Pyridine–Carbene Tautomerization

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Synthetic Routes to N-Heterocyclic Carbene Complexes: Pyridine–Carbene Tautomerizations**

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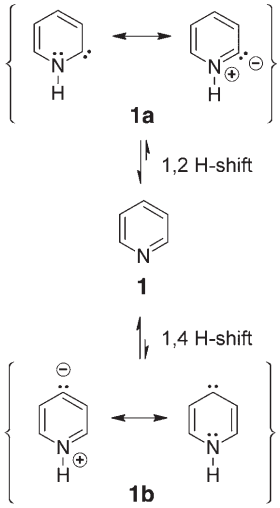
The mechanistic details of metal-induced acetylene–vinylidene rearrangements have been thoroughly examined in both theoretical and experimental studies.[1] Other tautomerizations or isomerizations of C=C or C=X bonds (X = O, N) by a formal 1,2 H-shift at a metal center are quite rare and hence less well-investigated. A 2-carbene tautomer of pyridine **1a** (Scheme 1)—postulated 70 years ago[2] and experimentally proved in the gas phase by mass spectrometry[3]—has now been synthesized by the groups of Poveda and Carmona[4] as a carbene complex starting from pyridine by metal-induced C–H activation. Concurrently, the same type of tautomerization has been found by Esteruelas et al. for quinoline.[5]

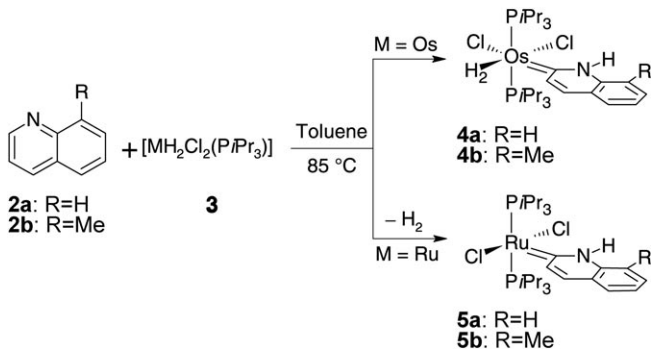


Scheme 1. 1*H*-pyridin-2-ylidene (**1a**) and 1*H*-pyridin-4-ylidene (**1b**) as carbene tautomers of pyridine.

The first example of a carbene complex synthesized by pyridine tautomerization was a pyridin-4-ylidene osmium complex reported by Taube et al. 20 years ago.[6] Other pyridin-2-ylidene complexes (as well as *N*-alkylpyridin-2-ylidene and -4-ylidene complexes) are known but were synthesized by other routes.[7]

Esteruelas et al. treated $[OsCl_2H_2(PiPr_3)_2]$ (**3**, M = Os) with 2.0 equiv of quinoline (**2a**) and 8-methylquinoline (**2b**) in toluene at 85 °C for 10 h to obtain the carbene complexes **4a** and **4b**, respectively, as orange solids in good yields (Scheme 2).[5] In the ^{13}C NMR spectra the signals at $\delta = 191$ ppm confirm the carbene structure for both complexes. An X-ray crystal structure analysis of **4b** proves the tautomeric carbene form of the 8-methylquinoline ligand. The $Os-C_{carbene}$ distance of 2.005(6) Å is in accordance with that of other N-heterocyclic carbene osmium complexes. In addition DFT calculations on a model system indicated that a weak hydrogen bond between Cl and NH (Cl···H: 2.05(7) Å; IR: $\tilde{\nu} = 3130\ cm^{-1}$) plays an important role in stabilizing the carbene tautomer. Under the same conditions the reaction with $[RuCl_2H_2(PiPr_3)_2]$ (**3**, M = Ru) leads—upon loss of H_2—to analogous carbene complexes **5a** and **5b**, as confirmed by analytical data and crystal structure analysis.

Poveda, Carmona et al. reported the reaction of 2-substituted pyridines **7** (R = Me, *t*Bu, NMe_2, Ph) with $[Tp^{Me_2}IrPh_2(N_2)]$ (Tp^{Me_2} = hydrotris(3,5-dimethylpyrazolyl)borate). In benzene at 60 °C the pyridine–carbene rearrangement yields the respective carbene complexes **9a–d** as two rotamers (Scheme 3).[4] In the case of 2-picoline the N-coordinated complex **8a** could also be isolated and converted to carbene complex **9a** at 90 °C. In the ^{13}C NMR spectrum the carbene signal is detected at $\delta = 175$ ppm, as expected for an N-heterocyclic carbene (NHC)



Scheme 2. Stabilization of quinoline carbene tautomers as osmium and ruthenium chloridophosphine complexes **4** and **5**, respectively.[5]

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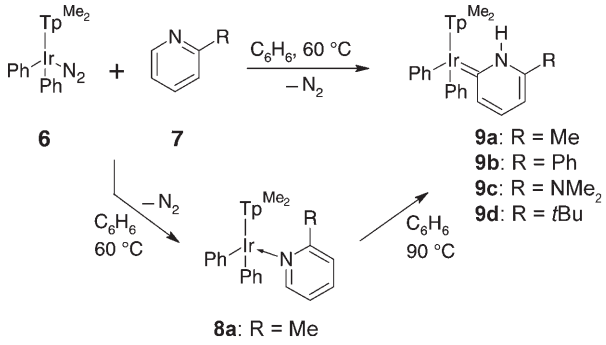


Scheme 3. Metal-induced tautomerization of 2-substituted pyridines to give the iridium–carbene complexes **9a–d** by Poveda, Carmona et al.[4]

complex. The X-ray structure analyses of complexes **9a** and **9b** confirm the carbene coordination, with a typical Ir–$C_{carbene}$ bond length of 1.98 Å.

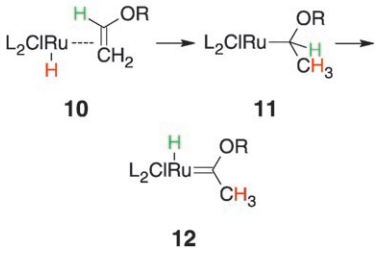
Interestingly, pyridine and 4-(dimethylamino)pyridine give only the N-coordinated adduct of type **8**. Exchange experiments with deuterated ligands show that 2-substituted pyridines are much more weakly N-coordinated than pyridine itself. Ligand exchange in complex **8a** with [D_7]picoline occurs at 60 °C, whereas the analogous pyridine complex shows no exchange with [D_5]pyridine even at 150 °C. Therefore steric demand is important in favoring C–H activation over N-coordination.[8]

No further mechanistic considerations or studies were discussed, but as the pyridine–carbene tautomerization seems to be a much more general reaction pattern and not a mere curiosity, a closer examination of similar reactions and their mechanisms is helpful for a better understanding of these findings.

Although the acetylene–vinylidene rearrangement is endothermic (the vinylidene isomer is about 43 kcal mol^{-1} higher in energy than the acetylene isomer),[9] transition-metal complexes can induce this isomerization and stabilize the vinylidene isomer by coordination so that the reaction becomes exothermic. Numerous examples for this transformation are reported in literature.[1] However, the ethylene–methyl carbene tautomerization is not observed, as this reaction is endothermic by 79 kcal mol^{-1}. The stabilizing effect of transition-metal coordination is not sufficient for this reaction to become exothermic. Investigations by Caulton, Eisenstein et al. showed that [RuHCl(PiPr$_3$)$_2$]$_2$ can induce this kind of rearrangement for vinylethers and vinylamides.[10]

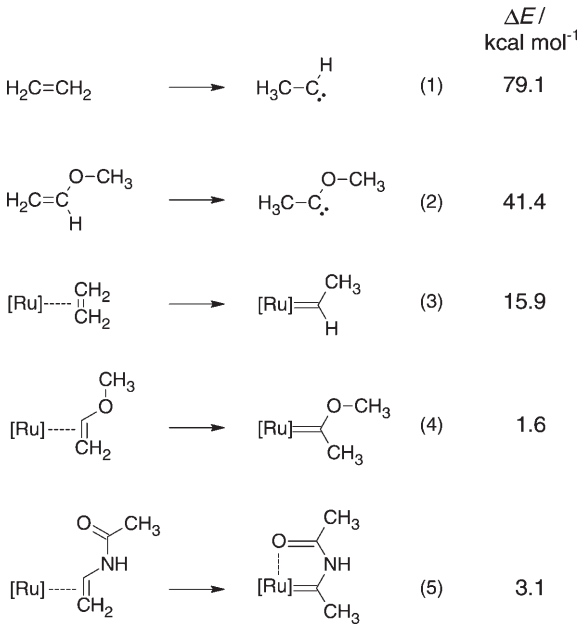
DFT calculations show that both the [Ru] fragment and the heteroatom stabilize the carbene tautomer (Scheme 4). The vinylether–carbene rearrangement, endothermic by 41 kcal mol^{-1} [Eq. (2)], is now in the same range as that calculated for the acetylene–vinylidene rearrangement. With the additional stabilizing effect of the [Ru] fragment, the rearrangement becomes thermoneutral [Eq. (4)], despite the fact that the stabilizing effect of the [Ru] fragment is stronger for ethyl carbene [Eq. (3) – Eq. (1)] than for the methoxyethyl carbene [Eq. (4) – Eq. (2)].

Other π-donor atoms like nitrogen can stabilize the carbene tautomer as well. For vinylacetamide this reaction is endothermic by only 3 kcal mol^{-1} [Eq. (5)]. In experiments with the ligand PiPr$_3$ only the carbene complex is observed. The mechanism of this reaction (Scheme 5) can be explained by a addition of [Ru]–H to the olefin (**10**) to form alkyl complex **11**, which subsequently rearranges to the hydridocarbene complex **12**.



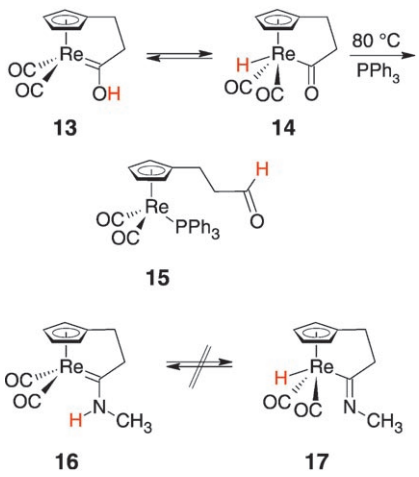
Scheme 5. Plausible mechanism of the vinylether–carbene isomerization on a {RuClHL$_2$} fragment (L = PiPr$_3$).[10]

Carbene formation by a formal 1,2 H-shift is not solely limited to C=C bonds. The C–H activation of aldehydes and aldimines results in formation of hydridoacyl and iminoacyl complexes, respectively.[11] For a better understanding of the mechanism, Casey et al. investigated the equilibrium between hydroxycarbene complex **13** and hydridoacyl complex **14** (the formal C–H



Scheme 4. Calculated energy differences for tautomerization reactions.[10] Both [Ru] and the heteroatoms stabilize the carbene isomer. [Ru] = {RuHCl(PH$_3$)$_2$}.

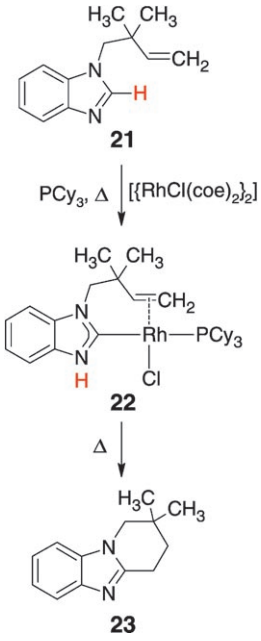
activation product of an aldehyde; Scheme 6).[12] In this special case the hydridoacyl complex **14** was favored as a result of reduced steric strain. Upon heating and addition of PPh_3 the phosphine complex **15** was formed. However, for the amine analogue **16**, a hydridoiminoacyl complex **17** (the formal C–H activation product of an acylimine) was not observed.



Scheme 6. Isomerization of hydroxycarbene complex **13** to the aldehyde **15** via the hydridoacyl species **14**. The analogous aminocarbene complex **16** does not isomerize.[12]

Formation of an aminocarbene complex by a formal 1,2 H-shift of acylimines was first observed by the group of Kirchner.[13] The chelate effect of the pyridine moiety in the substrate played a key role in the activation of the benzaldimine **18** by $[CpRu(CH_3CN)_2L]$ ($L = CH_3CN$, PMe_3), which subsequently gave the carbene tautomer **20**. Calculations are consistent with the mechanism shown in Scheme 7. The course of the reaction strongly depends on the ligand L as complexes with $L = CO$ or PPh_3 form only the N-coordinated species **19**. For $L = CH_3CN$ and PMe_3 the reaction proceeds further via the intermediates **A** and **B** to the C–H-activated iminoacylhydrido complex **C**. In a de/reprotonation sequence via **D**, the amino carbene complex **20** is formed. A possible direct, metal-assisted and concerted 1,2 H-shift from **B** to **20** was found to be energetically disfavored.

The high stability of N-heterocyclic carbenes and their complexes also favors the metal-assisted tautomerization of benzimidazoles to the respective NHC complexes. Bergman, Ellman et al. found carbenes of type **22** to be intermediates in the Rh-catalyzed C–C coupling reactions of imidazoles and similar heterocycles with a variety of olefins.[14] This reaction proceeds by an initial C–H activation step as well (Scheme 8).



Scheme 8. Formation of the N-heterocyclic carbene complex **22** upon C–H activation of benzimidazole **21** as an intermediate in the Rh-catalyzed C–C cross-coupling reaction of heterocycles and olefins. coe = cyclooctene.[14]

The pyridine–carbene tautomerizations described by Esteruelas, Poveda, Carmona et al. have shown once again that carbene tautomers can be important intermediates and in some special cases even stable products. For $[Ru_3(CO)_{12}]$-catalyzed C–C coupling reactions that occur upon C–H activation,[15] for example of pyridines, hydridovinyl complexes have been isolated as intermediates. However, in the light of the pyridine–carbene tautomerization, it is well possible that carbene isomers not only play a hypothetical role. Carbene intermediates could also be involved in C–C coupling reactions of α,β-unsaturated imines with mononuclear catalysts.[16] It remains an exciting question whether such carbene tautomerizations occur more frequently than previously thought in these kinds of C–H activation reactions.

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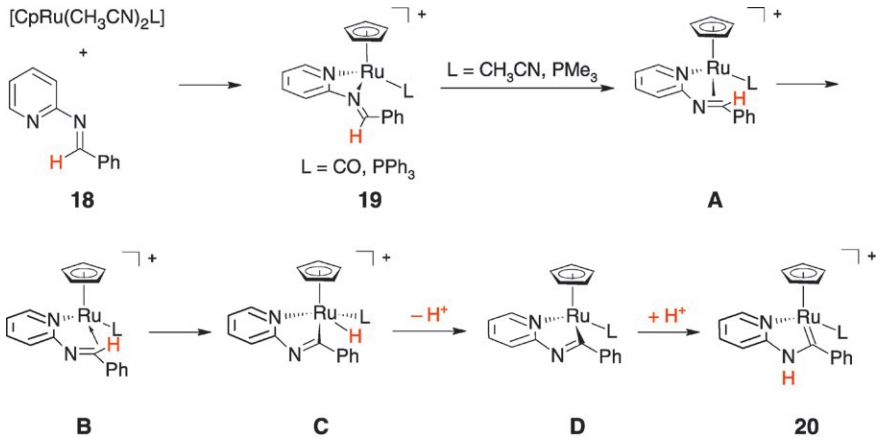

Scheme 7. Plausible mechanism of the benzaldimine–aminocarbene isomerization at a {CpRuL} fragment ($L = CH_3CN$, PMe_3) according to Kirchner et al.[13]

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