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A Cyclic Diaminocarbene with a Pyramidalized Nitrogen: A Stable NHC with Enhanced Electrophilicity

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Since their discovery,^[1,2] thousands of papers 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 since the high-energy LUMO is ruled by the strong π -donation of the two amino groups to the carbene vacant orbital.^[13] As shown in Figure 1, 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.^[14,15] Carbonyls can be introduced in the backbone in order to compete with the carbene center for the nitrogen π -donation. The so-called diamidocarbenes **C** are very electrophilic, but at the expense of their nucleophilicity.^[16–19] Here we report the synthesis and single crystal X-ray diffraction study of a cyclic diaminocarbene, which retains the nucleophilicity of classical NHCs, but displays enhanced electrophilicity.

We reasoned that for obtaining a carbene that retains the nucleophilicity of classical NHCs **A**, amino groups not bearing 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 of the parent NHC **A**, as shown in **A_{pyr}**, significantly decreases the energy of the LUMO, without lowering the HOMO energy (Figure 1).

The general reluctance, and sometimes the impossibility, for bridgehead double bond formation in a sufficiently strained polycyclic structure is well known as Bredt's rule.^[20] In the anti-Bredt diaminocarbene **A_{pyr}a**, the resonance form **A_{pyr}a'**, which features a bridgehead CN double bond, becomes irrelevant. As a consequence, **A_{pyr}a** can be described as a push-pull carbene,^[13] in which only one amino group is π -donating, the second acting as a σ -withdrawing group (resonance form **A_{pyr}a''**).

The N-bridgehead amidinium salt **2H⁺** was prepared in two steps (Scheme 1). The commercially available 3-piperidinemethanol was heated at 160°C with neat ethyl N-2,6-diisopropylphenylformamidine to quantitatively afford formamidine **1**. The latter was

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reacted with trifluoromethanesulfonic anhydride in presence of a base, and after work up the amidinium **2H⁺** was isolated in 70% yield as colorless crystals. Compound **2H⁺** is perfectly air and moisture stable in the absence of acidic impurities. The ¹³C and ¹H NMR signals for the carbenium center are shifted strongly downfield (168 and 8.6 ppm, respectively) compared to those of known 6-membered ring amidinium salts (~152 and ~7.5 ppm, respectively).^[21–23] An X-ray diffraction analysis (Figure 2, left)^[24] shows that the C1-N2 bond length is longer [1.341(2) Å] than the N1-C1 bond distance [1.310(2) Å]. As expected, N1 is in a planar environment, while the bridgehead nitrogen N2 is pyramidalized; the sum of the angles around N2 is 339°, a typical value for sp³-hybridized nitrogen 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 6-membered rings can meet an optimal chair conformation, thus limiting the ring strain.

Monitoring the deprotonation of **2H⁺** by ¹³C NMR spectroscopy with potassium hexamethyldisilazide (KHMDs) in THF at –78°C allowed for the observation of a low field ¹³C NMR signal, 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**, resulting from the formal carbene insertion into the N-H bond of hexamethyldisilazane, was isolated in 78% yield as a single diastereomer, the N(SiMe₃)₂ group being located on the less hindered *exo* face.

In order to prevent the addition of the amine, the deprotonation of **2H⁺** 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 ¹³C NMR chemical shift of **2** (282 ppm) is at much lower field than those for monocyclic 5- and 6-membered ring diaminocarbenes 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** revealed that the environment around N1 and N2 remains almost unchanged compared to **2H⁺** (N1 is planar and the sum of 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 6-membered NHCs,^[27] and the long N2-C1 bond distance [1.407(2) Å] clearly demonstrates the weak, if any, 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 as shown by the instantaneous and quantitative reaction at –78°C with carbon dioxide, which affords the betaine adduct **4** (Scheme 2).^[28,29] To assess the basicity of **2**, its protonated form **2H⁺** was reacted at –78°C with a stoichiometric amount of the classical six-membered NHC **5**^[21] (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 equivalent of **5H⁺**, carbene dimer **6** was also obtained instantaneously, demonstrating that the basicity of **2** and **5** is very similar.

The Tolman Electronic Parameter (TEP) is a well recognized measure of the net donation of an L ligand to transition metals.^[32] Addition of half an equivalent of 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 and X-ray crystallography. From the carbonyl infrared stretching frequencies, we inferred^[33] a TEP value of 2047 cm^{–1}, which is higher than that of classical six-membered NHC **5** (2044 cm^{–1}, see supporting information), and consistent with a ligand as 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 6-membered ring carbene **5'** (−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 nitrogens 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 can be modified at will. This simple topological modification should allow for 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 using standard Schlenk techniques. Solvents were dried by standard methods and distilled under argon. ¹H, ¹⁹F and ¹³C 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 Bruker Equinox Spectrometer. Mass spectroscopy experiments were performed on an Agilent LCTOF spectrometer.

N-Bridgehead amidinium triflate 2H⁺

Amidine **1** (12.8 g, 42.5 mmol) was dissolved in 20 mL of dried CH₂Cl₂ 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 affording 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 CH₂Cl₂, and the solution was dried with sodium sulfate. After filtration, a concentrated CH₂Cl₂ solution was layered with hexane, and the triflate salt **2H⁺** was isolated as colorless crystals upon cooling at −10°C overnight. 13.0 g; yield = 70 %. mp: 176–178°C; IR (CH₂Cl₂): 1620 (C=N), 1461, 1278, 1252, 1162, 1031 cm^{−1}; MS (m/z): [M+H]⁺ calcd. for C₁₉H₃₀N₂, 287.2435; found, 287.2436; ¹H NMR (CDCl₃, 300 MHz): δ 8.46 (s, 1H), 7.46 (pseudo t, *J* = 9 Hz, 1H), 7.28 (d, *J* = 9 Hz, 1H), 7.24 (d, *J* = 9 Hz, 1H), 4.3 (m, 1H), 3.85 (dd, *J* = 6 and 15 Hz, 1H), 3.63 (d, *J* = 12 Hz, 1H), 3.52 (d, *J* = 12 Hz, 2H), 3.28 (d, *J* = 12 Hz, 1H), 3.1 (br s, 1H), 2.7 (m, 2H), 2.2 (m, 1H), 2.0 (m, 1H), 1.7 (m, 2H), 1.30 (d, *J* = 6 Hz, 6H), 1.27 (d, *J* = 6 Hz, 3H), 1.12 (d, *J* = 6 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 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, CF₃), 60.1 (CH₂), 50.3 (CH₂), 49.2 (CH₂), 30.1 (CH), 28.8 (CH), 28.7 (CH), 25.1 (CH₃), 25.0 (CH₂), 24.8 (CH₃), 24.8 (CH₂), 24.5 (CH₃), 23.6 (CH₃); ¹⁹F (CDCl₃, 282 MHz): δ −79.0 ppm.

Isolation of carbene **2**

A THF solution (20 mL) of the triflate salt **2H**⁺ (1.46 g, 3.4 mmol) was added at -78°C to a THF solution (3 mL) of KHMDS (758 mg, 3.8 mmol). The solution was cooled to -95°C and 15 mL of pentane was slowly added, inducing the precipitation of a white solid. After stirring 10 minutes 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 (10 mL $\times$ 2), removal of the solvent, and drying under vacuum gave **2** as a white powder. 0.6 g; 62 % yield. Crystals suitable for an X-ray study were grown from a pentane/toluene solution at -15°C . mp: $138\text{--}141^{\circ}\text{C}$. ¹H NMR (C₆D₆, 300 MHz): 7.3 (m, 1H), 7.2 (m, 2H), 4.30 (broad d, $J = 12$ Hz, 1H), 3.8 (m, 1H), 3.4 (m, 2H), 3.3 (m, 2H), 3.1 (m, 2H), 2.91 (d, $J = 12$ Hz, 1H), 2.8 (m, 3H), 1.9 (broad s, 1H), 1.56 (d, $J = 7$ Hz, 3H), 1.39 (d, $J = 8$ Hz, 3H), 1.35 (d, $J = 8$ Hz, 3H), 1.31 (d, $J = 7$ Hz, 3H); δ ¹³C NMR (C₆D₆, 125 MHz): δ 23.5 (CH₃), 24.0 (CH₃), 25.4 (CH₃), 25.5 (CH₃), 26.8 (CH₂), 27.4 (CH₂), 28.6 (CH), 28.7 (CH), 30.0 (CH), 47.4 (CH₂), 49.7 (CH₂), 56.8 (CH₂), 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 (NCN).

Supplementary Material

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Acknowledgments

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References

1. Igau A, Grutzmacher H, Baceiredo A, Bertrand G. J Am Chem Soc. 1988; 110:6463–6466.
2. Arduengo AJ III, Harlow RL, Kline M. Am Chem Soc J. 1991; 113:361–363.
3. Vignolle J, Cattoën X, Bourissou D. Chem Rev. 2009; 109:3333–3384. [PubMed: 19368393]
4. Martin D, Melaimi M, Soleilhavoup M, Bertrand G. Organometallics. 2011; 30:5304–5313.
5. Schuster O, Yang L, Raubenheimer HG, Albrecht M. Chem Rev. 2009; 109:3445–3478. [PubMed: 19331408]
6. Melaimi M, Soleilhavoup M, Bertrand G. Angew Chem. 2010; 122:8992–9032. Angew Chem Int Ed. 2010; 49:8810–8849.
7. Díez-González, S., editor. N-Heterocyclic carbenes, from laboratory curiosities to efficient synthetic tools. Royal Society of Chemistry Publishing; Cambridge: 2011.
8. Droege T, Glorius F. Angew Chem. 2010; 122:7094–7107. Angew Chem Int Ed. 2010; 49:6940–6952.
9. Hahn FE, Jahnke MC. Angew Chem. 2008; 120:3166–3216. Angew Chem Int Ed. 2008; 47:3122–3172.
10. Vougioukalakis GC, Grubbs RH. Chem Rev. 2010; 110:1746–1787. [PubMed: 20000700]
11. Díez-González S, Marion N, Nolan SP. Chem Rev. 2009; 109:3612–3676. [PubMed: 19588961]
12. Grossmann A, Enders D. Angew Chem. 2012; 124:320–332. Angew Chem Int Ed. 2012; 51:314–325.
13. Bourissou D, Guerret O, Gabbai FP, Bertrand G. Chem Rev. 2000; 100:39–91. [PubMed: 11749234]
14. Lavallo V, Canac Y, Prasang C, Donnadiou B, Bertrand G. Angew Chem. 2005; 117:5851–5855. Angew Chem Int Ed. 2005; 44:5705–5709.
15. Lavallo V, Canac Y, Donnadiou B, Schoeller WW, Bertrand G. Angew Chem. 2006; 118:3568–3571. Angew Chem Int Ed. 2006; 45:3488–3491.

16. Hudnall TW, Bielawski CW. *J Am Chem Soc.* 2009; 131:16039–16041. [PubMed: 19842700]
17. Hudnall TW, Tennyson AG, Bielawski CW. *Organometallics.* 2010; 29:4569–4578.
18. César V, Lugan N, Lavigne G. *Chem Eur J.* 2010; 16:11432–11442. [PubMed: 20821762]
19. Braun M, Frank W, Reiss GJ, Ganter C. *Organometallics.* 2010; 29:4418–4420.
20. Buchanan GL. *Chem Soc Rev.* 1974; 3:41–63.
21. Alder RW, Blake ME, Bortolotti C, Bufali S, Butts CP, Linehan E, Oliva JM, Orpen AG, Quayle MJ. *Chem Commun.* 1999:241–242.
22. Iglesias M, Beetstra DJ, Cavell KJ, Dervisi A, Fallis IA, Kariuki B, Harrington RW, Clegg W, Horton PN, Coles SJ, Hursthouse MB. *Eur J Inorg Chem.* 2010; 11:1604–1607.
23. Benhamou L, Chardon E, Lavigne G, Bellemin-Lapponnaz S, Cesar V. *Chem Rev.* 2011; 111:2705–2733. [PubMed: 21235210]
24. CCDC 870898 (2), 870899 (2H⁺), 870900 (3), 870901 (6) and 870902 (7) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
25. Mez HC, Rihs G. *Tetrahedron Lett.* 1973; 14:3417–3420.
26. Tapu D, Dixon DA, Roe C. *Chem Rev.* 2009; 109:3385–3407. [PubMed: 19281270]
27. Iglesias M, Beetstra DJ, Knight JC, Ooi L-L, Stasch A, Coles S, Male L, Hursthouse MB, Cavell KJ, Dervisi A, Fallis IA. *Organometallics.* 2008; 27:3279–3289.
28. Delaude L. *Eur J Inorg Chem.* 2009:1681–1699.
29. Kuhn N, Kratz T. *Synthesis.* 1993:561–562.
30. Higgins EM, Sherwood JA, Lindsay AG, Armstrong J, Massey RS, Alder RW, O'Donoghue AC. *Chem Commun.* 2011; 47:1559–1561.
31. Alder RW, Blake ME, Chaker L, Harvey JN, Paolini F, Schütz J. *Angew Chem.* 2004; 116:6020–6036. *Angew Chem Int Ed.* 2004; 43:5896–5911.
32. Tolman CA. *Chem Rev.* 1977; 77:313–348.
33. Kelly RA III, Clavier H, Giudice S, Scott NM, Stevens ED, Bordner J, Samardjiev I, Hoff CD, Cavallo L, Nolan SP. *Organometallics.* 2008; 27:202–210.
34. Igau A, Baceiredo A, Trinquier G, Bertrand G. *Angew Chem.* 1989; 101:617–618. *Angew Chem Int Ed Engl.* 1989; 28:621–622.
35. Hudnall TW, Moorhead EJ, Gusev DG, Bielawski CW. *J Org Chem.* 2010; 75:2763–2766. [PubMed: 20297836]
36. Siemeling U, Färber C, Bruhn C, Leibold M, Selent D, Baumann W, von Hopffgarten M, Goedecke C, Frenking G. *Chem Sci.* 2010; 1:697–704.
37. Goedecke C, Leibold M, Siemeling U, Frenking G. *J Am Chem Soc.* 2011; 133:3557–3569. [PubMed: 21332207]
38. Alcarazo M, Stork T, Anoop A, Thiel W, Fürstner A. *Angew Chem.* 2010; 122:2596–2600. *Angew Chem Int Ed.* 2010; 49:2542–2546.
39. Khranov DM, Rosen EL, Er JAV, Vu PD, Lynch VM, Bielawski CW. *Tetrahedron.* 2008; 64:6853–6862.
40. Hadei N, Kantchev EAB, O'Brien CJ, Organ MG. *Org Lett.* 2005; 7:1991–1994. [PubMed: 15876037]

Figure 1.

Energy (eV) of frontier orbitals of classical NHC **A**, cyclic (alkyl)(amino)carbene **B**, diamidocarbene **C**, and N-pyramidalized (sum of the angle = 336 °) diaminocarbene **A_{pyr}** at the B3LYP/6-31G* level. Targeted carbene **A_{pyr}a** with its non-relevant and more representative resonance structures **A_{pyr}a'** and **A_{pyr}a''**, respectively.

Figure 2.

X-ray structure of **2H⁺** (left) and **2** (right) with thermal ellipsoids drawn at 50% probability level. For **2**, H1 is indicated, other hydrogen atoms and the triflate anion are omitted for clarity. Selected bond lengths [Å] and angles [deg]: **2H⁺**, 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).

Scheme 1.

Synthesis of amidinium **2H⁺**, carbene **2** and hexamethyldisilazane adduct **3**.

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