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Isolation of a C5-Deprotonated Imidazolium, a Crystalline “Abnormal” N-Heterocyclic Carbene

Eugenia Aldeco-Perez¹, Amos J. Rosenthal¹, Bruno Donnadieu¹, Pattiyil Parameswaran², Gernot Frenking², and Guy Bertrand^{1,*}

¹ University of California Riverside—CNRS Joint Research Chemistry Laboratory (UMI 2957), Department of Chemistry, University of California Riverside, Riverside, CA 92521-0403, USA

² Fachbereich Chemie, Philipps-Universität Marburg, Hans-Meerwein-Strasse, 35032 Marburg, Germany

Abstract

The discovery two decades ago of metal-free stable carbenes, especially imidazol-2-ylidenes [N-heterocyclic carbenes (NHCs)], has led to numerous breakthroughs in organic and organometallic catalysis. More recently, a small range of complexes has been prepared in which alternative NHC isomers, namely imidazol-5-ylidenes (also termed abnormal NHCs or *a*NHCs, because the carbene center is no longer located between the two nitrogens), coordinate to a transition metal. Here we report the synthesis of a metal-free *a*NHC that is stable at room temperature, both in the solid state and in solution. Calculations show that the *a*NHC is more basic than its normal NHC isomer. Because the substituent at the carbon next to the carbene center is a nonbulky phenyl group, a variety of substitution patterns should be tolerated without precluding the isolation of the corresponding *a*NHC.

For decades, carbenes, which feature a neutral divalent carbon atom with two nonbonding electrons, were considered prototypical reactive intermediates (1). Today, thanks to the availability of stable carbenes (2,3), these molecules, especially the so-called N-heterocyclic carbenes (NHCs) (**I**) (4–6) (Fig. 1, top left), are recognized as versatile ligands for transition metal-based catalysts (7–10) and as metal-free organic catalysts in their own right (11–14). As expected, NHCs **I** usually bind metals via the carbene center (C2) to give η^1 complexes **II**. However, in 2001, Crabtree and co-workers discovered that 2-pyridylmethyimidazolium salts react with $\text{IrH}_5(\text{PPh}_3)_2$ to give **1** with the imidazole ring bound the “wrong way,” at C5 and not at C2 (15,16) (Fig. 1, center). Since that time, a few other complexes of type **IV** featuring the so-called abnormal NHCs (*a*NHCs) (**III**) (17–20) as ligands have been prepared (21–23) (Fig. 1, top right). Experimental and theoretical data suggest that *a*NHCs **III** are even stronger electron-donor ligands than are NHCs **I**. In line with these observations, initial catalytic screening of *a*NHC metal complexes **IV** reveals promising results for the activation of unreactive bonds such as C–H and H–H (24–26). As an example, an *a*NHC palladium complex has been reported to be an efficient catalyst in the Heck olefination of aryl bromides, whereas the corresponding NHC analog is virtually inactive under identical conditions (24).

*To whom correspondence should be addressed. guy.bertrand@ucr.edu.

Supporting Online Material

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Materials and Methods

Lassaletta and co-workers (27) have shown that the deprotonation of imidazo [1,5-a] pyridinium salts **2** leads to free NHC **3** that can be isolated (Fig. 1, bottom). In contrast, using C2-substituted precursors, such as **4**, Lassaletta *et al.* did not observe the corresponding free *a*NHC. However, by performing the deprotonation reaction in the presence of [Rh(COD)Cl]₂, they were able to isolate the corresponding *a*NHC complex **5**. Because calculations predicted that the parent *a*NHC **III** (where R is equal to H) is only about 17 kcal mol⁻¹ higher in energy than its NHC isomer **I** (18), it seemed that free *a*NHC derivatives were reasonable synthetic targets. We report here the isolation of a metal-free member of this class of heterocyclic compound.

By analogy with the classical synthetic route used to prepare NHCs, we chose imidazolium salt **6** as a precursor to the desired *a*NHC **9** (Fig. 2). The p*K*_a (where *K*_a is the acid dissociation constant) for loss of the C5-bound proton in the parent imidazolium salt (~33) (28) was calculated to be nine units higher than that for loss of the C2-bound proton (29); we therefore replaced the C2 hydrogen with a phenyl group. To offer kinetic protection to the C5 position, we appended bulky 2,6-di-isopropyl-phenyl (Dip) substituents at both nitrogen atoms, as well as a second phenyl group at C4. Imidazolium salts **6** with various counterions were prepared in good yields after slight modifications to known synthetic procedures (30–32). They were fully characterized by spectroscopic methods, with a single-crystal x-ray diffraction study carried out for the bromide salt **6** (Br⁻) (Fig. 3, left).

All attempts to deprotonate the imidazolium tetrafluoroborate salt **6** (BF₄⁻) failed. However, small anions such as Cl⁻ and Br⁻ are known to accelerate heterolytic C–H bond cleavage through hydrogen bonding, and this effect has been used with C2- and C5-unsubstituted imidazolium salts to favor metallation of C2 (with the more acidic proton) over C5 (33). We reasoned that with C2 protected in **6**, small anions should promote the desired deprotonation reaction at C5. Indeed, when **6** (HCl•Cl⁻) was treated with two equivalents (34) of a lithium base such as *n*-butyllithium (*n*BuLi) or lithium diisopropylamide (LDA), the proton nuclear magnetic resonance (¹H NMR) spectrum of the resulting product showed the disappearance of the singlet at 8.7 parts per million (ppm) arising from C5(H) of **6**. In the ¹³C NMR spectrum, the C5 carbon gives rise to a very broad resonance at 190 ppm, which is significantly downfield of the corresponding resonance for the precursor **6** (124 ppm). Although these data indicated that a deprotonation had occurred, the shape of the ¹³C NMR signal, as well as the calculated chemical shift (32) for the C5 carbon of the free *a*NHC **9** (205 ppm), suggested that the new compound was the *a*NHC lithium **7**. Similar complexation has previously been observed for other singlet carbenes such as small NHCs (35) and bis (diisopropylamino) cyclopropenylidene (36,37); in both cases, coordination of the lithium cation was apparent from the broadening and the upfield shift of the carbene ¹³C NMR resonance. Subsequently, we sought to sequester the lithium cation through addition of excess [12] crown-4 to a diethylether solution of **7** (where X is Br). This treatment induced a clean rearrangement to generate **8**, which was isolated in 45% yield. This product formally results from the deprotonation of an isopropyl substituent of the Dip group by the carbene center of the *a*NHC lithium adduct **7**, followed by nucleophilic addition of the resulting benzyl anion to C2. However, calculations indicated that the rearrangement of **9** into **8** is exothermic by only 6.1 kcal mol⁻¹ and involves an activation barrier of 20.3 kcal mol⁻¹ for the proton transfer. Therefore, we hypothesized that the observed rearrangement was catalyzed by a component of the (crown)LiBr system, and that the formation of **8** did not imply that the free *a*NHC **9** was too reactive to be isolated.

Sodium and potassium bases have proven more appropriate than lithium bases in generating free carbenes (35–37), because the corresponding carbon-heavy alkali metal bonds are more labile, which favors precipitation of the salt. When the deprotonation of imidazolium **6** (HX•X⁻, where X is Cl or Br) was performed with two equivalents (34) of potassium

hexamethyldisilazide (KHMDs) in tetrahydrofuran, a clean reaction occurred, with the ^{13}C NMR spectrum of the resulting product showing a very sharp signal at 201.9 ppm. After the products were worked up, the free *a*NHC **9** was isolated as a green powder (480 mg, 68% yield), and single crystals were obtained by recrystallization from a dry hexane solution at -78°C (Fig. 3, right).

In the solid state, both the free *a*NHC **9** and the imidazolium salt **6** (Br^-) feature a fully planar ring (maximum deviation for N1–C2–N3–C4–C5–C21–C31–C41–C53 was 1.9 and 6.3 pm for **9** and **6**, respectively), confirming the delocalization of the π system. This electronic structure is corroborated by the values of the endocyclic C–N [**6**: 1.335 ± 5 to 1.409 ± 5 ; **9**: 1.354 ± 2 to 1.408 ± 3 Å] and C–C bond lengths [**6**: 1.351 ± 5 , **9**: 1.385 ± 3 Å], which are halfway between those of single and double bonds. The carbene bond angle N1–C5–C4 for **9** [$101.03 \pm 17^\circ$] is more acute than the corresponding angle in the cationic precursor **6** [$108.0 \pm 3^\circ$]. This feature is consistent with increased *s* character of the σ lone-pair orbital on the carbene atom in **9** as compared with the C–H $^+$ bonding orbital in **6**. A similar relationship is observed in NHCs and their NHC(H $^+$) precursors (3,4).

Calculations predict *a*NHC **9** to be $14.1 \text{ kcal mol}^{-1}$ less stable than its isomeric normal NHC with the phenyl group bonded to C5 instead of C2. Figure 4 shows the two highest occupied molecular orbitals (HOMOs) of **9**. The HOMO (-4.403 eV) is a σ -type lone-pair orbital at C5; the HOMO-1 (-4.879 eV) is a C5–C4 π -bonding orbital, which exhibits antibonding conjugation with the π orbital of the phenyl substituent at C4. These molecular orbitals are much higher in energy than those of the isomeric NHC (-5.000 and -5.279 eV , respectively), which indicates that *a*NHCs are more basic than NHCs. Indeed, calculations predict that the first ($287.0 \text{ kcal mol}^{-1}$) and second ($144.6 \text{ kcal mol}^{-1}$) proton affinity of *a*NHC **9** are significantly higher than those of normal NHCs (229.9 to 270.6 and 38.9 to $106.5 \text{ kcal mol}^{-1}$, respectively) (38).

Although abnormal NHC **9** is sensitive to air and quantitatively rearranges to **8** upon heating in benzene at 50°C for 48 hours, it is stable at room temperature for a few days both in the solid state (melting point: decomposition at 65°C) and in solution (39). The availability of stable *a*NHCs not only provides easy access to a variety of transition-metal complexes, but also allows for their use as organocatalysts. As a proof of concept (40–43), (*a*NHC) AuCl complex **10** and (*a*NHC)-CO $_2$ adduct **11** have been prepared in 79 and 95% isolated yields by simply reacting **9** with chloro (dimethylsulfide) gold(I) and CO $_2$, respectively (Fig. 2).

Because the substituent at the C4 of **9** is a nonbulky benzene ring, a variety of substitution patterns should be tolerated without precluding isolation of the corresponding *a*NHC. The substituent at C4 is in conjugation with the carbene center, which opens the possibility of substantially modulating the electronic character of the ring system.

Supplementary Material

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Acknowledgments

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Fig. 1. (Top) Resonance structures for NHC (**I/I'**) and *α*NHC (**III/III'**), and their corresponding C2 and C5 metal complexes, **II** and **IV**, respectively. (Center) Synthesis of *α*NHC metal complex **1** by Crabtree and co-workers (15). (Bottom) Synthesis of metal-free NHC **3**, and *α*NHC metal complex **5** by Lassaletta and co-workers (27).

Fig. 2.

Synthesis of *a*NHC lithium adduct **7**, rearrangement product **8**, free *a*NHC **9**, and its ensuing gold(I) complex **10** and CO_2 -adduct **11**.

Fig. 3.

Molecular views (50% thermal ellipsoids are shown) of imidazolium bromide **6** (Br^-) (left) and *a*NHC **9** (right) in the solid state (for clarity, H atoms are omitted, except for the ring hydrogen). Bond lengths and angles for **6** (Br^-) are as follows: C5–N1, 1.368 ± 4 Å; N1–C2, 1.334 ± 4 Å; C2–N3, 1.363 ± 4 Å; N3–C4, 1.408 ± 4 Å; C4–C5, 1.355 ± 5 Å; N1–C5–C4, $108.0 \pm 3^\circ$; C5–C4–N3, $106.0 \pm 3^\circ$; C4–N3–C2, $108.8 \pm 3^\circ$; N3–C2–N1, $106.9 \pm 3^\circ$; C2–N1–C5, $110.4 \pm 3^\circ$. Bond lengths and angles for **9** are as follows: C5a–N1a, 1.417 ± 2 Å; N1a–C2a, 1.357 ± 2 Å; C2a–N3a, 1.345 ± 2 Å; N3a–C4a, 1.412 ± 3 Å; C4a–C5a, 1.383 ± 3 Å; N1a–C5a–C4a, $101.03 \pm 17^\circ$; C5a–C4a–N3a, $111.01 \pm 16^\circ$; C4a–N3a–C2a, $107.97 \pm 15^\circ$; N3a–C2a–N1a, $106.25 \pm 16^\circ$; C2a–N1a–C5a, $113.72 \pm 15^\circ$.

Fig. 4. Plot of the calculated two highest-lying occupied orbitals HOMO (left) and HOMO-1 (right) of the *a*NHC **9**.