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Preferential C-Binding versus N-Binding in Imidazole Depends on the Metal Fragment Involved

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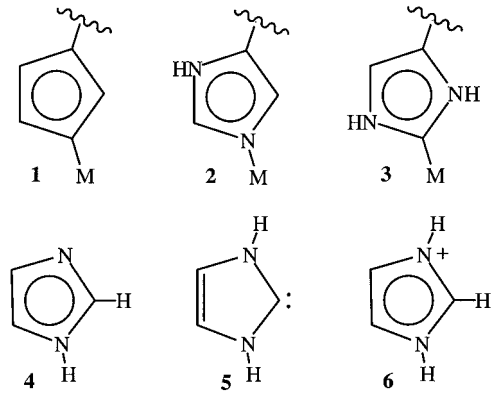
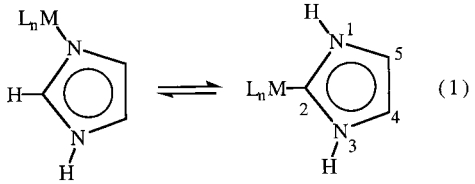
A metalloprotein X-ray structure can show situation **1**, where the imidazole ring atoms are undefined owing to similar scattering by CH vs N. Histidine is considered an N-donor, so structure **2** is assumed. Could the tautomeric C-donor **3** ever be the thermodynamically stable form? Binding to at least one electrophile, $E^+ = H^+$, does make the two forms isoenergetic by definition because protonation both of imidazole (**4**) and of its carbene form (**5**) leads to the same imidazolium salt (**6**). Complexation with other E^+ electrophiles should give tautomeric forms with similar energies if the E^+ electrophiles resemble H^+.



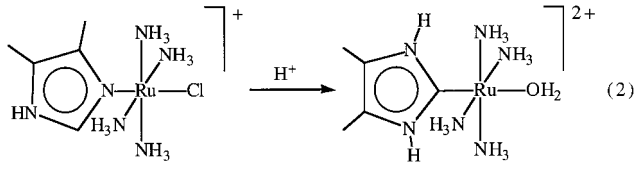
C-bound N-heterocyclic carbenes such as **7** have achieved prominence in recent years as spectator ligands for a variety of catalytic reactions.[1] Their high trans effect and tight binding to the metal make them very different from a N-bound imidazole. These species have both nitrogens alkylated, however, so there is no likelihood of isomerization to the N-bound form.

Here we address the relative stability of C- and N-bound isomers and therefore the position of equilibrium of eq 1 (L_nM = metal and ligands), where a N-bound imidazole rearranges to the C-bound form, with the proton originally bound to the 2-carbon moving to nitrogen.



Imidazole-derived carbenes bound at C-2 are known[2] where at least one N bears a proton and where the equilibrium of eq 1 could therefore in principle occur. The rearrangement is not seen, but this does not prove the C-bound form is more stable, because these species were only formed via nucleophilic attack by an amine on M(CNR), directly giving the C-bound imidazole. The C-bound form could be a kinetic product; failure to isomerize to the N-form is not informative because it can be very slow. The 1,2 shift from **5** to **4** has been shown to have a high activation energy.[4]

In just one case has a conversion directly related to eq 1 been seen. Taube showed H^+-catalyzed conversion from N- to C-binding occurs in eq 2. This presumably means that the C-form is the thermodynamically most stable one for $E^+ = Ru(II)$,[3] but no reversible equilibrium was seen, so the thermodynamics could not be unambiguously established.



Imidazolium salts **7** can be deprotonated to give carbenes **8**, which bind strongly to various metals to give complexes

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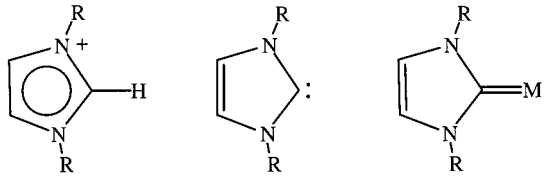
9 that can be highly catalytically active. Carbenes such as **8** normally resemble PR_3 in their properties, and so are soft ligands,[1] but with a high trans influence. A conventional *N*-imidazole, in contrast, resembles pyridine in being hard and having low trans influence. C-binding of histidine in metalloproteins, if possible, could usefully modulate the redox potential, the hardness/softness, and the trans influence of His.



Prior work shows that the C-binding mode has different chemical behavior[1] and in one case[3] may well be more stable, but it is not clear what factors affect the outcome and therefore when each form is likely to occur. Here we use DFT calculations to find the stability trends for N- vs C-binding for different metal fragments. DFT (B3PW91) calculations[5] were carried out for a number of representative complexes. The geometries of all species (fully optimized without symmetry constraints) present no unusual features. A decomposition analysis, to be discussed elsewhere,[6] uses the constrained space−orbital variation (CSOV)[7] method to give results in accord with the interpretations discussed here and with Frenking's[8a] CDA analysis.

Table 1 gives the metal fragments with their calculated ΔE for C- vs N-binding, with positive ΔE indicating more stable N-binding. When the metal is absent, the pure organic rearrangement of **4** to **5** has a calculated ΔE of 28.9 kcal/mol in agreement with previous studies.[1,4] This is large enough so the carbene tautomer is expected to be insignificant at equilibrium, but small enough so that coordination to a suitable metal fragment could compensate and stabilize the carbene complex. Coordination to a metal should stabilize the carbene because they usually bind much more strongly than amines.

Since protonation of both **4** and **5** gives **6**, the ΔE for H^+ is zero. For AuCl, isolobal with the proton, the calculations show a small negative ΔE (Table 1). Although also isolobal with H, CuCl significantly prefers the N-form, perhaps because the more electropositive Cu prefers to bond to the more electronegative N.

For the model Taube complex (unsubstituted imidazole), calculations indicate that the N-form is more stable, with ΔE = 3.7kcal/mol. With 3,4-dimethylimidazole, the real Taube complex, ΔE is calculated to be −1.5 kcal/mol. The Me groups have no influence on the ΔE for the free ligand (28.5 vs 28.9 kcal/mol), but steric factors favor C- over N-coordination. Hydrogen bonding with solvent water could also favor C-binding since the N-form has only one free N−H to form a hydrogen bond, while *C*-imidazole has two N−H bonds.

Table 1. Relative Energies ΔE (kcal/mol) of the C- vs N-Binding Forms along with the M═C and M−N Distances (Å)[a]

Metal fragment[b]	ΔE[c]	M═C	M−N
$\{Ru(NH_3)_4(CO)\}^{2+}$	13.1	2.130[d]	2.186
$\{Ru(NH_3)_5\}^{2+}$	7.3	2.018	2.115
$\{Ru(NH_3)_4Cl\}^{+}$	3.9	1.996	2.114
$\{Ru(NH_3)_4(H_2O)\}^{2+}$	3.7	1.986	2.074
$\{Os(NH_3)_4(H_2O)\}^{2+}$	−2.1	1.974	2.052
$\{Re(PH_3)_4Cl\}^{+}$	−6.2	2.035	2.145
$Ir(PH_3)_2Cl$	−8.3	1.949	2.047
$\{PtCl_2(NH_3)\}$	−10.6	1.951	2.025
$\{PtCl_3\}^{-}$	−14.1	1.946	2.057
$\{PtCl_2(H_2O)\}$	−15.0	1.922	1.984
$\{Pt(PH_3)_2Cl\}^{+}$	−5.1	1.996	2.056
$\{PdCl_3\}^{-}$	−7.1	1.975	2.104
$\{NiCl_3\}^{-}$	−2.1	1.910	2.002
$\{Au(NH_3)\}^{+}$	−3.2	1.987	2.024
AuCl[e]	−2.0	1.986	2.061
$\{Au(OH_2)\}^{+}$	−6.7	1.964	2.001
CuCl	10.0	1.912	1.930
H^+	0.0		
free imidazole	+28.9		

[a] Values refer to unsubstituted imidazole. [b] Imidazole trans to unique ligand. [c] Plus sign means *N*-imidazole is more stable. [d] X-ray value 2.128 Å[3]. [e] Geometry compares well with experiment.[8b]

Table 1 shows useful trends. For example, changing the trans X in $\{Ru(NH_3)_4X\}^{q+}$ from water to higher trans influence, less π-donor groups progressively favor the *N*-imidazole: X = Cl, 3.9 kcal/mol; NH_3, 7.3 kcal/mol; CO, 13.1 kcal/mol. Broadly similar trends are seen in $PtCl_2X$ and AuX, where X is always trans to imidazole. This is consistent with high trans effect ligands tending to avoid being mutually trans. M−C are shorter than M−N bond lengths in the optimized structures (Table 1) as expected.

Moving down the periodic table, in contrast, favors the C-form: $NiCl_3^-$, −2.1 kcal/mol; $PdCl_3^-$, −7.1 kcal/mol; $PtCl_3^-$, −14.1 kcal/mol. A similar trend is seen for Os vs Ru. First-row transition metals in general seem poor candidates for stabilizing *C*-imidazole; for example, the CuCl fragment has a ΔE of 10 kcal/mol.

The polarization of the imidazole C═N bonding orbitals toward the more electronegative N means the antibonding orbitals are polarized toward C, suggesting that the π*-acceptor ability should be greater at C than N, so strongly π-basic metal fragments should stabilize *C*-imidazole. Formation of an N_2 complex is a criterion for a strongly π-basic metal, and two such systems, $Re(PH_3)_4Cl$ and $Ir(PH_3)_2Cl$, models for $Re(PMePh_2)_4Cl$ and $Ir(PPh_3)_2Cl$,[9] indeed favor *C*-imidazole. *C*-Imidazole is not a very good π-acceptor,[1,10] however, as the M−C bonds are always closer to single than double (Table 1). Metal fragments essentially devoid of back-

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bonding ability are therefore still capable of stabilizing the *C*-imidazole form if the M−C σ-bond is strong (e.g., Au(I)).

A much less stable C-bound isomer results from metal binding to the 4(5) position, where only one N is now adjacent to the carbon. The free "carbene" at C-4 is calculated to lie 20.0 kcal/mol above the C-2 carbene. With $PtCl_3^-$ bound, the C-4 carbene lies 23.3 kcal/mol above the C-2 carbene.

The data reported here are valid for imidazole itself but cannot safely be extended to N-substituted imidazoles. In particular, the calculated structure of the $PtCl_3^-$ derivatives shows that the imidazole ring is coplanar with the $PtCl_3^-$ square plane. Both N−H protons are close to the corresponding *cis*-Cl groups (C-bound isomer, NH···Cl = 2.316 Å), and there is likely to be a significant energy contribution from the resulting N−H···Cl hydrogen bonds. The imidazole ring in N-alkylated derivatives would likely become noncoplanar, and N−H···Cl interactions would in any case no longer be possible. In a test calculation, when the C-bound imidazole ring was rotated 90° to become out-of-plane with respect to $PtCl_3^-$, the energy of the system rose by 13.3 kcal/mol. Although some of this amount may be ascribed to changes in M−L bonding, M−L back-donation usually plays a minor role, especially in square planar complexes,[11] so the overall energy change is probably largely the result of breaking two N−H···Cl hydrogen bonds on 90° rotation. Consistent with this picture, the C-bound form is not so much favored (2 kcal/mol) as the N-bound form for AuCl, where such hydrogen bonds cannot occur. In addition, when bound at the 4-position, the imidazole bends in such a way that the NH···Cl becomes much shorter (2.142 Å) than the CH···Cl (2.76 Å), again consistent with an attractive NH···Cl interaction in the case of the $PtCl_3^-$ fragment. Such hydrogen-bonding effects could easily occur in the protein, of course, but involving NH···OH_2 or NH···$^-$OOC− hydrogen bonding.

This study relies on the assumption that the relative energies of the C- and N-forms are properly calculated. This is particularly important in this case since the energy preference for the C-bonded forms is always small for the few systems where it is calculated to be preferred. Relative total energies of closely related systems are usually considered as calculated with good accuracy especially with DFT methods, and trends are usually reliably established. For this reason we hope to look for experimental examples of alternate imidazole binding modes and measure the equilibrium constant for eq 1 directly. Indeed, in very recent work, we have even seen preferential formation of a C-4-bound isomer when the C-2 isomer was expected, probably for kinetic rather than thermodynamic reasons, however.[12]

N-Imidazole is indeed by far the most likely tautomer for first-row elements. For second- and third-row elements, *C*-imidazole becomes possible. First-row elements dominate metalloenzymes, but Mo and W are sometimes present.[13] In addition, heavy metals, such as Au or Hg, are deliberately introduced into proteins, for example, to provide a strong scatterer for X-ray studies. A protein could in principle favor C- versus N-binding to some extent by having H-bond acceptors appropriate for the C- but not the N-form. The hydrogen-bonding pattern around the imidazole may therefore provide the best indication of binding type, as indeed was shown for the Taube example. Even so, aromatic C−H groups can also form weak H-bonds, so the H-bonding pattern may not be trivial to analyze.

Even where *C*-imidazole is more stable, there may be a significant interconversion barrier, as in Taube's case, where acid catalysis was needed. For a metalloprotein, any *N*- to *C*-imidazole interconversion may likewise need catalysis.

Computational Details

Calculations were carried out with the Gaussian 94 set of programs[14] with a Hay−Wadt ECP (quasi-relativistic for all metals,[15] P, and Cl[16]) with the associated double-ζ basis set augmented by polarization functions for P and Cl.[17] Other atoms were represented with a 6-31G** basis set.[18] MP2 and MP4 calculations for typical species gave insignificant $\Delta\Delta E$ from DFT.

Conclusion

C-bound imidazoles are predicted to be thermodynamically more stable than the conventional N-bound forms for several second- and third-row transition metals. Protein crystallographers may therefore need to be aware of the possibility of C-binding in heavy metal derivatives of proteins.

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