

N-Heterocyclic Carbene Nitric Oxide Radicals

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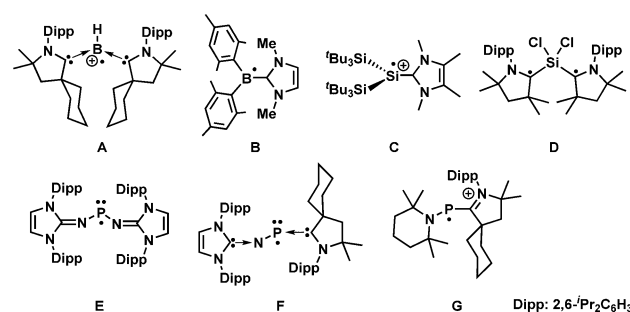
S Supporting Information

ABSTRACT: N-Heterocyclic carbene-stabilized nitric oxide radicals were prepared by direct addition of nitric oxide to two N-heterocyclic carbenes in solution phase. The compounds were fully characterized by X-ray crystallography and EPR. The nitric oxide moiety in the solid compounds obtained can be thermally transferred to another N-heterocyclic carbene, suggesting potential applications to NO delivery.

Nitric oxide (NO) is the simplest radical that exists in neat form at room temperature. NO plays important physiological roles as a mediator in relaxation of vascular muscles and as a messenger in cellular signaling; capture and controllable release of NO have therefore been extensively studied.¹ Nitric oxide has also been involved in organic radical reactions, and relevant mechanistic studies have led to the design of molecules that enable capture and release of nitric oxide in biological systems and in organic reactions.^{1,2} Transition metal complexes have long been known to react with nitric oxide directly to form numerous stable nitroso complexes.³

However, only few organic compounds have been employed to react with nitric oxide to form radical nitric oxide compounds,^{2a} and development of such reactivity with NO using N-heterocyclic carbenes (NHCs) has not been reported to date. NHCs are now well-known to stabilize main group radicals and radical ions.⁴ Pioneered by Bertrand, Roesky, Curran, and others, boryl (A and B), silyl (C and D), phosphoryl (E, F, and G), and other organic radicals with one or more NHC moieties have already been isolated or characterized spectroscopically (Scheme 1).⁴ Successful preparation of these radical compounds was attributed to the NHCs' π -accepting character, which imparts remarkable stability by enabling delocalization of spin density onto the carbene carbon.⁵ Bertrand and colleagues reported that cyclic (alkyl)(amino)carbenes (CAACs) enable activation of small molecules such as H₂, NH₃, and CO, demonstrating that carbene centers can act as potential mimics for transition metal centers.^{4c,6} Herein we report the direct addition of NO to two readily available N-heterocyclic carbenes,⁷ 1,3-bis(2,6-diisopropylphenyl)imidazolylidene (IPr) (1a) and 1,3-bis(2,4,6-trimethylphenyl)imidazolylidene (IMes) (1b), to form stable N-heterocyclic carbene nitric oxide radicals (NHCNOs).

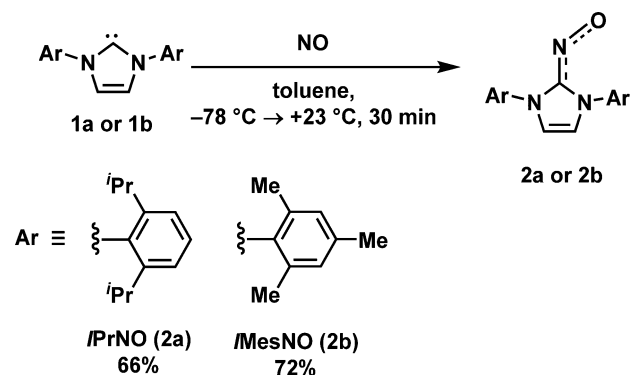
Scheme 1. Examples of NHC-Stabilized Main Group Radicals



Upon thermolysis, these NHCNOs transfer NO to another NHC.

Nitric oxide was introduced to a toluene solution of 1a or 1b at $-78\text{ }^{\circ}\text{C}$, and the colorless solution immediately became dark brown. The solution was warmed up to $23\text{ }^{\circ}\text{C}$ for 30 min, after which the solution became light brown. After workup, a light orange solid (IPrNO, 2a) or a yellow solid (IMesNO, 2b) was obtained as the final product (Scheme 2). Compound 2a was crystallized to yield brown crystals in toluene at $-30\text{ }^{\circ}\text{C}$. Single crystal X-ray analysis of 2a revealed that NO forms a covalent bond with the carbene center of 1a to form 2a (Figure 1a). This result clearly shows a difference between the reactivities of NO and CO toward NHCs; studies have shown that no

Scheme 2. Synthesis of N-Heterocyclic Carbene Nitric Oxide Radicals



Received: February 23, 2015

Published: April 6, 2015

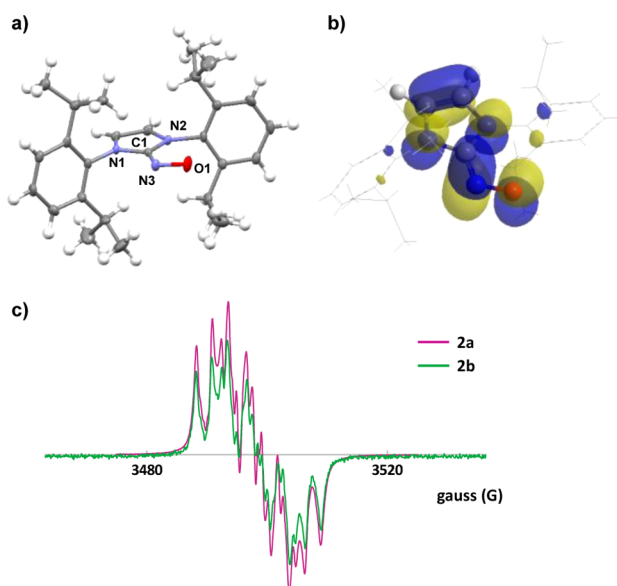


Figure 1. (a) Crystal structure of compound **2a**. Selected experimental [calculated at the B3PW91/6-31G(d,p) level for the optimized structure] bond lengths [Å] and angles [deg]. C1–N3 1.350(6) and 1.356(6) [1.343], N3–O1 1.309(5) and 1.311(5) [1.297], N1–C1 1.371(6) and 1.355(6) [1.374], C1–N2 1.373(6) and 1.363(6) [1.376]; C1–N3–O1 112.1(4) and 112.2(4) [112.9], N1–C1–N3 121.9(4) and 122.2(4) [122.1], N2–C1–N3 132.0(4) and 130.8(4) [131.4]. (b) SOMO of **2a** computed by B3PW91/6-31G(d,p). (c) EPR spectra of **2a** and **2b**.

reaction occurs between typical NHCs and CO.^{4b,8} We proposed that this difference results from a smaller energy gap between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of nitric oxide compared to that of CO, although the singlet–triplet energy gap of a typical imidazole-2-ylidene is larger than that of CAAC's, and the HOMO energy is lower.^{8a} Thus, the π^* -orbital in the singly occupied molecular orbital (SOMO) of nitric oxide enables the reaction between singlet carbenes of **1a** or **1b** and NO to form **2a** or **2b**, respectively. Most interestingly, the crystalline **2a** is stable in air and in water. For example, single crystals of **2a** float in water and do not lose their crystallinity, as confirmed by X-ray diffraction studies. However, in solution phase, **2a** decomposes to **1a** and 1,3-bis(2,6-diisopropylphenyl)-1H-imidazol-2(3H)-one (**IPrO**) (**3a**) over a time scale of days (Figure S4).

There are two independent molecules of **2a** in the asymmetric unit of the X-ray crystal structure of **2a**, which show slightly different bond distances within their heterocyclic groups (Table S3). The average C1–N3 bond length (1.353 Å) is roughly midway between a typical C–N double bond length (1.21 Å) and a C–N single bond length (1.46 Å). Likewise, the average N3–O1 bond distance (1.310 Å) is between that of a typical N–O double bond (1.18 Å) and an N–O single bond (1.43 Å). These data indicate a bond order of 1.5 for both the C1–N3 and N3–O1 bonds (Figure 1a).⁹ These results are also in good agreement with theoretical values obtained by density functional theory (DFT) calculations (Figure 1b and Table S5).¹⁰ In addition, DFT calculations show that the SOMO of **2a** mainly consists of the p-orbitals of the oxygen atom, the π -orbitals of the imidazole ring, and the C1–N3 bond of **2a**. We believe that the π - and σ -bonding orbitals of the C1–N3 bond

stabilize the nitric oxide moiety and engender the air- and moisture-stability of **2a** (Figure 1b).

Radicals **2a** and **2b** were characterized by X-band electron paramagnetic resonance (EPR) spectroscopy (Figure 1c). The room temperature EPR spectra of **2a** and **2b** in benzene are almost identical because the SOMOs of **2a** and **2b** are concentrated over the imidazole and nitric oxide fragments (Figure 1b and Figure S8). According to DFT calculations, the hyperfine couplings patterns of each spectrum result from three nitrogen atoms, two hydrogen atoms, and nearby hydrogen atoms around nitric oxide (Supporting Information). We suggest that the large hyperfine coupling among N1, N2, and N3 displays nine large peaks; the hyperfine coupling constants of the three nitrogen atoms are different due to the asymmetric character of **2a** and **2b**. However, more complex signals seem to result from hyperfine coupling between nitric oxide and nearby hydrogen atoms or from the spin coupling between nitrogen atoms and hydrogen atoms. The EPR spectra of NHCNOs clearly demonstrate that the NHCNOs maintain an intrinsic radical character.

After confirming the radical character of **2a** and **2b**, a mechanistic study for their formation was performed with the aid of DFT calculations (Figure 2a).¹⁰ Unlike the addition of

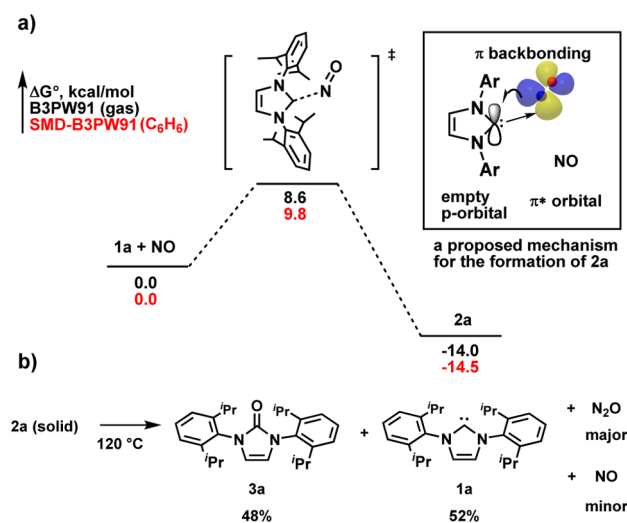


Figure 2. (a) Energy profile (computed by Gaussian 09, B3PW91/6-31G(d,p) level) and a proposed mechanism for the formation of **2a**. (b) Thermolysis of **2a** to release nitric oxide (minor) and nitrous oxide (major).

CO to NHCs, which is thermodynamically unfavorable,^{4b,8} the addition of NO to NHCs turned out to be favorable. According to intrinsic reaction path (IRC) calculations, the activation energy is only 10 kcal/mol in benzene (Supporting Information). For the formation of **2a**, we propose a possible mechanism that involves nucleophilic addition of the singlet carbene to the π^* -orbital of NO and π -backbonding of NO to the carbene's empty p-orbital (Figure 2a). From the DFT calculations, it was found that the reverse reaction (NO release) of the NHCNO formation is feasible because the corresponding activation energy is only 22.6 kcal/mol in a gas phase. However, the thermolysis of **2a** releases nitrous oxide as the major gaseous product, as detected by GC–MS. Stoichiometry of the reaction also supports the formation of nitrous oxide (N_2O) since the residue consisted of a 52:48 mixture of **1a** and **3a** (Figures 2b and S2). This reactivity is related to the thermal

decomposition of reported NHC nitrous oxides that affords **3a** and N_2 .¹¹ Interestingly, EPR analysis revealed that sparse amounts of NO released from **2a** upon thermolysis was captured by **1a** or **1b** to form **2a** or **2b**, respectively, in benzene (Figure S1 and Supporting Information). The complete mechanistic details regarding the thermolysis of **2a** are currently being investigated.

The cyclic voltammogram of **2a** in 0.1 M Bu_4NPF_6 MeCN solution shows a reversible one-electron oxidation at $E_{1/2} = +0.327$ V versus Ag/AgCl (Figure 3 and Supporting

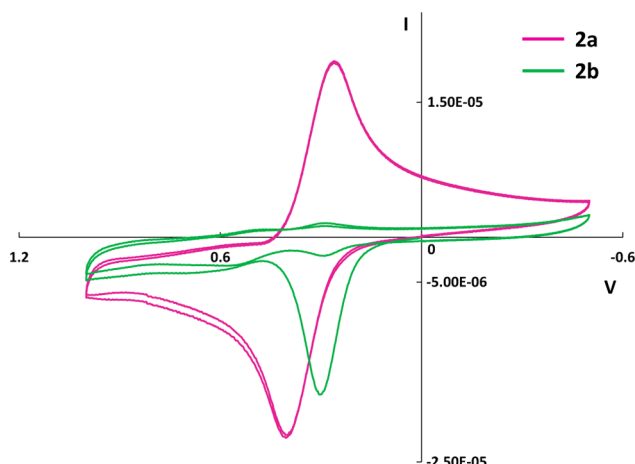


Figure 3. Cyclic voltammogram of **2a** and **2b**.

Information). The one-electron redox process is assumed to correspond to a $2a \rightleftharpoons 2a^+ + e^-$ reaction. In order to confirm the cationic $2a^+$ species formed upon oxidation, an independent synthesis was attempted by treatment of **1a** with $[NO]BF_4$ in tetrahydrofuran and toluene; however, this was not successful. Unlike that of **2a**, the cyclic voltammogram of **2b** in the same conditions shows an irreversible pathway for the one-electron redox process, which indicates an adsorption of **2b** itself or decomposed species on the surface of the electrode. These results illustrate that subtle changes in the structure of *N*-heterocyclic carbenes may affect interactions between the carbenes and the electrode surface dramatically.

In summary, NHC-stabilized nitric oxide radicals were prepared for the first time by direct addition of nitric oxide to two readily available *N*-heterocyclic carbenes in solution phase. The compounds, stable in air and in water, were fully characterized using X-ray crystallography and EPR. Although nitrous oxide was dominantly formed during the thermolysis of **2a**, nitric oxide was also found to be thermally transferred to other *N*-heterocyclic carbenes. This suggests potential biological applications for NO delivery. Furthermore, this study adds another example of stable singlet carbenes acting as mimics for transition metal centers.^{4c} Further studies on carbenes' reactivity with other small molecules will deepen our understanding of this interesting resemblance.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, spectroscopic data for all new compounds, and crystallographic data for **2a** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare the following competing financial interest(s): A patent application has been led through POSTECH and IBS on methods and reagents presented in this manuscript.

■ ACKNOWLEDGMENTS

This work was supported by the Institute for Basic Science (IBS; CA1303) in Korea. We thank Mr. Greg Boursalian and Prof. Byoung-Yong Chang for helpful discussion, and Dr. Yumi Yakiyama for assistance with EPR experiments.

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