Stable Carbenes

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A Cyclic Diaminocarbene with a Pyramidalized Nitrogen Atom: A Stable N-Heterocyclic Carbene with Enhanced Electrophilicity**

*David Martin, Nicolas Lassauque, Bruno Donnadieu, and Guy Bertrand**

Since their discovery,[1,2] thousands of reports have dealt with the preparation and use of stable carbenes. Arguably, among them,[3–6] the N-heterocyclic carbenes (NHCs) **A** have been the most studied.[7–12] Despite their widespread applications, NHCs still suffer from low modularity, which confines them to a narrow range of strong σ-donor ligands and nucleophiles. In recent years, several strategies have successfully been developed for tuning their σ-donor properties, which are mainly linked to the σ effect of the carbene substituents.[8] However, the modulation of the π-acceptor properties of NHCs is more challenging, because the high-energy LUMO is ruled by the strong π donation of the two amino groups to the carbene vacant orbital.[13] The replacement of a π-electron-donating and σ-withdrawing amino substituent by a σ-donating alkyl group (**B**) leads to an increase of electrophilicity but also nucleophilicity (Figure 1).[14,15] Carbonyl groups can be introduced into the backbone in order to compete with the carbene center for the π donation of the nitrogen atom. The so-called diamidocarbenes **C** are very electrophilic, but at the expense of their nucleophilicity.[16–19] Herein we report the synthesis and single-crystal X-ray diffraction study of a cyclic diaminocarbene, which retains the nucleophilicity of classical NHCs, but shows enhanced electrophilicity.

We reasoned that for obtaining a carbene that retains the nucleophilicity of classical NHCs **A**, amino groups that do not bear electron-withdrawing substituents should be used. To concomitantly enhance the electrophilicity, one of these amino substituents should be restricted from donating its lone pair to the carbene center. To support our hypothesis, we performed ab initio calculations, which predicted that the pyramidalization of one nitrogen atom of the parent NHC **A**, as shown in $\mathbf{A}_{\rm pyr}$, significantly decreases the energy of the LUMO, without lowering the energy of the HOMO (Figure 1).

The general reluctance, and sometimes the impossibility, to form bridgehead double bonds in a sufficiently strained polycyclic structure is well known as Bredt's rule.[20] In the anti-Bredt diaminocarbene $\mathbf{A}_{\rm pyr}$a, the resonance form $\mathbf{A}_{\rm pyr}$a′, which features a bridgehead C=N bond, becomes irrelevant. As a consequence, $\mathbf{A}_{\rm pyr}$a can be described as a "push–pull" carbene,[13] in which only one amino group is π-donating, the second one is acting as a σ-withdrawing group (resonance form $\mathbf{A}_{\rm pyr}$a″).

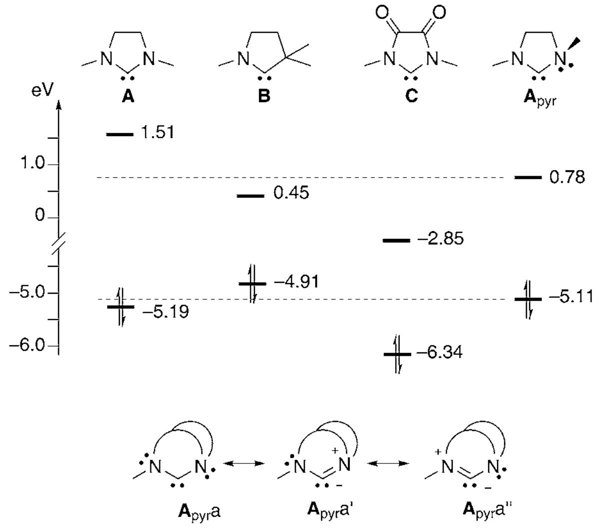
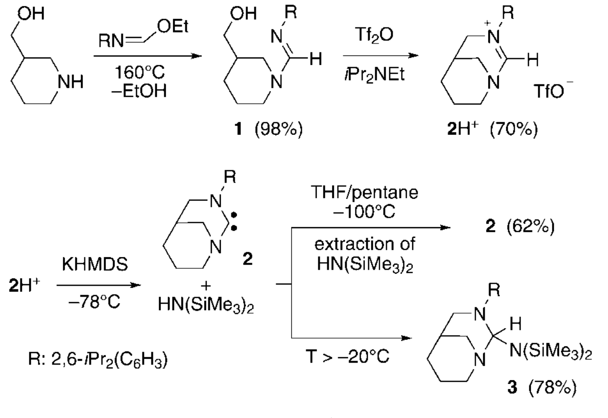


Figure 1. Energy (eV) of frontier orbitals of classical NHC **A**, cyclic (alkyl)(amino)carbene **B**, diamidocarbene **C**, and N-pyramidalized (sum of angles around N = 336°) diaminocarbene $\mathbf{A}_{\rm pyr}$ at the B3LYP/6-31G* level. Targeted carbene $\mathbf{A}_{\rm pyr}$a with its nonrelevant and more representative resonance structures $\mathbf{A}_{\rm pyr}$a′ and $\mathbf{A}_{\rm pyr}$a″, respectively.

The N-bridgehead amidinium salt $\mathbf{2}$H$^+$ was prepared in two steps (Scheme 1). The commercially available 3-piperidinemethanol was heated at 160 °C with neat ethyl *N*-2,6-diisopropylphenylformamidinate to quantitatively afford



Scheme 1. Synthesis of amidinium **2**H$^+$, carbene **2**, and hexamethyldisilazane adduct **3**.

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[*] Dr. D. Martin, Dr. N. Lassauque, B. Donnadieu, Prof. Dr. G. Bertrand
UCR-CNRS Joint Research Chemistry Laboratory (UMI 2957)
Department of Chemistry, University of California
Riverside, CA, 92521-0403 (USA)
E-mail: guy.bertrand@ucr.edu
Homepage: http://research.chem.ucr.edu/groups/bertrand/guy-bertrandwebpage/

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formamidine **1**. The latter was reacted with trifluoromethanesulfonic anhydride in the presence of a base, and after work-up, the amidinium **2**H^+ was isolated in 70% yield as colorless crystals. Compound **2**H^+ is air and moisture stable in the absence of acidic impurities. The ^{13}C and ^{1}H NMR signals for the carbenium center are shifted strongly downfield (168 and 8.6 ppm, respectively) compared with those of known amidinium salts containing six-membered rings ($\approx$152 and $\approx$7.5 ppm, respectively).[21–23] An X-ray diffraction analysis (Figure 2, left)[24] shows that the C1–N2 bond is longer (1.341(2) Å) than the C1–N1 bond (1.310(2) Å). As expected, N1 is in a planar environment, while the bridgehead nitrogen atom N2 is pyramidalized; the sum of the bond angles around N2 is 339°, a typical value for sp^3-hybridized nitrogen atoms in 1-aza[3.3.1]bicyclononane derivatives.[25] In addition to this pyramidalization, there is also a significant torsion around the C1–N2 bond. Indeed, a geometric analysis indicates that the dihedral angle between the lone pair of N2 and the formal vacant p orbital of the carbene is approximately 34°. Of note, one of the six-membered rings can have an optimal chair conformation, thus limiting the ring strain.

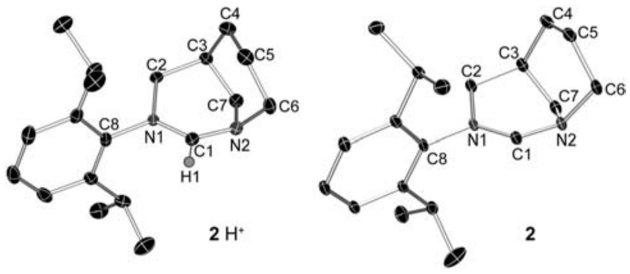
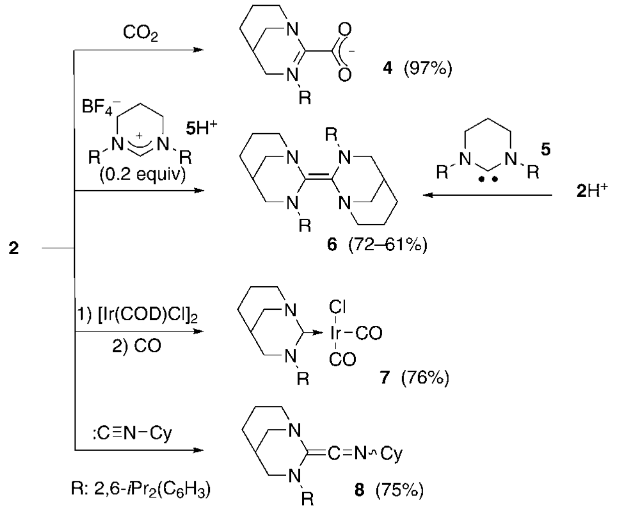


Figure 2. X-ray structures of **2**H^+ and **2** with thermal ellipsoids drawn at 50% probability level. For **2**H^+, H1 is indicated, other hydrogen atoms and the triflate anion are omitted for clarity. Selected bond lengths [Å] and angles [deg]: **2**H^+, C1–N1 1.310(2), C1–N2 1.341(2), N1–C2 1.490(2), N1–C8 1.451(2), N2–C6 1.497(2), N2–C7 1.475(2); N1-C1-N2 122.73(14), C1-N1-C2 120.49(14), C1-N1-C8 120.78(13), C2-N1-C8 118.43(13), C1-N2-C7 115.45(14), C7-N2-C6 111.22(14), C6-N2-C1 112.17(13). **2**, C1–N1 1.349(2), C1–N2 1.407(2), N1–C2 1.489(2), N1–C8 1.461(1), N2–C6 1.488(2), N2–C7 1.464(2); N1-C1-N2 112.9(1), C1-N1-C2 126.0(1), C1-N1-C8 118.7(1), C2-N1-C8 114.3(1), C1-N2-C7 118.2(1), C7-N2-C6 110.2(1), C6-N2-C1 113.5(1).

Monitoring the deprotonation of **2**H^+ by ^{13}C NMR spectroscopy with potassium hexamethyldisilazide (KHMDS) in THF at −78 °C allowed the observation of a ^{13}C NMR signal at a low field, thus suggesting the formation of carbene **2**.[26] However, when the solution was warmed to −20 °C, this signal disappeared and after work-up, derivative **3**, which results from the formal carbene insertion into the N–H bond of hexamethyldisilazane, was isolated in 78% yield as a single diastereomer with the $N(SiMe_3)_2$ group located on the less-hindered *exo* face.

In order to prevent the addition of the amine, the deprotonation of **2**H^+ with KHMDS was carried out at −78 °C. The solution was cooled to −90 °C, and addition of pentane induced the precipitation of carbene **2**, which was isolated as a white powder in 62% yield. The ^{13}C NMR chemical shift of **2** (282 ppm) is at much lower field than those for monocyclic diaminocarbenes containing five- and six-membered rings, such as **A** (210–245 ppm),[8,26] but close to those of the more electrophilic cyclic (alkyl)(amino)carbenes **B** (300–320 ppm)[6] and diamidocarbenes **C** (262–280 ppm).[16] A single-crystal X-ray diffraction analysis of **2** showed that the environment around N1 and N2 remains almost unchanged compared to **2**H^+ (N1 is planar and the sum of the angles around N2 is 342°). The N1–C1 bond length (1.349(2) Å) and the N1-C1-N2 angle (112.9(1)°) compare well with the values known for NHCs containing six-membered rings,[27] and the long N2–C1 bond distance (1.407(2) Å) clearly shows the weak or nonexistent π donation of N2 (Figure 1, right). Interestingly, carbene **2** proved to be stable at room temperature both in solution and in the solid state (mp: 138–141 °C).

Similarly to classical NHCs, carbene **2** is a strong nucleophile, shown by the instantaneous and quantitative reaction at −78 °C with carbon dioxide, affording the betaine adduct **4** (Scheme 2).[28,29] To assess the basicity of **2**, its protonated form **2**H^+ was reacted at −78 °C with a stoichiometric amount of the classical NHC **5**[21] containing a six-membered ring ($pK_a = 28$),[30] and the instantaneous formation of the N-bridgehead carbene dimer **6** was observed. Many diaminocarbenes are also known to dimerize upon "proton catalysis".[31] Importantly, when **2** was reacted with 0.2 equivalents of **5**H^+, carbene dimer **6** was also obtained instantaneously, thus demonstrating that the basicity of **2** and **5** is very similar.



Scheme 2. Reactivity of carbene **2**.

The Tolman electronic parameter (TEP) is a well recognized measure of the net donation of a ligand (L) to transition metals.[32] Addition of half an equivalent of a chloro(1,5-cyclooctadiene)iridium dimer to **2**, followed by treatment with carbon monoxide afforded the cis-chlorodicarbonyliridium complex **7**, which was fully characterized by NMR spectroscopy and X-ray crystallography. From the stretching frequencies of the carbonyl groups in IR measurements, we inferred[33] a TEP value of 2047 cm^{-1}, which is higher than that of classical NHC **5** containing a six-membered ring

(2044 cm^{-1}, see the Supporting Information), and consistent with a ligand as strongly σ-donating as **5**, but significantly more π-accepting. DFT calculations at the B3LYP/6-311g** level on the parent N-methyl-substituted carbenes **2′** and **5′** (R = Me) are in line with our experimental findings. The energy of the HOMO (−4.8 eV) and the proton affinity (272 $kcal\,mol^{-1}$) of **2′** are similar to those of carbene **5′**, which contains a six-membered ring (−5.0 eV, 270 $kcal\,mol^{-1}$). Conversely, carbene **2′** has a smaller singlet–triplet gap (43 $kcal\,mol^{-1}$) than **5′** (62 $kcal\,mol^{-1}$), which confirms the enhanced electrophilicity of **2′**. To further prove this point experimentally, **2** was reacted with cyclohexylisocyanide at −78 °C, and we observed the clean formation of keteneimine **8**. This coupling reaction does not occur with classical NHCs, and is only known for electrophilic carbenes.[34–37]

These results, as a whole, demonstrate that the placement of one of the two nitrogen atoms of an NHC in a bridgehead position considerably increases the electrophilic character of the carbene center, without diminishing its nucleophilicity. Because a variety of bicyclic scaffolds are available, the pyramidalization of the bridgehead nitrogen atom can be modified at will. This simple topological modification should allow the fine tuning of the π-accepting properties of NHCs, and consequently of the catalytic properties of the corresponding metal complexes.[38–40]

Experimental Section

All experiments were performed under an atmosphere of dry argon with standard Schlenk techniques. Solvents were dried by standard methods and distilled under argon. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded on a Bruker Avance 300 or Varian Inova 500 spectrometer. NMR multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, sept = septet, m = multiplet, br = broad signal. Melting points (uncorrected) were measured with an Electrothermal MEL-TEMP apparatus. IR spectra were recorded on a Brucker Equinox Spectrometer. Mass spectroscopy experiments were performed on an Agilent LCTOF spectrometer.

N-Bridgehead amidinium triflate $\mathbf{2}H^{+}$: Amidine **1** (12.8 g, 42.5 mmol) was dissolved in 20 mL of dried CH_2Cl_2 and cooled to −78 °C. Diisopropylethylamine (8.9 mL, 51 mmol) was added to the solution, followed by the dropwise addition of trifluoromethanesulfonic anhydride (7.1 mL, 42.5 mmol). The solution was stirred for 30 min at −78 °C and then warmed to room temperature. The volatiles were removed under reduced pressure to afford an orange solid, which was washed with diethylether until no colored impurities remained. The resulting white powder was washed with water (3 × 50 mL), and with technical grade diethylether (3 × 30 mL), dissolved in CH_2Cl_2, and the solution was dried with sodium sulfate. After filtration, the concentrated solution was layered with hexane, and the triflate salt $\mathbf{2}H^{+}$ (13.0 g, 70 %) was isolated as colorless crystals upon cooling at −10 °C overnight. mp: 176–178 °C; IR (CH_2Cl_2): 1620 (C=N), 1461, 1278, 1252, 1162, 1031 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.46$ (s, 1 H), 7.46 (pseudo t, $J = 9$ Hz, 1 H), 7.28 (d, $J = 9$ Hz, 1 H), 7.24 (d, $J = 9$ Hz, 1 H), 4.3 (m, 1 H), 3.85 (dd, $J = 6$ and 15 Hz, 1 H), 3.63 (d, $J = 12$ Hz, 1 H), 3.52 (d, $J = 12$ Hz, 2 H), 3.28 (d, $J = 12$ Hz, 1 H), 3.1 (br s, 1 H), 2.7 (m, 2 H), 2.2 (m, 1 H), 2.0 (m, 1 H), 1.7 (m, 2 H), 1.30 (d, $J = 6$ Hz, 6 H), 1.27 (d, $J = 6$ Hz, 3 H), 1.12 ppm (d, $J = 6$ Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 166.2$ (NCHN), 145.9 (C_{aro}), 143.8 (C_{aro}), 133.8 (C_{aro}), 131.5 (CH_{aro}), 125.6 (CH_{aro}), 124.9 (CH_{aro}), 120.9 (q, $J = 320$ Hz, CF_3), 60.1 (CH_2), 50.3 (CH_2), 49.2 (CH_2), 30.1 (CH), 28.8 (CH), 28.7 (CH), 25.1 (CH_3), 25.0 (CH_2), 24.8(CH_3), 24.8(CH_2), 24.5 (CH_3), 23.6 ppm (CH_3); ^{19}F ($CDCl_3$, 282 MHz): $\delta = -79.0$ ppm; MS (m/z): $[M+H]^{+}$ calcd for $C_{19}H_{30}N_2$, 287.2435; found, 287.2436.

Isolation of carbene **2**: A solution of the triflate salt $\mathbf{2}H^{+}$ (1.46 g, 3.4 mmol) in THF (20 mL) was added at −78 °C to a solution of KHMDS (758 mg, 3.8 mmol) in THF (3 mL). The solution was cooled to −95 °C and pentane (15 mL) was slowly added and induced the precipitation of a white solid. After stirring for 10 min at this temperature, the supernatant was removed by a dry canula equipped with a filter. The resulting solid was warmed to room temperature, and dried under vacuum. Extraction with toluene (2 × 10 mL), removal of the solvent, and drying under vacuum gave **2** (0.6 g, 62 %) as a white powder. Crystals suitable for an X-ray crystallographic study were grown from a pentane/toluene (1:1) solution at −15 °C. mp: 138–141 °C. ^{1}H NMR (C_6D_6, 300 MHz): $\delta = 7.3$ (m, 1 H), 7.2 (m, 2 H), 4.30 (broad d, $J = 12$ Hz, 1 H), 3.8 (m, 1 H), 3.4 (m, 2 H), 3.3 (m, 2 H), 3.1 (m, 2 H), 2.91 (d, $J = 12$ Hz, 1 H), 2.8 (m, 3 H), 1.9 (broad s, 1 H), 1.56 (d, $J = 7$ Hz, 3 H), 1.39 (d, $J = 8$ Hz, 3 H), 1.35 (d, $J = 8$ Hz, 3 H), 1.31 ppm (d, $J = 7$ Hz, 3 H); δ ^{13}C NMR (C_6D_6, 125 MHz): $\delta = 23.5$ (CH_3), 24.0 (CH_3), 25.4 (CH_3), 25.5 (CH_3), 26.8 (CH_2), 27.4 (CH_2), 28.6 (CH), 28.7 (CH), 30.0 (CH), 47.4 (CH_2), 49.7 (CH_2), 56.8 (CH_2), 123.6 (CH_{aro}), 124.8 (CH_{aro}), 127.1 (CH_{aro}), 143.8 (C_{aro}), 145.4 (C_{aro}), 146.2 (C_{aro}), 282 ppm (NCN).

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