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Proton Affinities of Phosphines versus N-Heterocyclic Carbenes

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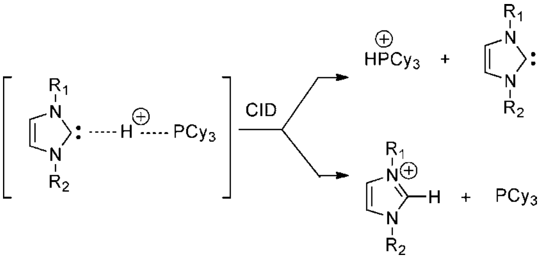
ABSTRACT



The gas-phase proton affinities of unusually basic phosphines and N-heterocyclic carbenes are compared and contrasted both computationally and experimentally.

N-Heterocyclic singlet carbenes (NHCs, such as imidazol-2-ylidenes, **1**, and the saturated derivatives, **2**, Figure 1) are stable carbenes that were first isolated by Arduengo and co-workers in 1991.[1−8] Such species are of fundamental organic interest but also have biological counterparts, the most well-known being thiamine pyrophosphate (coenzyme form of vitamin B_1), which contains a "stabilized" carbene.[9−12] Furthermore, NHCs are effective novel ligands for transition-metal-catalyzed reactions, including Grubbs ruthenium olefin metathesis catalysis, palladium-catalyzed cross-coupling reactions, and nickel-catalyzed cycloadditions.[13−16] NHCs themselves have also been found to be versatile catalysts for a wide variety of organic transformations.[17,18] The dialkylimidazolium salts (which can form stabilized carbenes when deprotonated) are also an important class of room-temperature ionic liquids, environmentally "clean" nonvolatile solvents that are increasingly used in organic synthesis.[19−22]

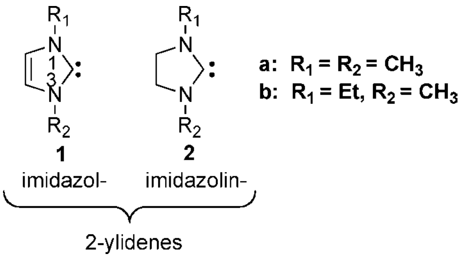


Figure 1. N-Heterocyclic singlet carbenes.

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Despite the widespread use of these carbenes as novel ligands and of the dialkylimidazolium salts as ionic liquids, the experimental acidity of the imidazolium ions (the proton affinity (PA = $\Delta H°$) of the carbenes) is surprisingly little-studied, both in solution and in the gas phase.[6,23a] Characterizing the fundamental properties is therefore warranted.

Because NHCs are more effective ligands than the classic first-generation tricyclohexylphosphine (PCy_3) species in the ruthenium catalysts used for Grubbs' olefin metathesis, one interest is to compare the proton affinities of carbenes with phosphines.[24] The pK_a of a series of imidazolium cations at C2 (pK_a's ranging from 21−24; deprotonation yields the corresponding singlet N-heterocyclic carbenes) was measured in an elegant deuterium exchange reaction in water by Amyes, Diver, Richard, and co-workers.[6,25] The gas-phase PA of 1-ethyl-3-methylimidazol-2-ylidene **1b** was previously measured by Cooks and co-workers to be 251.3 ± 4 kcal mol^{-1}.[23a] Cooks et al. also ascertained that the 1-ethyl-3-methyl-substituted substrate has a lower PA than the more highly substituted compound 1,3-di-*tert*-butylimizadol-2-ylidene, which in turn has a lower PA than 1,3-di-(2,6-isopropylphenyl)imizadol-2-ylidene. To our knowledge, there are no other measurements of N-heterocyclic diamino carbene PA, in any medium.[25]

We first repeated the experimental measurement of the gas-phase PA of the 1-ethyl-3-methyl carbene (**1b**). Using the Cooks kinetic method[23c] and 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN, PA = 248.16 kcal mol^{-1}) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, PA = 250.45 kcal mol^{-1}) as reference bases, we obtain a PA of 250 ± 3 kcal mol^{-1}, which is consistent with the previous Cooks group measurement (251.3 ± 4 kcal mol^{-1}).[23a]

We next examined the PA of PCy_3, which has not heretofore been measured. Using DBU and DBN as reference bases and using the Cooks kinetic method, we obtain a PCy_3 PA of 249 ± 3 kcal mol^{-1}. Therefore, the PAs of PCy_3 and 1-ethyl-3-methyl carbene appear to be very similar. Whether the PAs of 1-ethyl-3-methyl carbene and PCy_3 are slightly different is not discernible from these data, as the error on the experimental measurement is around 3 kcal mol^{-1}.

In an effort to discriminate the relative PA of carbene **1b** versus PCy_3, we conducted Cooks experiments with the protonated dimers comprised of each (i.e., carbene•phosphine protonated dimer **3b**, Figure 2).

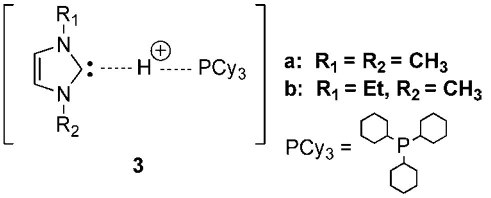

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Figure 2. Proton-bound dimer of PCy_3 and NHC.

The protonated dimer of 1-ethyl-3-methyl carbene and PCy_3 (**3b**) has a *m/z* ratio of 391. CID on this dimer produces each protonated product ($HPCy_3^+$ (*m/z* 281) and protonated carbene (*m/z* 111)), the ratio of which can yield the relative proton affinity. This experiment is not easy to conduct in that the protonated dimer yields a fairly weak signal. Subsequent isolation and CID result in increasingly weak daughter ion signals. Furthermore, initial CID of **3b** yields some unexpected fragmentation products that could affect the relative proton affinity estimation.[26] We conducted this "relative PA" experiment six times, and the results consistently indicate that PCy_3 is slightly more basic than 1-ethyl-3-methyl carbene **1b** (by less than 2 kcal mol^{-1}). We find that PCy_3 is also a little more basic than the dimethyl-substituted carbene **1a**, again by less than 2 kcal mol^{-1}. Given the difficulty of the experiment, it is probably reasonable to conclude that, essentially, PCy_3 and carbenes **1a** and **1b** have similar PAs.

We also explored the PA of 1-ethyl-3-methyl carbene (**1b**) with theory to probe the accuracy of various methods and levels. For the carbene, we tried RHF/6-31+G*, B3LYP/6-31+G*, M06-2X/6-31+G*, MP2/6-311+G(2d,p)//B3LYP/6-31+G(d), M06-2X/aug-cc-pVTZ//B3LYP/6-31+G*, and CBS-QB3.[27−36] As can be seen in Table 1, all these methods appear to overestimate the PA of the carbene, with M06-2X/6-31+G* coming the closest to experimental, although at

Table 1. Proton Affinity Calculations on 1-Ethyl-3-methylimidazol-2-ylidene **1b**

method/level	PA, kcal mol^{-1}
RHF/6-31+G*	262.4
B3LYP/6-31+G*	261.4[a]
M06-2X/6-31+G*	257.8
MP2/6-311+G(2d,p)//B3LYP/6-31+G(d)	270.8
M06-2X/aug-cc-pVTZ//B3LYP/6-31+G*	268.3
CBS-QB3	264.5

[a] Ref 23b.

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(25) The gas phase PAs of other "nonstabilized" carbenes have been measured. See: Tian, Z.; Kass, S. R. *Int. J. Mass Spectrom.* **2007**, *267*, 288–294, and references therein.

(26) These fragmentation pathways are being further examined and will be the subject of a future paper.

Table 2. Summary of Results for PA Bracketing of PCy_3

ref base[c]	PA[a] kcal mol^{-1}	proton transfer[b] ref base[c]	proton transfer[b] conj. acid
N,*N*,*N*′,*N*′-tetramethyl-1,4-butane-diamine	250.1 ± 2.0	+	−
N,*N*,*N*′,*N*′-tetramethyl-1,3-propane-diamine	247.4 ± 2.0	−	+
N,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalene-diamine	245.8 ± 2.0	−	+

[a] Values are in kcal mol^{-1}.[38] [b] A "+" indicates the occurrence, and a "−" indicates the absence of proton transfer. [c] "ref" = reference.

258 kcal mol^{-1} the calculated value is still some 7−8 kcal mol^{-1} higher than the measured value of 250−251 kcal mol^{-1}.

The discrepancy between the calculated and experimental PA values for 1-ethyl-3-methyl carbene is somewhat disconcerting, and ideally, a second independent measurement of the carbene PA by a different nonkinetic method would be warranted. However, the carbene is not easily generated for bracketing experiments, so we turned our attention to additional phosphine experiments.

The bracketing results for PCy_3 are shown in Table 2. Protonated tricyclohexylphosphine undergoes proton transfer with neutral *N*,*N*,*N*′,*N*′-tetramethyl-1,4-butane-diamine (PA = 250.1 kcal mol^{-1}); the reverse reaction does not occur. Protonated PCy_3 does not react with *N*,*N*,*N*′,*N*′-tetramethyl-1,3-propane-diamine (PA = 247.4 kcal mol^{-1}); the opposite reaction does. We therefore bracket the PA of PCy_3 to be 249 ± 3 kcal mol^{-1}.[37]

The Cooks kinetic method can be problematic, including the possibly compromised accuracy of measurements when the reference bases differ in structure from the unknown substrate.[39−42] Bracketing experiments are generally more reliable. In the case of PCy_3, the kinetic method measurement using DBU and DBN as reference bases is in agreement with the bracketed measurement, implying the accuracy of the value (249 ± 3 kcal mol^{-1}).

What does this imply about the accuracy of the experimental PA value of 250−251 kcal mol^{-1} for the ethyl methyl carbene **1b**, measured by both the Cooks group and us? The successful measurement of the PA of PCy_3 using the same method and reference bases lends some confidence to the carbene PA measurement, though not completely as the phosphine and carbene are quite different species. Our kinetic method experiment with the protonated dimer of PCy_3 and **1b** (**3b**) also lends confidence to the experimental measurement as it indicates that PCy_3 and **1b** have similar PAs, though as we mention earlier, this experiment is difficult to execute and yields fragmentation pathways in addition to proton transfer. However, given these caveats, our experiments do all give a consistent story: the PAs of PCy_3 and carbene **1b** are similar, at about 250 kcal mol^{-1}. This is to our knowledge the first measurement of PCy_3 PA, both independently and relative to 1-ethyl-3-methylimidazol-2-ylidene (**1b**).[42]

Given that the calculations of the PA of **1b** are not consistent with experiment, we sought to compile a full picture of calculations versus experiments for phosphines. Toward this end, we bracketed the PA of $HPCy_2$ as well (Table 3). Piperidine (PA = 228 kcal mol^{-1}) cannot deprotonate protonated $HPCy_2$, while $HPCy_2$ can deprotonate protonated piperidine. 2,4-Lutidine (PA = 230.1 kcal mol^{-1}) deprotonates protonated $HPCy_2$, but the reverse reaction does not occur. We therefore bracket the PA of $HPCy_2$ to be 229 ± 3 kcal mol^{-1}.

Table 3. Summary of Results for PA Bracketing of $HPCy_2$

ref base[c]	PA[a] kcal mol^{-1}	proton transfer[b] ref base[c]	proton transfer[b] conj. acid
1-methylpiperidine	232.1 ± 2.0	+	−
1-methylpyrrolidine	230.8 ± 2.0	+	−
2,4-lutidine	230.1 ± 2.0	+	−
piperidine	228.0 ± 2.0	−	+
4-picoline	226.4 ± 2.0	−	+

[a] Values are in kcal mol^{-1}.[38] [b] A "+" indicates the occurrence, and a "−" indicates the absence of proton transfer. [c] "ref" = reference.

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(37) DBU and DBN were used in the Cooks kinetic method experiment because they yielded a reasonable protonated dimer signal. However, they were not volatile enough to use in the bracketing experiments, so we used the bases listed in Table 2.

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(42) Interestingly, in recent work, Turecek and co-workers have calculated a comparably high PA for the related species 4-methyl-*N*-3-H-imidazole radical: Turecek, F.; Chung, T. W.; Moss, C. L.; Wyer, J. A.; Ehlerding, A.; Holm, A. I. S.; Zettergren, H.; Nielsen, S. B.; Hvelplund, P.; Chamot-Rooke, J.; Bythell, B.; Paizs, B. *J. Am. Chem. Soc.* **2010**, *132*, 10728–10740.

Table 4. Experimental and Computational Proton Affinity Values for Various Phosphines and 1-Ethyl-3-methylimidazol-2-ylidene **1b**

	proton affinity (PA), kcal mol^{-1}	
substrate	experiment[a]	B3LYP/6-31+G* calculations
PH_3	188[g]	185.7
H_2PMe	203.5[g]	201.6
$HPMe_2$	218.0[g]	215.3
PMe_3	229.2[g]	225.8
H_2PCy	210.3[h]	210.6
$HPCy_2$	229[c]	228.6
PCy_3	249[b,c]	243.3
1b	250−251[b,d,f]	261.4[f]

[a] Experimental values have a 2−3 kcal mol^{-1} error bar. [b] This work, Cooks kinetic method experiments. [c] This work, bracketing experiments. [d] Ref 23a. [e] Ref 46. [f] Ref 23b. [g] Ref 38. [h] Ref 45.

In Table 4, we compile the computational and experimental data on the phosphines and on the ethyl methyl carbene **1b**. The B3LYP/6-31+G* calculations on the methyl phosphine system (first four rows of Table 4) are in agreement with experiment; in general, the B3LYP/6-31+G* calculations are around 2−3 kcal mol^{-1} lower in value than the experimentally measured values. For the PAs of H_2PCy and $HPCy_2$, the B3LYP/6-31+G* calculated and measured values are quite close (about 210 kcal mol^{-1} for the former and 229 kcal mol^{-1} for the latter). However, for PCy_3, the measured value is some 6 kcal mol^{-1} higher than the calculated. As mentioned earlier, because we measured the PCy_3 value using two methods (Cooks kinetic method in a linear quadrupole ion trap and PA bracketing experiments in a Fourier Transform ion cyclotron resonance mass spectrometer), we believe the value of 249 ± 3 kcal mol^{-1} is accurate.

Increasing errors for DFT/B3LYP-calculated enthalpies of formation with increasing molecule size have been previously observed, with attribution to the neglect of medium-range electron correlation effects.[43−45] We therefore calculated the PCy_3 PA using MP2/6-311+G(2d,p)//B3LYP/6-31+G(d) and find the value to be much closer to experiment (248.6 kcal mol^{-1}).[47] The PCy_3 system thus appears to be sufficiently electronically crowded to require adequate electron correlation for accurate description.[43−45]

In contrast, no common computational method/level appears adequate to calculate the PA of 1-ethyl-3-methylimidazol-2-ylidene (**1b**) accurately (Table 1). Tables 1 and 4 indicate the importance of good measurements as these highly basic species appear to be difficult to accurately calculate.

In summary, we have established that PCy_3 has a proton affinity similar to the N-heterocyclic carbenes **1a** and **1b** in the gas phase. All are very basic, with PAs around 250 kcal mol^{-1}. This would be consistent with both being effective ligands for Grubbs olefin metathesis, though it does not provide an explanation for the NHCs being more effective than phosphines. We also find that the proton affinities are difficult to calculate accurately; for PCy_3 this may be a “crowdedness issue” since inclusion of medium-range electron correlation provides better agreement with experiment. For the 1-ethyl-3-methyl NHC **1b**, no level or method used agrees with experiment.

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Supporting Information Available: Experimental and computational details are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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