



## Primary amine diazeniumdiolate ions of structure $\{RNN(O)NOR'\}^-$ as ambident nucleophiles

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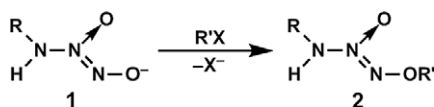
Bidentate anion

### ABSTRACT

An  $O^2$ -substituted primary amine diazeniumdiolate  $RHN-N(O)=NOR'$  is ionized to an anion that attacks an electrophile  $R'X$  via either of two nitrogens to form both  $RR''N-N(O)=NOR'$  and  $R-N=N(O)-N(R'')OR'$ . The bidentate character of such anions should be kept in mind when planning or evaluating drug discovery efforts involving diazeniumdiolates of structure  $RHN-N(O)=NOR'$ .

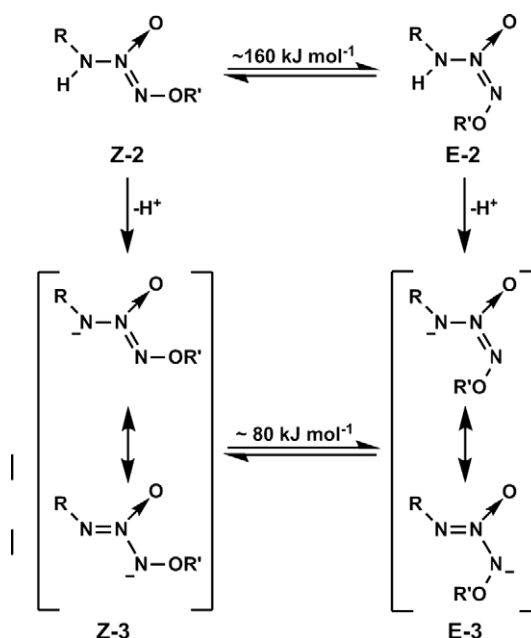
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Diazeniumdiolated primary amines are of growing interest as caged forms of the recently discovered bioeffector molecule nitroxyl (HNO).<sup>1</sup> We are exploring the fundamental chemistry of these ions (**1**) and their  $O^2$ -substituted derivatives (**2**) as a platform for rational development of prodrugs designed to deliver HNO to specific bodily compartments for therapeutic benefit.



An interesting feature of neutral molecules having structure **2** is their ability to ionize at mildly basic pH, forming anions of structure **3** that are capable of  $Z \rightleftharpoons E$  fluxional behavior. In the case of **2** with  $R = R' = \text{Me}$ , the interconversion barrier has been calculated to drop from a prohibitive  $160 \text{ kJ mol}^{-1}$  for **2** to a value about half that for the anionic form **3** (Scheme 1).<sup>2</sup> Experimental confirmation that isomerization of  $Z\text{-3}$  to  $E\text{-3}$  occurs under mildly basic conditions was provided for **3** with  $R = \text{isopropyl}$  and  $R' = \text{CH}_2\text{CH}_2\text{Br}$  by trapping the  $E$  form in a novel six-membered heterocyclic arrangement. These results can be easily rationalized in terms of the

extensive delocalization of the  $N=N$  linkage of **2** and consequent decrease in its double-bond character on ionization, as summarized in Scheme 1.<sup>2</sup>



Scheme 1. Mechanism of isomerizing  $Z\text{-2}$  to  $E\text{-2}$  ( $R=\text{Me}=R'$ ) via conjugate base **3**.<sup>2</sup>

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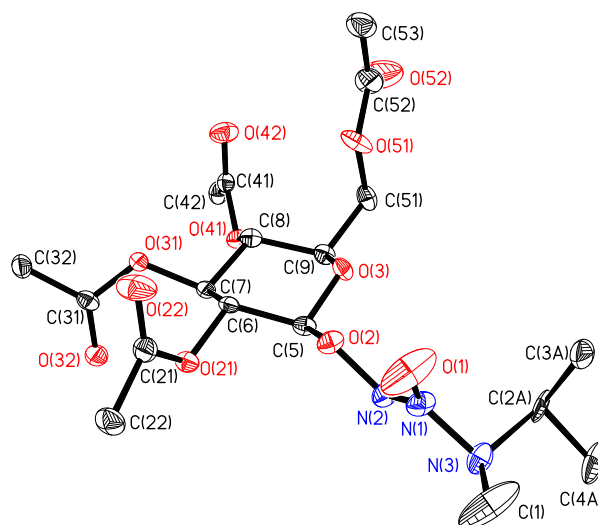
We sought to extend the earlier work<sup>2</sup> by trapping an anion of structure **3** as an acyclic *E* derivative. Surprisingly, the outcome of our experiment revealed a second novel implication of the electronic delocalization shown in Scheme 1: by distributing the  $\pi$  electrons more evenly between the first and third nitrogens in *Z*-**3**, electrophilic attack at either N can be observed. As summarized in Scheme 2, treatment of **4** with dimethyl sulfate in DMSO containing 1.5 equiv of 30% sodium hydroxide led to generation of two different alkylation products of ion **5**. The expected methylation product **6**<sup>3</sup> was produced in only 2% yield, while isomer **7** accounted for the remaining 98%. Previously reported<sup>3</sup> alkylations of anions having structure **3** provided adducts **2** in yields of at least 28%. It is not clear why derivatization of **3** at the NO nitrogen should so dramatically predominate in the present case.

Both **6** and **7** have been spectroscopically characterized, and their structures have been determined by single crystal X-ray diffraction (Figs. 1 and 2). The structural and spectroscopic contrasts between **6** and **7** are significant and indicate the extensive electronic reorganization in **7** as contrasted with diazeniumdiolates such as **4** and **6**.<sup>4</sup> While **6** has strong UV bands at 226 and 258 nm, these are absent in **7**, which has a single band at 216 nm. The structural data of Figures 1 and 2 clearly indicate rehybridization of N(1) and N(3), giving longer N(2)–N(1) and shorter N(1)–N(3) bonds in isomer **7** relative to **6**.

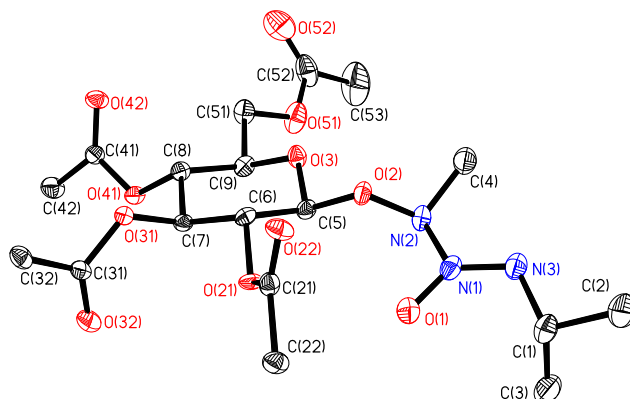
Spectroscopically, there is no indication for the presence of the isomer corresponding to the *E* conformation resulting from rotation around the N(1)=N(3) bond by the isopropyl group in **7**. Theoretically, by ab initio DFT calculations [B3LYP/6-311+G\*\* for MeON(Me)–N(O)=N(*i*Pr) (Supplementary data)], the crystallographically observed *Z*-isomer for **7** is circa 48 kJ mol<sup>-1</sup> more stable than its *E*-isomer.

Electrophilic addition at N(2) in neutral diazeniumdiolates such as **4** or at nitrogen in hyponitrite remains a very unusual reaction.<sup>5</sup> Clearly, the lone pair at this nitrogen is not part of a strongly nucleophilic HOMO orbital and is likely to be too low in energy to act as either a ligand or a nucleophile.

An important implication in this work is that the reactivity of the anions derived from the primary amine diazeniumdiolates might provide synthetic access to a wide new class of potential



**Figure 1.** Single crystal structure of **6**. Important metric parameters (Å) and (°): N(2)–N(1) 1.280(4), N(1)–N(3) 1.441(4), N(2)–O(2) 1.398(4), N(1)–O(1) 1.226(4), O(2)–N(2)–N(1) 107.8(3), N(2)–N(1)–O(1) 126.8(3), N(2)–N(1)–N(3) 110.3(3) and O(1)–N(1)–N(3) 122.9(3). Hydrogen atoms are omitted and only one position of the disordered isopropyl group is shown for clarity.



**Figure 2.** Single crystal structure of **7**. Important metric parameters (Å) and (°): N(2)–N(1) 1.469(3), N(1)–N(3) 1.260(3), N(2)–O(2) 1.420(2), N(1)–O(1) 1.244(3), N(2)–C(4) 1.464(3), O(2)–N(2)–N(1) 104.0(2), O(2)–N(2)–C(4) 106.5(2), C(4)–N(2)–N(1) 112.5(2), N(2)–N(1)–O(1) 114.5(2), N(2)–N(1)–N(3) 116.0(2), O(1)–N(1)–N(3) 129.2(2), and N(1)–N(3)–C(1) 112.2(2). Hydrogen atoms are omitted for clarity.

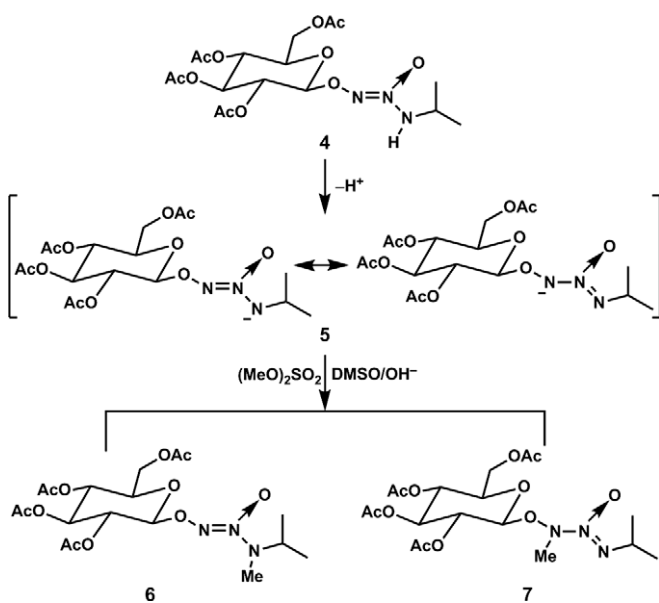
HNO and NO donors. Exploration of this chemistry remains an active theme in our laboratories.

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## Supplementary data

Supplementary data (single crystal X-ray analysis, synthetic details, and density functional calculations) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.012.



**Scheme 2.** Methylation of ambident anion **5**.

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