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The Mechanism of NO Formation from the Decomposition of Dialkylamino Diazeniumdiolates: Density Functional Theory and CBS-QB3 Predictions

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The mechanism of decomposition of dialkylamino diazeniumdiolate salts, $R_2N[NONO]^-M^+$, to form nitric oxide, NO, was explored using theoretical methods. B3LYP/6-311+G(d) density functional theory calculations gave the optimized geometries, and energetics were further evaluated with the high accuracy CBS-QB3 method, when feasible. Relative pK_a values were estimated using the PCM model for aqueous solvation. The terminal oxygen is the most basic site, followed closely by the internal oxygen. Protonation of these sites does not lead to decomposition. However, protonation of the weakly basic amino nitrogen leads to very rapid decomposition and NO generation.

1. Introduction

Dialkylamino diazeniumdiolate salts, $R_2N[NONO]^-M^+$, also called "NONOates", are a class of compounds that generate nitric oxide, NO, in neutral or acidic aqueous solutions.[1] Discoveries of the various biological roles of NO have made diazeniumdiolates an important experimental tool for in vivo and in vitro studies.[2−4] The synthesis of the diazeniumdiolates is relatively simple and has been known since the early 1960s.[5,6] Diazeniumdiolates are produced by the reaction of 2 equiv of an amine and 2 equiv of NO or 1 equiv of an amide anion with 2 equiv of NO, as indicated in eqs 1 and 2.

$$2R_2NH + 2NO \rightarrow R_2N[NONO]^- + R_2NH_2^+ \qquad (1)$$

$$R_2N^-M^+ + 2NO \rightarrow R_2N[NONO]^-M^+ \qquad (2)$$

Diazeniumdiolates are stable in basic solution and, depending on the substitution of the amine, are stable as crystals in a freezer or at room temperature.[1] However, when basic diazeniumdiolate solutions are neutralized or acidified, decomposition to the amine and NO occurs.[7] The half-life of this process depends dramatically on the substitution of the amine and can vary from seconds to hours.[8] The decomposition of diazeniumdiolates has been investigated experimentally, and various mechanisms have been proposed.[7,8]

Keefer and co-workers measured rates and spectral data to determine important pK_a's and possible intermediates along the path of decomposition. For the dialkylamino diazeniumdiolates that were studied, lowering the pH of the solution increases the rate of decomposition.[8] For the diethylamino diazeniumdiolate salt, a pK_a of 4.5 ± 0.2 was obtained spectroscopically by following the change in the UV absorption of the diazeniumdiolate functional group as the pH of the solution was lowered. A double reciprocal plot of experimentally measured k_{obs} versus $[H^+]$ yielded a pK_{AH} of 5.04 ± 0.17, which was assigned to the protonation of the amino nitrogen that triggers decomposition.[8] A first-order rate constant of $1.11 \pm 0.44\ s^{-1}$ was also determined from the double reciprocal plot for decay of the diazeniumdiolate.

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[†] Department of Chemistry and Biochemistry.
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(1) Ragsdale, R. O.; Karstetter, B. R.; Drago, R. S. *Inorg. Chem.* **1965**, *4*, 420−422.
(2) Ignarro, L. J. *Nitric Oxide Biology and Pathobiology*; Academic Press: San Diego, CA, 2000.
(3) Keefer, L. K. *CHEMTECH* **1998**, *28*, 30−35.
(4) Saavedra, J.; Keefer, L. *Chem. Br.* **2000**, *36*, 30−33.
(5) Reilly, E. L. German Patent 1 085 166, July 14, 1960; *Chem. Abstr.* **1962**, *56*, 4594h.
(6) Drago, R. S.; Paulik, F. E. *J. Am. Chem. Soc.* **1960**, *82*, 96−98.
(7) Hrabie, J. A.; Klose, J. R.; Wink, D. A.; Keefer, L. K. *J. Org. Chem.* **1993**, *58*, 1472−1476.
(8) Davies, K. M.; Wink, D. A.; Saavedra, J. E.; Keefer, L. K. *J. Am. Chem. Soc.* **2001**, *123*, 5473−5481.

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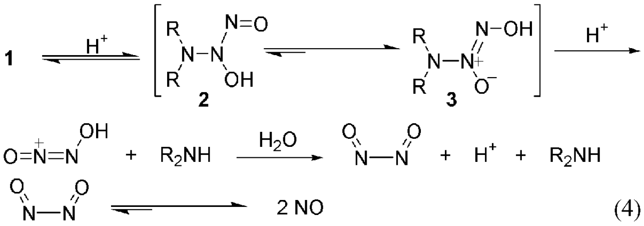
On the basis of their experimental findings, Davies et al. proposed the mechanism shown in eq 3, where protonation at the amine nitrogen at physiological pH leads to decomposition.[8]

$$\underset{\mathbf{1}}{\mathrm{R_2N[NONO]^-}} + \mathrm{H_3O^+} \rightleftharpoons \mathbf{1}\cdot\mathrm{H^+} \rightleftharpoons \mathrm{R_2NH} + 2\mathrm{NO} \quad (3)$$

Hall and co-workers optimized structures with HF/6-31G(d) and computed energies at the MP2/6-31G(d) level for various substituted diazeniumdiolates and their protonated analogues.[9] They focused on the oxygen protonation sites and demonstrated that the terminal oxygen would be protonated most easily. From these theoretical calculations they suggested the mechanism shown in eq 4.[9]



(4)

Here, the diazeniumdiolate, **1**, is protonated to form the thermodynamically most stable form, **3**. A second protonation at the amino nitrogen, with the accompanying release of the free amine, gives the protonated NO dimer. Deprotonation and homolytic cleavage generates 2 equiv of NO. This mechanism requires both specific and general acid catalysis for NO release.

We have investigated the mechanism of dialkylamino diazeniumdiolate decomposition, using the amino and dimethylamino analogues as models for the experimentally studied dialkylamino diazeniumdiolates. We first describe the formation of diazeniumdiolates from amides and NO, then discuss the electronic structures of these species, and finally describe our exploration of the mechanism of decomposition of NONOates to generate NO.

2. Methods

All structures were optimized using the B3LYP method with a 6-311+G(d) basis set using the Gaussian 98 program.[10] Structures that required more accurate energy calculations were recomputed by CBS-QB3, a method that involves reoptimization of the structure with the B3LYP functional and the 6-311G(2d,d,p) basis set and then computes a series of higher level calculations with this geometry, generally giving energies within ±1 kcal/mol of experimentally measured values for the G3 data set.[11] Free energies are given for 298 K. Aqueous solvation energies, ΔG_{aq}'s, were calculated as single points on the B3LYP/6-311+G(d) optimized geometries using a 6-311+G(d) basis set in the PCM model, implemented in Gaussian 98. The solvation energies were applied to the B3LYP/6-311+G(d) and CBS-QB3 optimized gas-phase energies. Structures **22** and **23** were optimized in water using the PCM model with B3LYP/6-311+G(d). To allow comparison of **22** and **23** to the rest of the calculated structures, the aqueous optimized geometries were computed as single points using the B3LYP/6-311+G(d) method. All values reported in the text are at the CBS-QB3 level of theory unless otherwise noted. The relative pK_{a}'s were predicted using the relationship between ΔG_{aq} and pK_{a}. The most basic computed pK_{a} was set equal to the experimentally measured pK_{a}, and all others were computed relative to this.

3. Results and Discussion

a. NO Dimerization. Nitric oxide is known to form a dimer when present at high concentrations.[12] The NO dimer has been studied extensively using both experimental[13−26] and theoretical[27−48] methods. X-ray diffraction experiments show that the most stable form of the dimer is a trapezoidal

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(9) Taylor, D. K.; Bytheway, I.; Barton, D. H. R.; Bayse, C. A.; Hall, M. B. *J. Org. Chem.* **1995**, *60*, 435−444.

(10) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.1; Gaussian, Inc.: Pittsburgh, PA, 1998.

(11) Montgomery, J. A.; Ochterski, J. W.; Peterson, G. A. *J. Chem. Phys.* **1994**, *101*, 5900.

(12) Park, J. K.; Sun, H. *Bull. Korean Chem. Soc.* **1999**, *20*, 1399−1408.

(13) Saavedra, J. E.; Srinivasan, A.; Bonifant, C. L.; Chu, J.; Shanklin, A. P.; Flippen-Anderson, J. L.; Rice, W. G.; Turpin, J. A.; Davies, K. M.; Keefer, L. K. *J. Org. Chem.* **2001**, *66*, 3090−3098.

(14) Lipscomb, W. N.; Wang, F. E.; May, W. R.; Lippert, E. L. *Acta Crystallogr.* **1961**, *14*, 1100.

(15) Western, C. M.; Langridge-Smith, P. R. R.; Howard, B. J.; Novick, S. E. *Mol. Phys.* **1981**, 145.

(16) Kukolich, S. G. *J. Mol. Spectrosc.* **1983**, *98*, 80.

(17) Mckellar, A. R. W.; Watson, J. K. G.; Howard, B. J. *Mol. Phys.* **1995**, *86*, 273.

(18) Dinerman, C. E.; Ewing, G. E. *J. Chem. Phys.* **1970**, *53*, 626.

(19) Ohlsen, J. R.; Laane, J. *J. Am. Chem. Soc.* **1978**, *100*, 6948

(20) Kasal, P. H., Gaura, R. M. *J. Chem, Phys.* **1982**, *86*, 4257.

(21) Holland, R. F.; Maier, W. B., II. *J. Chem. Phys.* **1983**, *78*, 2928.

(22) Herzberg, G. *Molecular Spectra and Structure I, Spectra of Diatomic Molecules*, 2nd ed.; Van Nostrand: New York, 1950.

(23) Slanger, T. G.; Cosby, P. C. *J. Chem. Phys.* **1988**, *92*, 267.

(24) Stewart, J. J. P. *J. Comput. Aided Mol. Des.* **1990**, *4*, 1.

(25) Hetzler, J. R.; Casassa, M. P.; King, D. S. *J. Phys. Chem.* **1991**, *95*, 8086.

(26) Dkhissi, A.; Soulard, P.; Perrin, A.; Lacome, N. *J. Mol. Spectrosc.* **1997**, *183*, 12.

(27) Fischer, I.; Strobel, A.; Staecker, J.; Niedner-Schatteburg, G.; Müller-Dethlefs, K.; Bodybey, V. E. *J. Chem. Phys.* **1992**, *96*, 7171.

(28) Canty, J. F.; Stone, E. G.; Bach, S. B. H.; Ball, D. W. *Chem. Phys.* **1997**, *216*, 81.

(29) Stirling, A.; Pápai, I.; Mink, J.; Salahub, D. R. *J. Chem. Phys.* **1994**, *100*, 2910.

(30) Duarte, H. A.; Proynov, E.; Salahub, D. R. *J. Chem. Phys.* **1998**, *109*, 26.

(31) Lee, T. J.; Rice, J. E.; Scuseria, G. E.; Schaefer, H. F., III. *Theor. Chim. Acta* **1989**, *75*, 81.

(32) Ha, T.-K. *Theor. Chim. Acta* **1981**, *58*, 125.

(33) Nguyen, K. A.; Gordon, M. S.; Boatz, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 9241.

(34) Nguyen, K. A.; Gordon, M. S.; Montgomery, J. A., Jr.; Michels, H. H. *J. Phys. Chem.* **1994**, *98*, 10072.

(35) Nguyen, K. A.; Gordon, M. S.; Montgomery, J. A., Jr.; Michels, H. H.; Yarkony, D. R. *J. Phys. Chem.* **1993**, *98*, 3845.

(36) Chaban, G.; Gordon, M. S.; Nguyen, K. A. *J. Phys. Chem.* **1997**, *101*, 4283.

(37) East, A. L. *J. Chem. Phys.* **1998**, *109*, 2185.

(38) Andzelm, J.; Wimmer, E. *J. Chem. Phys.* **1992**, *96*, 1280.

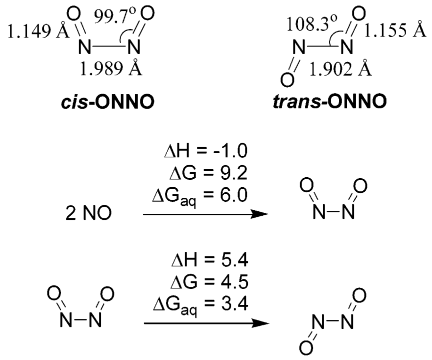

Figure 1. Gas-phase structures of the *cis* and *trans* NO dimers and energetics of dimerization. Changes in enthalpies and free energies in the gas phase and in water are given in kcal/mol (CBS-QB3).

geometry (C_{2v}), with NN and NO distances and ONN bond angle of 2.18 ± 0.06 Å, 1.12 ± 0.02 Å, and 101.3°, respectively.[13] Various experiments using gaseous N_2O_2 have determined that a *cis*, acyclic form (C_{2v}) is the most stable structure. Depending upon the spectroscopic technique employed, the NN, NO, and ONN distances and bond angle range from 2.33 Å, 1.15 Å, and 95°, respectively, for molecular beam spectroscopy to 1.75 Å for the NN distance and 90° for the bond angle using IR spectroscopy.[16,18] DFT methods predict that the acyclic *cis*-ONNO (C_{2v}) form is the most stable.[11,29,30,32,33]

CBS-QB3 calculations performed here give both *cis* (C_{2v}) and *trans* (C_{2h}) NO conformers of the dimer. The free energy of the *cis* isomer is 4.5 kcal/mol more stable than the *trans* isomer in the gas phase. Upon aqueous solvation, the free energy difference between *cis* and *trans* is lowered to 3.4 kcal/mol. The energies and geometries are summarized in Figure 1.

These structures are weakly bound as can be seen by the long NN bonds and the approximate thermodynamics of dimerization. In agreement with experiment and previous theory, the *cis* structure is more stable than the *trans*, and the NN bond length is about 2.0 Å, more or less the median of previously reported values.[13,16,18] The dimerization is essentially thermoneutral, but endergonic at 1 atm in the gas phase or 1 M in aqueous solvation. K_d for this process is predicted to be $10^{-4.4}$ M^{-1} in aqueous solution, so only a small percentage of NO is present as the dimer in solution.

Interestingly, when attempting to optimize the *trans* isomer, a higher energy stationary point is obtained if the starting NN bond length is too short. This structure is 14.1 kcal/mol higher in free energy in the gas phase than the *trans* ground state and has a much shorter NN bond length, with longer NO bonds. It corresponds to the electronically doubly excited ($2n \rightarrow 2\pi^*$) state, shown in Figure 2. It has the same ^{1}A symmetry as the ground state. Sayós et al. have performed a thorough theoretical investigation of the NO dimer and the 8 lowest excited states.[46] They found that at least three singlet excited states of the *trans* NO dimer within 2 kcal/mol of the ground state and all of these excited states possessed a long NN bond length of 2.817 Å. This structure of the excited *trans* dimer is better solvated, in the aqueous PCM model, than the *trans* ground state. This species will be discussed later in the context of NO generation from diazeniumdiolate decomposition.

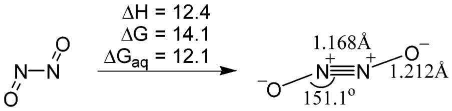

Figure 2. Structure of a *trans* excited state isomer. Changes in enthalpies and free energies in the gas phase and in water are given in kcal/mol (CBS-QB3).

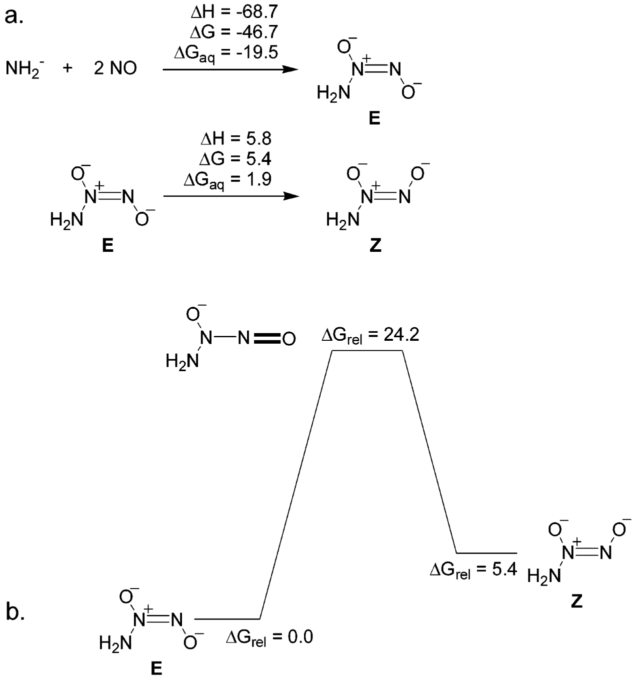

Figure 3. Energetics at the B3LYP/6-311+G(d) level for (a) formation of the diazeniumdiolates; (b) the rotation about the NN bond of the diazeniumdiolate.

b. Formation of Diazeniumdiolates. The formation of diazeniumdiolates, from amides and NO, is calculated to be exothermic. The reactions of the amide anion with 2 equiv of NO to form the simplest diazeniumdiolate are shown in Figure 3. The parent diazeniumdiolate can exist as two geometrical isomers, with the *E* isomer being favored. The free energy of the *E* isomer was calculated to be lower than that of the *Z* isomer by 5.4 kcal/mol with B3LYP/6-311+G(d) in the gas phase. The free energy barrier to rotation was calculated as 24.2 kcal/mol in the gas phase at the B3LYP/

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(39) Eriksson, L. A.; Wang, J.; Boyd, R. J.; Lunell, S. *J. Phys. Chem.* **1994**, *98*, 792.

(40) Johnson, B. G.; Gill, P. M.; Pople, J. A. *J. Phys. Chem.* **1990**, *94*, 5463.

(41) Partridge, H.; Bauschlicher, C. W., Jr.; Langhoff, S. R. *J. Chem. Phys.* **1991**, *92*, 8292.

(42) Lee, T. J.; Rendell, A. P.; Taylor, P. R. *J. Chem. Phys.* **1990**, *94*, 5463.

(43) González-Luque, R.; Merchán, M.; Roos, B. O. *Theor. Chim. Acta* **1994**, *88*, 425.

(44) Skaarup, S.; Skancke, P. N.; Boggs, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 6106.

(45) Jursic, B. S.; Zdravkovski, Z. *Int. J. Quantum Chem.* **1995**, *54*, 161.

(46) Sayós, R.; Valero, R.; Anglada, J. M.; González, M. *J. Chem. Phys.* **2000**, *112*, 6608.

(47) Stewart, W. E.; Siddall, T. H., III. *Chem. Rev.* **1970**, *70*, 517.

(48) Hasimoto, K.; Oxamura, Y. *J. Chem. Phys.* **1991**, *95*, 1121.

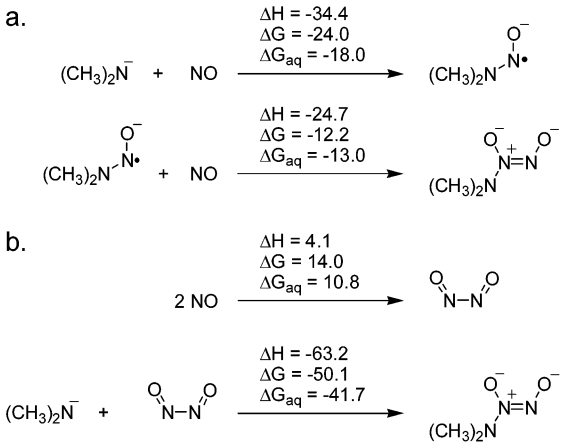
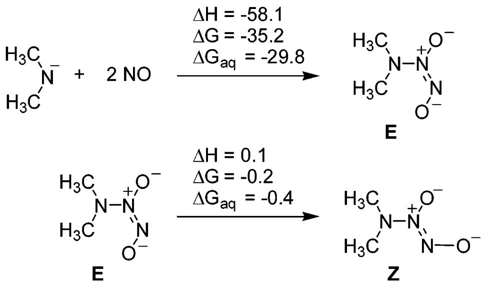


Figure 4. B3LYP/6-311+G(d) energetics for formation of dimethylamino diazeniumdiolate: (a) reaction pathway via monomeric NO, and (b) reaction pathway via the NO dimer.

6-311+G(d) level, a value similar to that for rotation about the CN bond in amides.[47]

The greater stability of the *E* isomer is attributed to intramolecular H-bonding between the terminal oxygen and the amino group.[9] This parent diazeniumdiolate is unknown. The dimethylamino diazeniumdiolate is the simplest of the dialkyamino diazeniumdiolates and was studied in order to model dialkyl species such as the common diethylamino diazeniumdiolate (DEA/NO). The CBS-QB3 energetics for the formation of dimethylamino diazeniumdiolate are shown in eq 5.



(5)

In contrast to the simplest diazeniumdiolate, there is no significant preference for the *E* or *Z* isomers. This difference from the parent diazeniumdiolate can be explained by the absence of intramolecular H-bonding in the dialkyl derivative.

The formation of the dialkylamino diazeniumdiolates can proceed via two mechanisms, the reaction between the amine and monomeric NO to form a radical anion intermediate followed by another addition of NO, or the reaction of the amine with the NO dimer. These pathways and their energetics are shown in Figure 4. B3LYP/6-311+G(d) predicts the NO dimerization to be 5 kcal/mol more endothermic than the more accurate CBS-QB3 method, so the results here may be skewed by the error in the B3LYP calculations. Nevertheless, assuming no significant difference in barriers for NO dimer dissociation or for the dissociation of the radical anion, it is likely that the direct mechanism via the radical anion is favored.

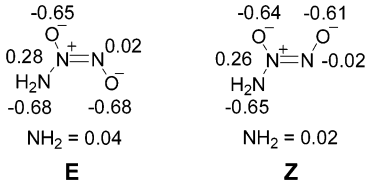


Figure 5. Partial atomic charges from NBO analysis and charges for the NH_2 group are shown.

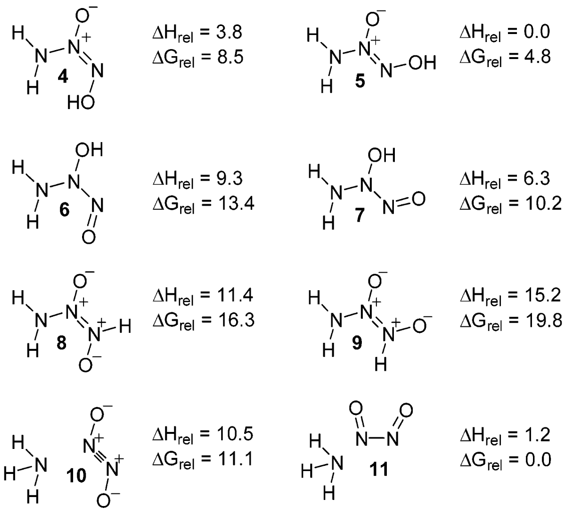


Figure 6. Relative energies of protonated amino diazeniumdiolate. Relative enthalpies and free energies for the gas phase are in kcal/mol (B3LYP/6-311+G(d)).

c. Analysis of Electronic Structures of Amino Diazeniumdiolates. The optimized *E* and *Z* isomers of the simplest amino diazeniumdiolate were subjected to natural bond orbital,[48,49] NBO, analysis to determine bonding and electrostatic properties. This provided insight into the most favored resonance structures, which are shown in Figure 5 along with the atomic charge densities.

It is clear from the atomic charges that the oxygens and the amino nitrogen should be the most probable protonation sites. The energies to protonate each oxygen, the amino nitrogen, and the terminal nitrogen were computed. The corresponding optimized structures were subjected to NBO analysis and are displayed in the favored resonance form with relative energies in Figure 6.

In agreement with previous calculations,[9] the oxygens are the most basic sites on **1**. Protonation of the terminal oxygen to give **4** or **5** is favored. Protonation of the amino nitrogen leads to spontaneous dissociation, as in **10** and **11**. In **11**, protonation of the amino nitrogen generates the free amine and the weakly bonded *cis* dimer. When protonated at the amino nitrogen, the *E* isomer leads directly to **10**, ammonia complexed to the excited state *trans* dimer, discussed earlier. However, if the NN bond distance of the dimer is further lengthened and the complex is optimized again, the dimer optimizes to the ground state *trans* geometry, so the reaction in solution is expected to form the ground state NO dimer.

The origin of the formation of this excited state dimer, is the orbital correlation between the N-protonated amino

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(49) Carpenter, J. E.; Weinhold, F. *THEOCHEM* **1988**, *169*, 41.

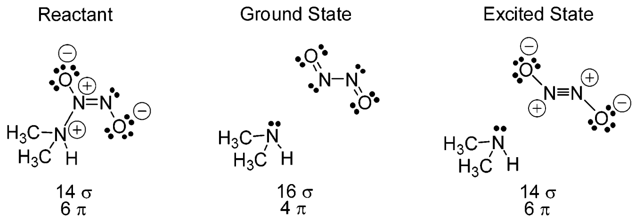

Figure 7. Dominant valence bond structures of N-protonated dimethyl diazeniumdiolate, amine plus the ground state of the *trans*-$(NO)_2$ and amine plus the doubly excited state of the *trans*-$(NO)_2$ with the σ and π electron count of the $(NO)_2$ group for each structure.

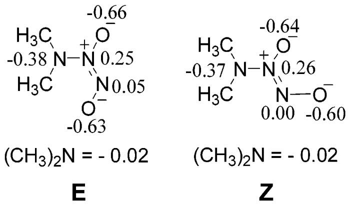

Figure 8. Dimethylamino diazeniumdiolate partial atomic charges and $(CH_3)_2N$ group charges according to NBO analysis.

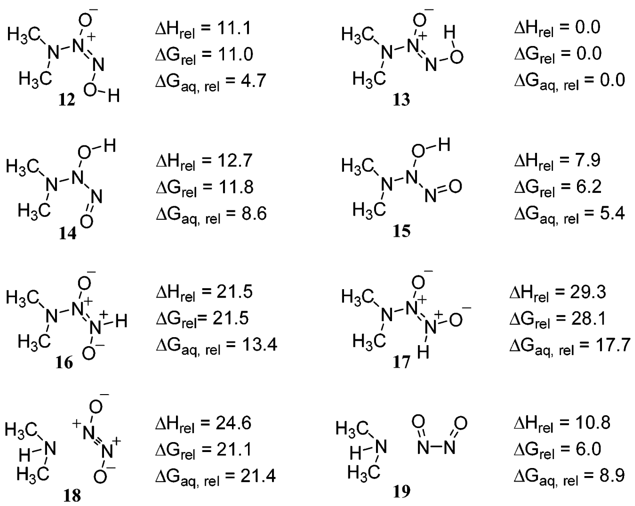

Figure 9. Relative energetics of protonated dimethylamino diazeniumdiolates. Relative enthalpies and free energies in gas phase and water are given in kcal/mol (CBS-QB3, PCM).

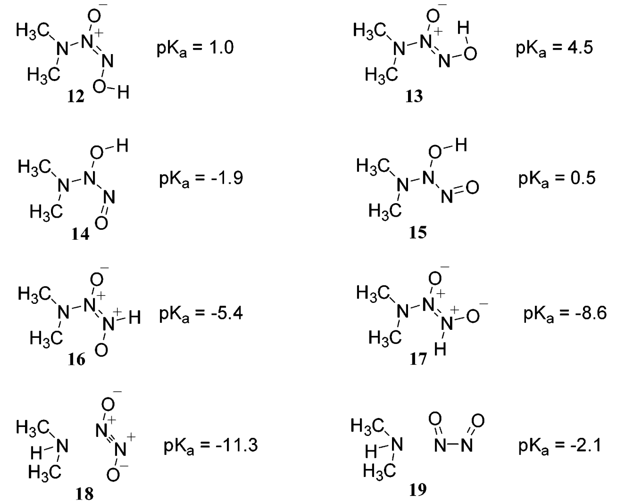

Figure 10. Calculated pK_a's for the various protonated dimethylamino diazeniumdiolates, determined using pK_a = $-0.74(\Delta\Delta G_{aq}) + 4.5$.

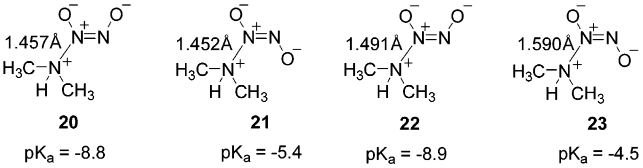

Figure 11. Constrained bond lengths and pK_a values for the *E* and *Z* isomers of N-protonated dimethylamino diazeniumdiolate for the optimized anion bond length (**20** and **21**) and the solvent optimized structures (**22** and **23**).

diazeniumdiolate and amine plus NO dimer. Figure 7 shows the valence electrons distributed in the dominant valence bond structures for the N-protonated diazeniumdiolate and for the amine plus ground state and doubly excited state of the *trans* NO dimer. The ground state of the amino diazeniumdiolate reactant correlates with the amine plus the doubly excited singlet state of the *trans* NO dimer, since this maintains the number of σ and π electrons. This correlation is typical of an orbital symmetry forbidden process, in that the ground state of the reactant correlates with an excited state of the product. Although this crossing should be avoided at the state correlation level, it could nevertheless impose a barrier on the exothermic dissociation to the ground state of the product.

The optimized structures of the dimethylamino diazeniumdiolates were also subjected to NBO analysis, and the results, summarized in Figure 8, are very similar to those for the parent system.

The CBS-QB3 structures and relative energies for protonated species of dimethylamino diazeniumdiolate are shown in Figure 9. Aqueous solvation energies have also been calculated, and the free energies in aqueous solution are also shown.

The results for dimethylamino diazeniumdiolate mirror those for the parent diazeniumdiolate shown previously. In this case, however, there is a strong preference for the *Z* isomers, as seen in the energies of the right column versus the energies in the left column of Figure 9. The terminal oxygen is more basic than the inner oxygen, which can be seen by comparing **13** to **15** and **12** to **14**. Protonation of the amine nitrogen leads to dissociation to the amine and the NO dimer. Protonation of the oxygens is favorable but does not lead directly to products. As seen previously, when the protonated *E* isomer dissociates, **18**, the NO dimer is formed in the excited state.

The pK_a's for the protonation sites were predicted from the relationship between the CBS-QB3 calcualated ΔG_{aq} and pK_a. Since the pK_a of DEA/NO has been measured as 4.5, we set the pK_a of the least acidic tautomer, **13**, to 4.5.[8] The pK_a's for the remaining structures, **14**−**21**, were then determined relative to **13** using the calculated ΔG_{aq} shown in Figure 9. The pK_as calculated in this way are shown in Figures 10 and 11.

It is clear that the most basic site is the terminal oxygen, and protonation leads to structure **13**, but there will be less than one percent each of **15** and **12,** and even smaller amounts of **14** present at equilibrium. At neutral pH the diazeniumdiolate should exist primarily as the free base species **1**, and it will be half protonated at pH ∼ 5. To approximate the pK_a for amine protonation, structures were

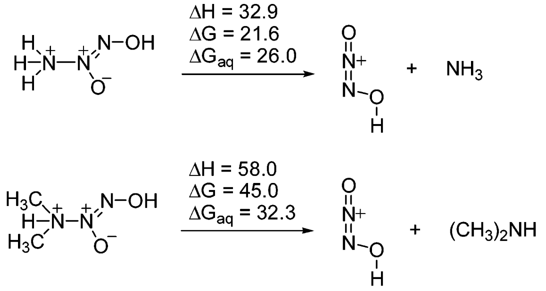

Figure 12. Proposed dissociation steps in the Taylor et al. decomposition mechanism[9] (B3LYP/6-311+G(d)).

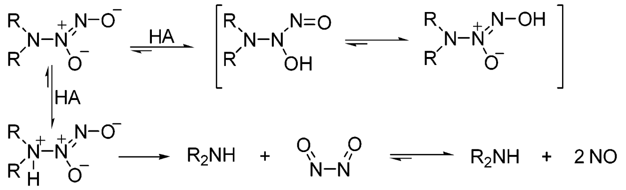

Figure 13. Mechanism for the production of NO from the decomposition of dialkylamino diazeniumdiolates.

optimized with constraint of the NN bond lengths to values of 1.457 and 1.452 Å in the *E* and *Z* isomers, respectively. These values are the NN bond lengths of the corresponding optimized anionic species. Full optimization of structures **20** and **21**, without the NN bond constraint, in the PCM solvent model gave structures **22** and **23**. Upon optimization in the water solvent model, spontaneous dissociation does not occur, and energy minima are obtained with long NN bonds lengths of 1.491 and 1.590 Å in **22** and **23,** respectively. The structures were then used to approximate the pK_a's for **22** and **23**. These structures are summarized in Figure 11 along with computed pK_a values.

These calculations suggest a mechanism of decomposition via the monoprotonation of the amine nitrogen, since only a small barrier is likely to separate **22** or **23** from products, amine plus NO dimer. Previously, Taylor et al. proposed that protonation of the terminal oxygen is followed by diprotonation, with the second protonation occurring at the amino nitrogen.[9] Keefer and co-workers implied direct protonation of the amine nitrogen to give products, as is also predicted in our calculations.[8] However, the experimental pK_a of the diazeniumdiolate is not that of the reactive site which leads to decomposition.

We further explored the mechanism postulated by Taylor et al. with the model parent amino and the dimethylamino diazeniumdiolate. The structures of the doubly protonated *E* and *Z* isomers were optimized, using the B3LYP/6-311+G(d) level of theory; neither diprotonated species dissociates directly to products in the gas phase. In fact, this key step in their proposed mechanism is endothermic, as shown in Figure 12 for the simplest amine case and the dimethylamine analogue.

The data presented here, along with the published experimental data, suggest that protonation of the amino nitrogen leads to release of the amine and the NO dimer directly. Our calculations predict that protonation of the amino nitrogen leads to rapid decomposition as shown in Figure 13.

Davies et al. monitored the disappearance of the diazeniumdiolate UV absorption at decreasing pH levels for a variety of diazeniumdiolates.[8] From a plot of the rate data for DEA/NO, they obtained a rate expression, eq 6, based upon the assumption that protonation of DEA/NO leads to decomposition. They reported a rate constant, k_{AH}, of 1.11 ± 0.44 s^{-1} and a pK_{AH} of 4.5 ± 0.2.

$$\text{rate} = k_{obs}[\text{NONOate}]_T,\ \text{with}\ k_{obs} = \frac{k_{AH}[AH]}{([A^-] + [HA])} = \frac{k_{AH}}{\left(1 + \frac{K_{AH}}{[H^+]}\right)} = \frac{k_{AH}[H^+]}{([H^+] + K_{AH})} \quad (6)$$

Our results suggest that dialkylamino diazeniumdiolates can be protonated at a variety of positions, but decomposition only occurs when the amino nitrogen is protonated. For decomposition of the *cis*-dimethylamino diazeniumdiolate, employing the simplifying assumption that the total diazeniumdiolate composition prior to decomposition will be a mixture of compounds the unprotonated species, **13**, and **22**, the rate expression, eq 7, was derived. [NH], [A$^-$], and [OH] are concentrations of **22**, the diazeniumdiolate anion, and **13**, respectively. K_{OH} and K_{NH} correspond to the acid dissociation constants for **13** and **22**, respectively, while k_{NH} is the rate constant for the decomposition of structure **22**.

$$\text{rate} = k_{obs}[\text{NONOate}]_T,\ \text{with}\ k_{obs} = \frac{k_{NH}[NH]}{([NH] + [A^-] + [OH])} = \frac{k_{NH}}{\left(1 + \frac{K_{AH}}{[H^+]} + \frac{K_{NH}}{K_{OH}}\right)} = \frac{k_{NH}[H^+]K_{OH}}{(K_{OH}K_{NH} + K_{OH}[H^+] + K_{NH}[H^+])} \quad (7)$$

Using the rate data published by Davies et al. for diethylamino diazeniumdiolate, the data[8] were fitted to eq 7. The experimental value of p$K_{OH} = 4.5$ measured by Davies et al. was used. Values for pK_{NH} and k_{NH} of -6.9 ± 0.5 and $7.2 \pm 0.5 \times 10^{11}$ s^{-1}, respectively, were obtained. The value of pK_{NH} found in this way falls within the theoretical estimates of -4.5 to -8.9 shown in Figure 11. As expected from our assumptions and computations, the value of k_{NH} is extremely large, near the maximum of 6×10^{13} s^{-1} expected from transition state theory.

The general expression for decomposition of amino diazeniumdiolates by this mechanism, with many possible sites of protonation in the amino substituents to form NH and other species collectively referred to as XH, is given by eq 8.

$$\text{rate} = k_{obs}[\text{NONOate}]_T,\ \text{with}\ k_{obs} = \frac{k_{NH}}{K_{NH}\left(\frac{1}{[H^+]} + \sum_{x} \frac{1}{K_{XH}}\right)} \quad (8)$$

Assuming that the rate of decomposition of the diazeniumdiolate is always very fast, then the rate of reaction will be enhanced by making it easier to protonate the amine nitrogen (increase in pK_{NH}). Increasing the pK_a values of sites of protonation, unreactive toward decomposition, will decrease the rate of reaction.

The theoretical studies presented in this paper suggest that the decomposition of dialkylamino diazeniumdiolates of structure **1** will occur via protonation at the amino nitrogen. Additional basic sites in the alkyl chains are known to yield longer half-lives for NO production.[8] This can be a direct consequence of the influence on concentration of the reactive species as indicated by eq 8, or might arise by lowering the pK_a of the amino nitrogen when the basic sites in the side chain are protonated. These systems are currently being studied in more detail.

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Supporting Information Available: Plot of the rate data versus pH for DEA/NO fitted with eq 7, and the Cartesian coordinates for all optimized structures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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