts also complicate studies of their mechanism. We are developing methods to study these complex systems.[4] Here, we have unambiguously determined the location and hydrogen bonding of a reactive proton in a bifunctional catalyst structure. Our methods should be useful in other studies of bifunctional catalysis.

Complex **3** and its imidazolyl analog **3-Im** (Scheme 1) were synthesized[5] from **1** and **1-Im**[3b,6] by a route similar to that reported recently for an analog.[4] In the pyridyl case, on removal of solvent and water, nearly complete formation of **4** is seen, because the complex is in equilibrium with water and **3**. With the ligands shown, under anhydrous conditions, **4** or **4-Im** could also be obtained directly as the major product. When a terminal alkyne is added to pyridyl species **3** or **4** at −40 °C, vinylidene **5** (R = H) forms within 3 h. An intermediate alkyne π-complex[4] is not detected with this phosphine ligand set, even under what would be optimal conditions,[7] with acetylene, the smallest alkyne.

When pyridyl derivative **3** is allowed to react with acetylene and water (4 equiv) at 0 °C for 4 h, up to 91% of an acyl complex (**A**) is observed. Possible tautomeric structures **6**, **7**, and **8** (R = H) are collectively referred to as **A**. Acyl complexes have been identified in other alkyne hydrations,[8] but these were not synthetically useful catalytic systems. The acyl complex (R = H) is somewhat stable near 0 °C but at higher temperatures cleanly releases CH_3CHO, forming **3** or **4**, depending on the amount of water. The fact that **A** accounts for almost all of the catalyst added means that turnover under the conditions described is determined by the rate at which **A** releases product. This makes the identity of **A** and its structure and reactivity of special interest.

The ^{1}H NMR data for **A** revealed a broadened singlet near δ 19 ppm,[9a,b] suggesting a ^{1}H nucleus involved in hydrogen bonding as shown in tautomers **6**−**8**. When the alkyne $H^{13}C^{13}CH$ was used, this resonance remained unchanged, but intense ^{13}C NMR signals

Scheme 1. Formation of Key Intermediate **6**



near[9a,b] δ 293 (broad) and 50 ppm (d, $^1J_{CC}$ = 22.3 Hz[9b]) were now seen. The chemical shift of the downfield carbon fits better a hydroxycarbene complex (**7**) than an acyl.[10] However, we note that the few literature comparisons available are between *neutral* acyl

† San Diego State University.
‡ University of Cyprus.

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(like **9**) and *cationic* hydroxy- or alkoxycarbene complexes (resembling **7**, but without the intramolecular hydrogen bond). To probe the effect of protonation, to **A**-($^{13}C)_2$ was added Et_3N (3 equiv), forming **9**-($^{13}C)_2$ with ^{13}C shifts[9a] of 259.4 and 53.0 ppm (two d, $^1J_{CC} = 18.2$ Hz). For **9**, $\upsilon_{CO} = 1567$ cm^{-1}. Notably, **9** could be isolated, unlike **A** which releases aldehyde above 0 °C.

The NH−N unit in **8** resembles that proposed for a hydride complex with ligands like **1** but without the *t*-butyl groups.[11] Our DFT calculations suggest that because of the *t*-Bu groups, **8** is energetically unfavorable, with either **6** or **7** being favored depending on the methods used.[12] Experimental data arguing against **8** include the large changes in ^{13}C NMR and IR data for the acyl moiety accompanying deprotonation of **A**-($^{13}C)_2$.

In order to determine which tautomer of **A** formed, ligand **1**-^{15}N was synthesized and incorporated into the various intermediates shown in Scheme 1. Of particular interest, the ^{15}N chemical shifts for **1**-^{15}N, **2**-, **3**-, and **5**-($^{15}N)_2$ are −55.7, −59.1, −80.7, and −59.8 ppm, respectively.[9c,d] These data show that ligand coordination at P or overall charge of a complex do not significantly affect the ^{15}N shift (**1**, **2**, **5**) whereas hydrogen bonding does (**3** vs **2** and **5**). Significantly, the ^1H NMR peak for coordinated water protons in **3**-($^{15}N)_2$ appears as a slightly broadened singlet,[13a] consistent with location of the water protons on O and not on N.

In sharp contrast, the ^{15}N NMR data for **A**-($^{15}N)_2$($^{13}C)_2$ at −100 °C[9b] show two signals at very different chemical shifts (−63.6 and −146.8 ppm). The large upfield shift of the latter resonance shows *protonation at one nitrogen* (**6** or **8**), as does the ^1H NMR spectrum at −100 °C[9a] showing the downfield N*H* resonance as a *doublet of large magnitude* ($^1J_{HN} = 56.8$ Hz).[13b] However, the value of $^1J_{NH}$ is only 62% of that in the model salt **10**-^{15}N made by protonating **1**-^{15}N ($^1J_{HN} = 92.3$ Hz,[9d] consistent with related data[14]), which underscores the presence of hydrogen bonding in **6**.

The foregoing data conclusively place a hydrogen-bonded proton on one nitrogen. To show that the proton indeed interacts with the acyl *oxygen*, **A**-($^{13}C)_2$ was formed as usual, using H_2O in THF-d_8. Then, D_2O was added to create a mixture of **A** and its N-deuterated isotopomer. A remarkably large[15] perturbation of the ^{13}C chemical shift for the acyl carbon of 1.6 ppm was observed, unequivocally demonstrating an O−HN interaction as in **6**.[15]

Having identified **6** under near-stoichiometric conditions of high catalyst loading and low water content, we looked for its presence during catalyzed alkyne hydration using **3** or **11** on $Ph(CH_2)_3C^{13}CH$. Indeed, hydration of this alkyne in d_6-acetone (0.25 M) using 5 equiv of water and 4 mol % of catalyst revealed ^{13}C, ^{31}P, and ^1H NMR peaks for **6**-^{13}C [R = $(CH_2)_3$Ph], along with peaks for the vinylidene intermediate **5**-^{13}C preceding it.

Here for the first time in a practical catalytic system for *anti*-Markovnikov alkyne hydration, we have identified an acyl intermediate (**6**). More significantly, we have conclusively shown the special role of bifunctional ligands: the proton needed for catalyst turnover is located on one pyridine base, and this pyridinium moiety donates a hydrogen bond to the acyl oxygen. Ongoing work seeks to clarify role of the bifunctional ligands in *formation* of **6** and in its *release* of the aldehyde product, where intramolecular proton transfer is likely to be crucial. Elucidation of the roles of proton transfer or hydrogen bonding with NMR techniques such as ^{15}N coupling and isotopic perturbation are expected to have applicability in other catalytic reactions.

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Supporting Information Available: Details of compound preparation and characterization and calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Solvents used: (a) THF-d_8; (b) acetone-d_6; (c) $CDCl_3$; (d) CD_2Cl_2. Of particular note, the data for complex **6** in solvents of different polarity were quite similar, consistent with an intramolecular hydrogen bond.
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(12) The predicted stability of **6** equaled that of **7** only with explicit quantum treatment of the phenyl groups, and with a triple-ζ basis set for atoms in and adjacent to the H-bond. In **3-Im**, where the heavy atom geometry is determined from x-ray diffraction,[3a] the computed geometry is in good agreement with experiment. At the optimized **6** geometry ($R_{NH} = 1.09$ Å, $R_{HO} = 1.48$ Å), the predicted $^1J_{HN}$ value is −68.6 Hz. The lower experimental magnitude (56.8 Hz) is consistent with a larger vibrationally averaged N−H separation, as zero-point motion carries the proton towards the O atom.
(13) (a) The ^1H and ^{15}N NMR data[5] for the imidazole analog **3-Im**-($^{15}N)_2$ made with **1-Im**-^{15}N are similar, showing no observable coupling between ^{15}N and water protons; moreover, X-ray data for the triflate salt of **3-Im**[3a] show the H_2O protons on O not N. (b) Interestingly, there is evidence of a fluxional process by which the NH proton may be transferred between the two nitrogens, perhaps via **7**. As the sample of **6**-($^{15}N)_2$ is warmed above −80 °C, the ^{15}N peaks broaden to the point of invisibility, whereas the ^1H resonance becomes more complicated between −80 and −40 °C, and a triplet ($J = 25.5$ Hz)[9a] at higher temperatures. The changes in ^1H spectra were modeled as a dynamic AA′X-A_2X system (X = H, A = ^{15}N), line-shape analysis giving $E_a = 8$ kcal mol^{-1} for the fluxional process.[13c] Similarly, the ^{31}P signals for **6** (δ 60.7 and 51.9 ppm at −100 °C[8b]) coalesced near −55 °C. (c) The structure of **3-Im** (X = OTf)[3a] shows slightly different O−H−N bonds. Low-temperature spectra of **3** and **3-Im** show two ^{31}P and ^{15}N NMR signals, the latter very close (with in 1 ppm of each other),[5] suggesting slightly different hydrogen bonding environments. Line-shape analyses give $E_a = 7$ and 10 kcal mol^{-1} for **3** and **3-Im**, respectively, consistent with a rocking motion of the two ligands.
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