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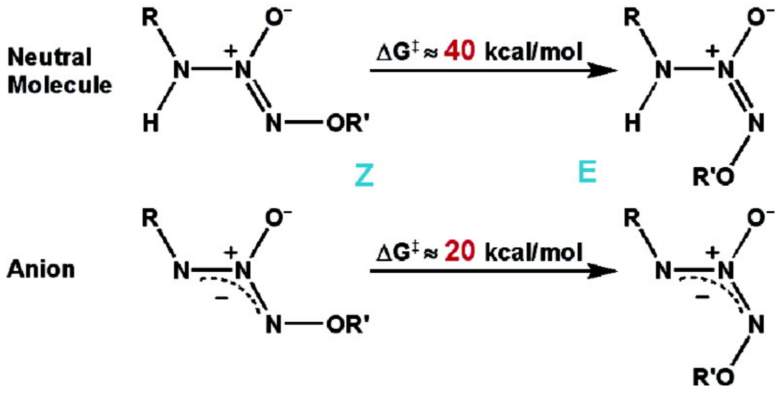

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Chemistry of the Diazeniumdiolates: $Z \rightleftharpoons E$ Isomerism

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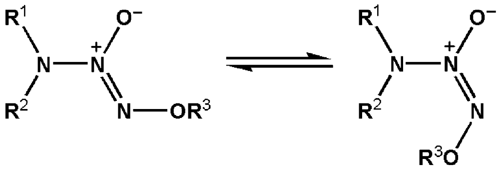
Abstract: Here, we explore the chemistry of the previously undocumented *E* form of diazeniumdiolates having the structure $R^1R^2NN(O){=}NOR^3$. Reported crystallographic studies have uniformly revealed the *Z* configuration, and our attempts to observe a $Z \rightarrow E$ conversion through thermal equilibration or photochemical means have, until now, consistently failed to reveal a significant amount of a second conformer. As a typical example, the NMR spectrum of trimethyl derivative $Me_2NN(O){=}NOMe$ revealed no evidence for a second configuration. Electronic structure calculations attribute this finding to a prohibitively high interconversion barrier of ~40 kcal/mol. A similar result was obtained when we considered the case of $R^1 = Me = R^3$ and $R^2 = H$ at the same levels of theory. However, when $MeHNN(O){=}NOMe$ was ionized by dissociating the N−H bond, the barrier was calculated to be lower by approximately 20 kcal/mol, with the *E* form of the anion being favored over *Z*. This circumstance suggested that an *E* isomer might be isolable if a *Z* anion were formed and given sufficient time to assume the *E* configuration, then quenched by reaction with an electrophile to trap and neutralize the *E* form and restore the putatively high interconversion barrier. Consistent with this prediction, basifying $i\text{PrHNN(O)}{=}NOCH_2CH_2Br$ rapidly led to a six-membered heterocycle that was crystallographically characterized as containing the −N(O)=NO− functional group in the *E* configuration. The results suggest an approach for generating pairs of *Z* and *E* diazeniumdiolates for systematic comparison of the rates at which the individual isomers release bioactive NO and of other physicochemical determinants of their biomedical utility.

Introduction

Nitrogen-bound diazeniumdiolate derivatives **1** (Scheme 1) are of current interest for their ability to release bioactive nitric oxide (NO) on physiological activation.[1] Crystallographic studies of such species performed to date have uniformly shown their oxygen atoms to be arranged cis to each other about the N−N double bond.[2,3] Previous theoretical studies have concluded, however, that these species could also exist with *E* stereochemistry, as in structure **2** (Scheme 1).[4,5] We have been looking for ways to isolate examples for comparisons with their *Z* analogues because differences in, for example, NO release rates could dramatically affect their pharmacological properties, and knowledge about the factors that govern their interconversion could

Scheme 1. Hypothetical Interconversion of *Z* and *E* Isomers in a Nitrogen-Bound Diazeniumdiolate



1 **2**

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be of considerable value in efforts to design improved drugs and biomedical devices.

Here, we examine exemplary diazeniumdiolates both experimentally and theoretically with the goal to estimate the relative energies of their *Z*/*E* pairs as well as of the transition states that separate them. We conclude with the characterization of what we believe to be the first reported example of a nitrogen-bound diazeniumdiolate having the *E* configuration, as in structure **2**.

Experimental Section

Computational Details. We have studied the two neutral species, Me$_2$NN(O)═NOMe (**3**) and MeHNN(O)═NOMe (**4**), as well as the deprotonated species, [MeNN(O)NOMe]$^-$ ([**4**]$^-$). In each case, structures for the *Z* and *E* isomer minima together with any transition states for the *Z*/*E* interconversions were determined. Computations were carried out at the restricted Hartree−Fock[6] (RHF), Density Functional Theory (DFT), and second-order Møller−Plesset[7,8] (MP2) levels of theory. DFT calculations used the hybrid B3LYP[9,10] functional. We have used the aug-cc-pVDZ[11] basis set in all cases as this basis contains diffuse functions which allow more reliable electronic descriptions of anions and electron-rich species. Spherical harmonic d functions have been used throughout. Vibrational frequencies were calculated for all stationary points in order to define them as either minima or transition states. To verify that the transition states were correctly associated with *Z* ⇌ *E* interconversions, minimum energy paths, at the RHF level of theory, were calculated using the intrinsic reaction coordinate (IRC) following the method of Gonzalez and Schlegel.[12,13] The effect of solvent (water) upon the heights of the *Z*/*E* interconversion barriers was determined by using the Polarized Continuum model (PCM)[14−22] with the DFT and MP2 levels of theory. Single-point DFT/PCM and MP2/PCM calculations were carried out at DFT and MP2 gas-phase-optimized geometries, respectively. All of the calculations described above were performed using Gaussian 98.[23]

One may question whether the electronic structures of the minima and transition states are adequately described by a closed-shell reference function in which all electrons are paired. To this end, we have used the GAMESS[24] package to determine MP2 natural orbitals[25] at the MP2 optimized geometries. Occupations of these natural orbitals can be used as a diagnostic for possible multireference character. The smallest occupation of an RHF-like highest occupied molecular orbital (HOMO) was 1.91 and occurred in one of the *E*/*Z* transition states of the [MeNN(O)NOMe]$^-$ anion. The highest occupation of a natural virtual orbital, at 0.09, occurred in the same species. These maximum and minimum electron occupation numbers suggest that closed-shell RHF determinants may be adequate zeroth-order descriptions for all species studied here. However, to be sure of this, both orbitals mentioned above, which are of bonding and antibonding π character, together with all remaining RHF-like occupied orbitals, were used as initial guess orbitals for a complete-active-space self-consistent-field[26,27] (CASSCF) calculation with an active space of two electrons and two orbitals. Geometry optimization to the transition state resulted in minor differences in structural parameters, and the two optimized natural orbitals had occupations of 1.90 and 0.10, which are nearly identical to the MP2 natural orbital occupations. This result suggests that the B3LYP and MP2 methods, which are based upon single reference functions, should each provide a reasonable description for the [MeNN(O)NOMe]$^-$ anion. Very similar results were obtained for the neutral Me$_2$NN(O)═NOMe and MeHNN(O)═NOMe species. The CASSCF calculations were run using GAMESS.[24]

General. Sodium 1-(*N*-isopropylamino)diazen-1-ium-1,2-diolate[28] and compound **3**[29] were prepared as previously described. Proton NMR spectra were obtained in deuteriochloroform, except as otherwise indicated; the proton spectra for the conversion of **5** to the cyclic *E* derivative **6** were recorded in methanol-*d*$_4$. Resonances are reported in δ units downfield from tetramethylsilane. Low- and high-resolution mass spectral measurements were carried out on a VG-Micromass Model 7070 spectrometer. Ultraviolet spectra were run as aqueous solutions on an HP8451A Diode Array spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Inc. and Atlantic Microlab, Inc.

***O*^{2}-(2-Bromoethyl)-1-(*N*-isopropylamino)diazen-1-ium-1,2-diolate (5).** A slurry of 2.5 g (17.7 mmol) of sodium 1-(*N*-isopropylamino)diazen-1-ium-1,2-diolate in 20 mL of *N*,*N*-dimethylformamide was cooled to 0 °C and treated with 1.6 mL (18 mmol) of 1,2-dibromoethane. The mixture was allowed to warm to room temperature, stirred for 48 h, cooled in an ice bath, quenched with 100 mL of distilled water, and extracted with ether. Thin layer chromatography of the ether solution using 5:1 dichloromethane/ethyl acetate gave a spot at R_f 0.65 corresponding to **5** and a second one of R_f 0.60 for compound **6**. The ether solution was dried over sodium sulfate, filtered through magnesium sulfate, and evaporated to give 1.85 g of an amber oil. Column chromatographic purification of the reaction mixture on silica gel, eluted with 10:1 dichloromethane/ethyl acetate, gave 340 mg of **5**: UV (H$_2$O) $\lambda_{\max}$ (ϵ) 240 nm (8.7 mM^{-1} cm^{-1}); NMR δ 1.19 (d, $J = 6.4$ Hz, 6 H), 3.57 (m, 2 H), 3.99 (septet, $J = 6.4$ Hz, 1 H), 4.44 (m, 2 H); MS (chemical ionization, positive ion spectrum, NH$_3$) exact mass calcd for C$_5$H$_{12}$N$_3$O$_2$Br: [MNH$_4$]$^+$ 243.0457 and 245.0437; measured 243.0471 and 245.046. Anal. Calcd for C$_5$H$_{12}$BrN$_3$O$_2$: C, 26.56; H, 5.35; N, 18.59; Br, 35.36. Found: C, 27.58; H, 5.64; N, 18.01; Br, 30.53.

Cyclic *trans*-Diazeniumdiolate 6. This compound may be prepared by exposing the bromoethyl derivative **5** to methanolic sodium methoxide. However, the chromatographic separation described above provided 920 mg of crystalline **6**. A sample for combustion analysis was recrystallized from ether/petroleum ether: mp 155−156 °C; UV (H$_2$O) $\lambda_{\max}$ (ϵ) 234 nm (4.1 mM^{-1} cm^{-1}); NMR δ 1.23 (d, $J = 6.8$ Hz, 6 H), 3.72 (m, 2 H), 4.25 (m, 2 H), 4.88 (septet, $J = 6.8$ Hz, 1 H). Anal. Calcd for C$_5$H$_{11}$N$_3$O$_2$: C, 41.37; H, 7.48; N, 28.95. Found: C, 40.87; H, 7.48; N, 28.60.

X-ray Crystallography. Single-crystal X-ray diffraction data for **6** were collected at −50 °C using a Bruker P4 diffractometer equipped with a graphite monochromator and Cu Kα ($\lambda = 1.54178$ Å) radiation. Three check reflections were measured after every 97 reflections. On the basis of these check reflections, the crystal was stable during data collection. Corrections were applied for Lorentz and polarization effects. The structure was solved by direct methods and refined by full-matrix

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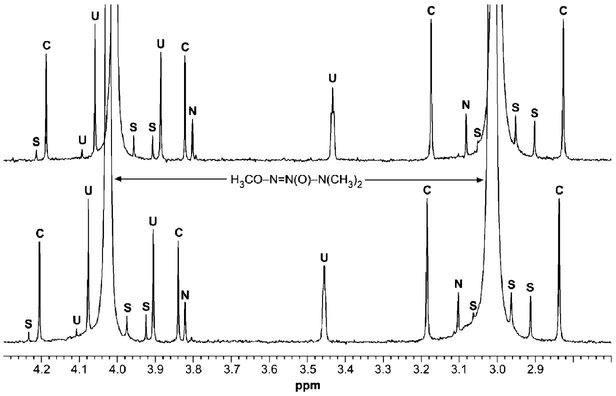


Figure 1. Proton spectra of a 34 mM solution of **3** in chloroform-*d*: 10 min after dissolving at 0 °C (bottom); after 120 h at 27 °C (top). [S = spinning sideband; C = ^{13}C satellite; U = unknown; N = *N*-nitrosodimethylamine].

Table 1. Integrals of Unknown Peaks Seen in Proton Spectra of Figure 1

	Concentration (% relative to total –OCH$_3$ integral = 1.000) at t =	
shift	0	120 h
4.11	0.06	0.03
4.08	0.96	0.94
3.91	0.82	0.71
3.46	1.23	1.08

least-squares on F^2 values using programs found in the SHELXTL system of programs. Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms on carbons were included using a riding model [coordinate shifts of C applied to H atoms] with C−H distance set at 0.96 Å.

Results and Discussion

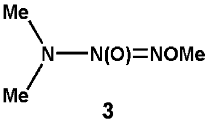
Search for $Z \rightleftharpoons E$ Isomerism in Me$_2$N−N$_2$O$_2$−Me (3). We first examined the ^{1}H NMR spectrum of the simplest N-bound diazeniumdiolate available to date, **3**. In this experiment, spectra of chloroform-*d* solutions were run at 0 °C immediately after dissolving and again after 5 days at 27 °C. The results are shown in Figure 1. A pair of singlets in an integral ratio of 2:1 dominated the spectrum at each time point.

Using the integrals of the O−CH$_3$ peak's ^{13}C satellites (each 0.55% of the parent peak) as a reference, signals not otherwise assignable were integrated to provide the data summarized in Table 1. It is conceivable that the three largest of the listed unknown peaks reflect the presence of a second Me$_2$NN(O)═NOMe isomer, but we view this as unlikely for three reasons: (1) the integral ratio appears to be significantly different from 1:1:1; (2) even if these peaks are indeed equally intense, it is not clear how the two *N*-methyl groups could be magnetically nonequivalent when this has not been seen with other N-bound diazeniumdiolates, including the major constituent of the sample examined here; and (3) it is also unclear how the peak at δ 3.44 of this hypothetical Me$_2$NN(O)═NOMe structure could appear as a multiplet, while the other two are sharp singlets. We conclude that the data provide no convincing evidence for observable *Z*/*E* isomerism in this simple diazeniumdiolate, and that even if the unknown peaks do reflect the presence of a second isomer of **3**, its abundance can represent no more than about 1% of the total.

This result is typical of many attempts we have made to observe the presence of a second isomer in other R^{1}R^{2}NN(O)═NOR^3 systems. Substantially pure diazeniumdiolates have sometimes displayed small HPLC peaks with ultraviolet spectra very similar to those of the major component, which on further examination, proved to be due to impurities. Similarly frustrating results have been seen in probes of the identity of suggestive peaks in the NMR spectra of other diazeniumdiolates. Attempts to induce a $Z \rightarrow E$ interconversion by tickling various R^{1}R^{2}NN(O)═NOR^3 molecules with ultraviolet irradiation have led instead to an interesting photochemical cleavage of the double bond.[30]

Scenarios that could account for these results are based on the possibility that both isomers are present in the isolated material, but the interconversion barrier is (a) so high that it prohibits significant progress toward equilibrium under the conditions employed; (b) low, but the equilibrium constant strongly favors one isomer (by ≥100:1 in the case of **3**); (c) not prohibitively high but the peaks for the less abundant isomer are fortuitously obscured; (d) so low that only the time-averaged spectrum is seen. (Scenario d would seem to be excluded by the fact that previous crystallographic studies for a variety of R^{1}R^{2}NN(O)═NOR^3 structures have all shown substantial double bond character for the N(O)−NO linkage.[2,3])

Calculation of $Z \rightleftharpoons E$ Energetics for Me$_2$NN(O)═NOMe (3) and MeHNN(O)═NOMe (4). To guide us in our quest to explain the apparent single isomer dominance described above and consistently seen in the prior literature,[2,3] and with the hope of using any insights gained in an effort to generate a pair of bona fide *Z*/*E* diazeniumdiolate isomers for individual scrutiny, we launched a comprehensive computational study of **3** and an analogue in which one of the *N*-methyl groups was replaced by a proton (**4**).



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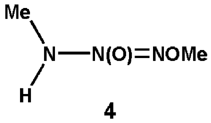

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In each case, *Z* and *E* minimum energy structures were located together with the transition state associated with their interconversion. Figure 2 illustrates the MP2 optimized geometries of the three stationary points for each of **3** and **4**. We find that all *Z* and *E* minima have predicted N1−N3 distances which indicate the presence of single bonds, and the calculated N1−N2 bond lengths suggest the presence of double bonds. These features together with the isostructural N3N1(O1)N2 units suggest that all *Z* and *E* species contain comparable bonding environments. However, the optimized transition state structures show marked differences from the minima. As shown in Figure 2, the N3−N1 distances, at 1.33 Å, become shorter, and the N1−N2 distances, at approximately 1.37 Å, become longer. These predicted bond lengths suggest that the N3−N1 units acquire double bond character, while the N1−N2 bonds become weaker. Furthermore, the environments around the N3 atoms are very nearly planar in the transition states. This feature supports the

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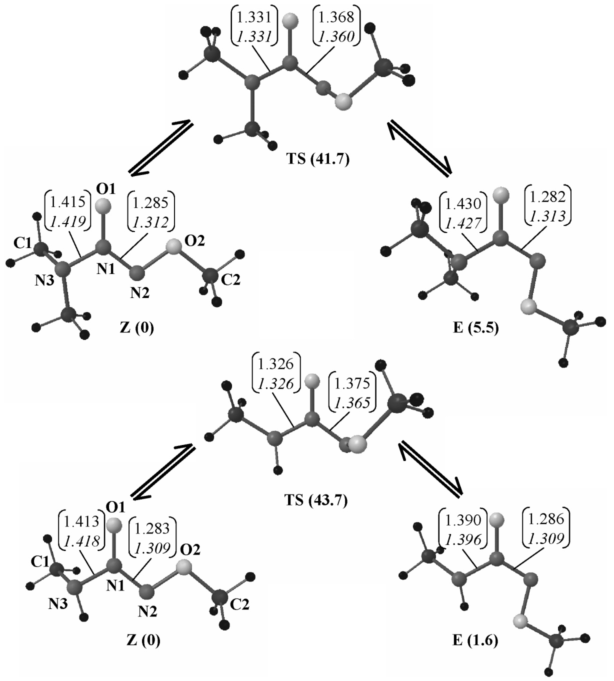


Figure 2. MP2 optimized stationary points and relative energies (kcal/mol) for the $Me_2NN(O)NOMe$ (**3**) (top) and MeNHN(O)NOMe (**4**) (bottom) species. Predictions of N3−N1 and N1−N2 interatomic distances (angstroms) are given in brackets where normal font represents B3LYP values and italic font represents MP2 values.

Table 2. Calculated Relative Energies and Lowest Vibrational Frequencies for Stationary Points of the Neutral $Me_2NN(O)$═NOMe Species

system	method[a]	relative energy (kcal/mol)	lowest frequency (cm^{-1})
Z	RHF	0	58
	B3LYP	0	61
	B3LYP/PCM[b]	0	
	MP2	0	59
	MP2/PCM[b]	0	
TS	RHF	40.6	172 *i*
	B3LYP	39.6	412 *i*
	B3LYP/PCM[b]	37.8	
	MP2	41.7	292 *i*
	MP2/PCM[b]	39.5	
E	RHF	6.5	66
	B3LYP	5.9	68
	B3LYP/PCM[b]	6.3	
	MP2	5.5	61
	MP2/PCM[b]	6.5	

[a] All calculations used aug-cc-pVDZ basis sets.[11] [b] Single point Polarized Continuum Model (PCM) calculations performed at gas-phase-optimized geometries.

Table 3. Calculated Relative Energies and Lowest Vibrational Frequencies for Stationary Points of the Neutral MeNHN(O)═NOMe Species

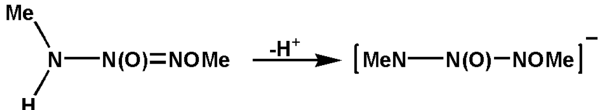
system	method[a]	relative energy (kcal/mol)	lowest frequency (cm^{-1})
Z	RHF	0	67
	B3LYP	0	72
	B3LYP/PCM[b]	0	
	MP2	0	68
	MP2/PCM[b]	0	
TS	RHF	40.8	176 *i*
	B3LYP	40.8	422 *i*
	B3LYP/PCM[b]	36.5	
	MP2	43.7	285 *i*
	MP2/PCM[b]	38.5	
E	RHF	2.3	55
	B3LYP	0.9	62
	B3LYP/PCM[b]	2.2	
	MP2	1.6	56
	MP2/PCM[b]	2.9	

[a] All calculations used aug-cc-pVDZ basis sets.[11] [b] Single point Polarized Continuum Model (PCM) calculations performed at gas-phase-optimized geometries.

assertion that the N3−N1 bonds have double bond character. Relative energies of stationary points for species **3** and **4** are given in Tables 2 and 3, respectively. We find that in the gas phase the *Z* isomers are consistently predicted to be more stable than the *E* isomers for both **3** and **4**, with energy differences of 5.5−6.5 and 0.9−2.3 kcal/mol, respectively. It is interesting to note that calculated *E*−*Z* energy gaps for **4** are always smaller than those for **3**. The stabilization of the *E* isomer of **4** is presumably due to the presence of a hydrogen bond between atom O2 and the hydrogen atom attached to atom N3, that is, of the form N3−H···O2. A previous study by Taylor et al.[4] on the similar system $H_2NN(O)$═NO^- demonstrated that the predicted stability of the *E* isomer over the *Z* was a consequence of formation of a hydrogen bond analogous to that described above. Solvent (water) effects were taken into account by performing single point B3LYP/PCM and MP2/PCM calculations at B3LYP and MP2 gas-phase-optimized geometries, respectively. At these levels of theory, the *Z* isomers are stabilized, relative to the *E* isomers, by 0.4 (B3LYP/PCM) and 1.0 kcal/mol (MP2/PCM) for **3** and 1.3 kcal/mol (B3LYP/PCM and MP2/PCM) for **4**. Transition state barriers for the *Z* → *E* interconversion, in the gas phase, are predicted to lie between 39.6 and 43.7 kcal/mol for both **3** and **4**. Solvent effects bring these barriers down a little to 37.8 (B3LYP/PCM) and 39.5 kcal/mol (MP2/PCM) for **3**, and 36.5 (B3LYP/PCM) and 38.5 kcal/mol (MP2/PCM) for **4**. These results indicate that *Z*/*E* isomerizations for species **3** and **4** are unlikely because barriers of close to 40 kcal/mol must be overcome. One would expect this to be the case for other $R^1R^2N{-}N(O){=}NOR^3$ systems where R^1R^2 are not electron withdrawing.

It is important to note here that all levels of theory give predictions which are in very close agreement. Furthermore, the inclusion of solvent effects reduces the *Z*/*E* interconversion barriers by only small amounts.

Calculation of *Z* ⇌ *E* Energetics for $[MeNN(O)NOMe]^-$. Previous theoretical studies have led us to postulate that the primary amine derivatives $R^1HNN(O){=}NOR^3$, such as **4**, might more readily undergo *Z* ⇌ *E* isomerizations when ionized.[3]



$$\mathrm{MeHN{-}N(O){=}NOMe} \xrightarrow{-H^+} [\mathrm{MeN{-}N(O){-}NOMe}]^-$$

4 **[4]$^-$**

These studies showed that ionization of the N−H bond when the R^3O bond is covalent greatly decreases the double bond character of the N(O)−NO linkage and presumably produces a significant lowering of the interconversion barrier between the *Z* and *E* forms. Figure 3 illustrates the stationary points located for the $[MeNN(O)NOMe]^-$ anion. The *Z* and *E* isomer structures have similar backbones to those of **3** and **4**, with the exception that the torsion angle N1−N2−O2−C2 is now approximately 90°. For the *Z* isomer, one might ask whether this is due to the

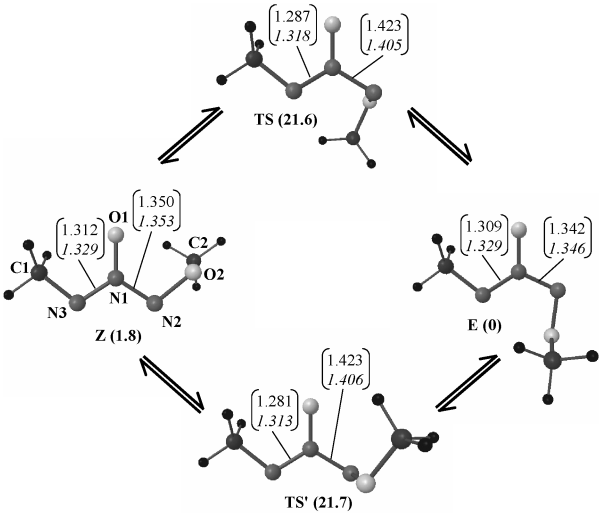


Figure 3. MP2 optimized stationary points and relative energies (kcal/mol) for the $[MeNN(O)NOMe]^-$ anion. Predictions of N3−N1 and N1−N2 interatomic distances (angstroms) are given in brackets where normal font represents B3LYP values and italic font represents MP2 values.

Table 4. Calculated Relative Energies and Lowest Vibrational Frequencies for Stationary Points of the $[MeNN(O)NOMe]^-$ Anion

system	method[a]	relative energy (kcal/mol)	lowest frequency (cm^{-1})
Z	RHF	0	119
	B3LYP	0	98
	B3LYP/PCM[b]	0	
	MP2	0	83
	MP2/PCM[b]	0	
TS	RHF	18.5	134 *i*
	B3LYP	20.1	201 *i*
	B3LYP/PCM[b]	18.4	
	MP2	19.8	165 *i*
	MP2/PCM[b]	18.0	
TS′	RHF	18.2	131 *i*
	B3LYP	19.9	191 *i*
	B3LYP/PCM[b]	18.6	
	MP2	19.9	155 *i*
	MP2/PCM[b]	17.6	
E	RHF	−1.4	120
	B3LYP	−1.2	109
	B3LYP/PCM[b]	−0.8	
	MP2	−1.8	127
	MP2/PCM[b]	−1.9	

[a] All calculations used aug-cc-pVDZ basis sets.[11] [b] Single point Polarized Continuum Model (PCM) calculations performed at gas-phase-optimized geometries.

anion providing a stronger C2−H···O1 interaction. However, the *E* isomer of the anion contains a N1−N2−O2−C2 torsion angle similar to that of the *Z* isomer, and the only possible similar stabilizing effect is a long-range C2−H···N3 attraction. We did, in fact, find a minimum for the *Z* isomer of **4** at the MP2 level of theory in which the N1−N2−O2−C2 torsion angle was approximately 90°, but this geometry was 2.2 kcal/mol higher in energy than that of the *Z* isomer minimum shown in Figure 2. For the anion, we located another *Z* isomer minimum with a N1−N2−O2−C2 torsion angle of 180°, also at the MP2 level of theory, but this was higher than the structure shown in Figure 3 by 2.5 kcal/mol. Rotation about the N2−O2 bonds for all species studied here is expected to be nearly barrierless, and the reasons why a particular orientation of the O2−CH3 group is very slightly preferred over the other are not immediately obvious. Predicted N3−N1 bond lengths are shorter, and N1−N2 bond lengths are longer in the anion when compared to the minima of **3** and, in fact, resemble those of the *Z*/*E* transition state for **3**. This would suggest that the N1−N2 bonds of the minima are weaker for the anion than for **3** or **4**. Two transition states for the *Z*/*E* isomerization were located for the anion. As shown in Figure 3, these structures appear similar to the transition states located for **3** and **4**. However, atoms N3 and N1 are now clearly connected by a double bond, whereas the N1−N2 linkage is only a single bond. Relative energies are given in Table 4. We find that all levels of theory, in both gas and solvent phases, predict the *E* isomer to be more stable than its *Z* counterpart, with calculated energy differences of less than 2 kcal/mol. The two transition states have almost identical energies at each level of theory, and estimated barrier heights for the *Z*/*E* interconversions, with one small exception, are all less than 20 kcal/mol. In this study, the most reliable estimates of barrier heights, in water, are expected from the B3LYP/PCM and MP2/PCM levels of theory. These are 18.4 (TS) and 17.6 kcal/mol (TS′), respectively, and are approximately 20 kcal/mol less than those seen for the neutral species **3** and **4**. Again, all levels of theory are in very good agreement, and solvent effects are predicted to reduce the *Z*/*E* interconversion barriers by very little.

A reasoning into why the anion, $[\mathbf{4}]^-$, has a *Z* → *E* rotational barrier lower than that of its neutral counterparts, **3** and **4**, can be deduced from the predicted bond lengths. We see from Figure 2 that species **3** and **4** each contain a N3−N2═N1 skeleton, that is, the π bond is localized to atoms N2 and N1 and atom N3 contains a lone pair. However, the bond lengths given in Figure 3 suggest that the anion $[\mathbf{4}]^-$ has its π electrons, and hence negative charge, delocalized over atoms N3 and N2. This would suggest that atoms N2 and N1 are connected by a bond order of approximately 1.5, if not less. The weaker N1−N2 bond in the anion would imply that rotation about this bond requires less effort than that required for both **3** and **4**.

Isolation of a *trans*-Diazeniumdiolate. The above theoretical considerations suggest that the chances of seeing *Z* → *E* isomerization in a species of structure $R^1R^2NN(O){=}NOR^3$ would be most favorable if R^1 or R^2 is hydrogen. When $R^1 = Me = R^3$ and $R^2 = H$, the calculations pointed to a preference for the *Z* form, with a barrier of ~40 kcal/mol, impeding its conversion to the *E* isomer, but on ionization of the N−H bond, the calculations indicated a preference for *E* via a transition state with a relatively small activation energy. If these theoretical predictions can be generalized to analogues with larger R groups, one might be able to engineer a means of directly observing the resulting *Z* → *E* interconversion.

We have succeeded in documenting just such a situation. Isopropylamine derivative **5** was prepared and, despite its lability as reflected, for example, in its unsatisfactory elemental analysis, shown to be relatively stable in methanol solution. As demonstrated in Figure 4, however, addition of an equivalent of 30% NaOD in D_2O led to complete disappearance of **5** with concomitant appearance of a new set of NMR signals similar to those of the starting material but attributable to cyclic product **6**. The structure of this diazeniumdiolate was confirmed as having the *E* configuration about the N−N double bond by X-ray crystallography, as shown in Figure 5.

We were able to gain some experimental insight into the energetics and mechanism of the cyclization by observing the

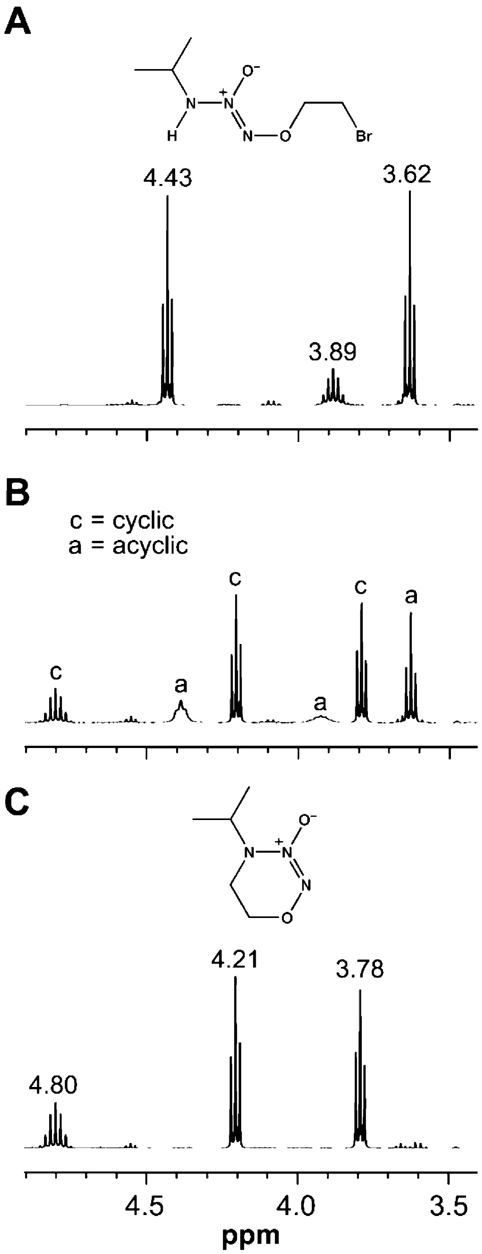


Figure 4. Conversion of **5** to cyclic *E* derivative **6** at 0 °C in methanol-d_4 solution after adding 1 equiv of 30% NaOD in D_2O. Proton spectra shown were recorded at (A) time zero; (B) 15 min; (C) 2 h.

reaction's progress, as further illustrated in Figure 4. Panel B shows that the reaction is nearly 50% complete within 15 min at 0 °C in the indicated methanolic solution. Evaluation of starting material/product integral ratios observed at this and a series of subsequent time points gave a first-order rate constant estimated to be $(4.6 \pm 0.4) \times 10^{-4}\ s^{-1}$. Assuming that **5** has the *Z* configuration, as has every other N-bound diazeniumdiolate whose structure has been crystallographically confirmed, this value can be taken as a lower limit for the rate constant governing *Z* → *E* isomerization in **5**.

To the extent that the rate for nucleophilic attack of the anionic nitrogen center on the bromomethyl carbon of **5** can be expected to be similar to those of other six-membered ring closures, it is perhaps useful to compare this value of $4.6 \times 10^{-4}\ s^{-1}$ with the rate constant for cyclization of $Br(CH_2)_5NH_2$. Freundlich and Bartels[31] reported a value of $3 \times 10^{-4}\ s^{-1}$ for the latter reaction in water at 0 °C. The similarity within a factor of 2 between the rate constants for formation of **6** in methanol and the published value for cyclization of $Br(CH_2)_5NH_2$ in water suggests that the ring closure step, k_2, of Scheme 2 is rate-limiting. This suggests, in turn, that all precyclization events in the conversion of **5** to **6**, including the $Z \rightleftharpoons E$ equilibration steps illustrated in the inferred reaction sequence of Scheme 2, must be fast, perhaps very fast, by comparison.

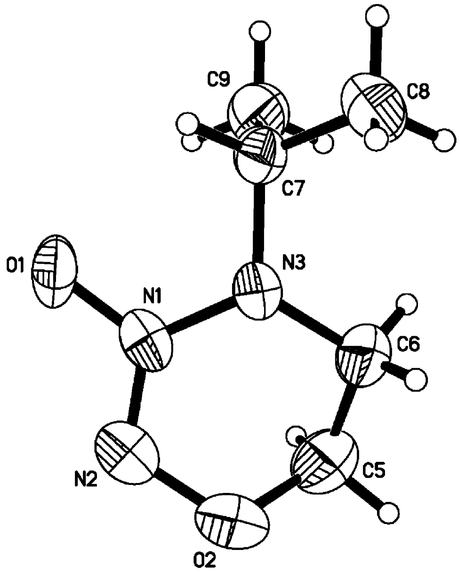
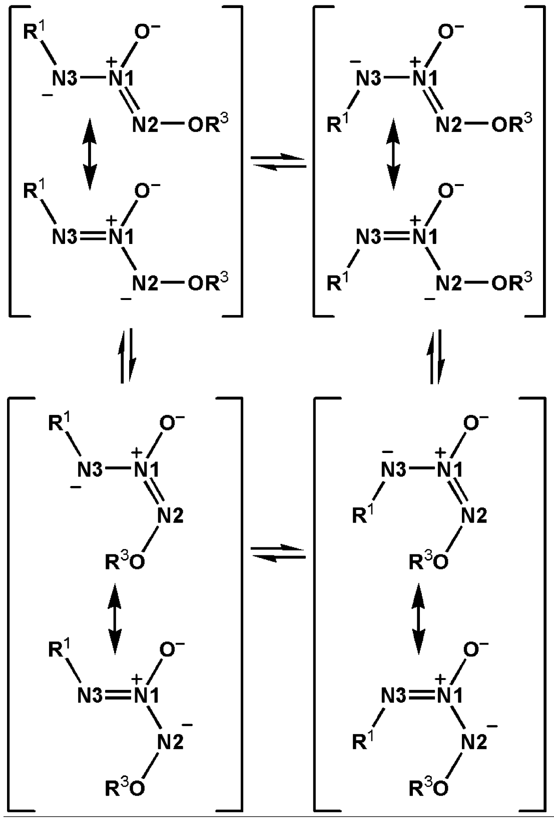


Figure 5. View of cyclic (*E*)-diazeniumdiolate **6** showing the single molecule in the asymmetric unit. Thermal ellipsoids (50%) are shown for heavy atoms. Key metric parameters (Å) include: O2−N2 1.393(3); N2−N1 1.292(3); N1−O1 1.264(3); and N1−N3 1.373(3).

Consistent with this view, the ^1H NMR signals for the C−H protons geminal to nitrogen or oxygen are seen in panel B of



(1)

Scheme 2. Presumed Mechanism of $Z \rightarrow E$ Isomerization Made Possible on Ionization of **5** En Route to Formation of (*E*)-Diazeniumdiolate **6**

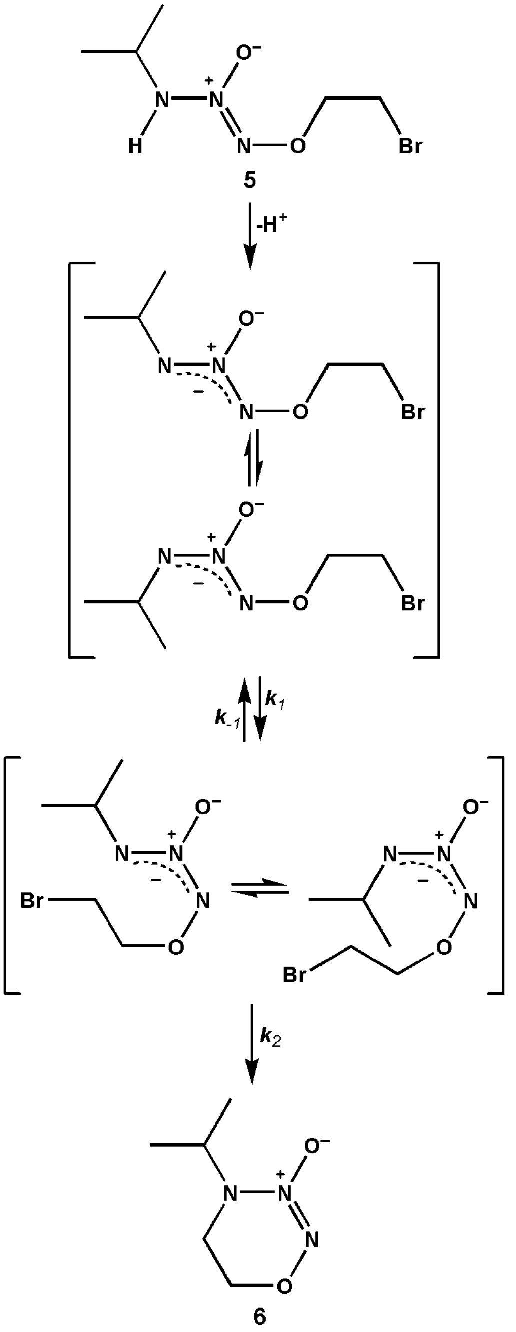


Figure 4 to be substantially broadened in anionic **5** but to remain characteristically sharp in **6**. Such line broadening has been seen before in ions of structure $[R^1NN(O)NOR^3]^-$ and interpreted as reflecting a fluxional behavior that may involve some or all of the structures shown in eq 1.[3] The rate constant for the case in which R^1 = isopropyl and R^3 = methyl, assuming that the observed exchange was occurring between two equally populated structures, was estimated to be roughly 1×10^3 s^{-1} at pH near the pK_a in aqueous medium.[3] We take this value as a tentative estimate of the upper limit for k_1 of Scheme 2, assuming that the rate of the observed fluxional behavior is determined by $Z \rightleftharpoons E$ interconversion around the central N−N bond of the ON−NO fragment and not that of the RN−NN moiety.

Having bracketed the rate constant for the $Z \rightarrow E$ isomerization, k_1 of Scheme 2, as likely falling within the range of 4.6×10^{-4} and 1×10^3 s^{-1}, we applied classical transition state theory to the model deprotonated anion $[MeNN(O)NOMe]^-$ to estimate k_1 directly. At the MP2 level of theory, a free energy of activation at 298 K, $\Delta G^{\ddagger}(298)$, for $Z \rightarrow TS'$ was determined to be 19.7 kcal/mol. Taking the solvent into account by adding in the difference determined at 0 K gives a best estimate for $\Delta G^{\ddagger}_{aq}(298)$ of 17.4 kcal/mol, which gives a calculated first-order rate constant of 1.1 s^{-1}.

Our results suggest that the failure to document an *E* configuration of structure $R^1R^2NN(O){=}NOR^3$, heretofore, is due at least in part to a prohibitively high barrier to $Z \rightleftharpoons E$ interconversion, estimated here to be near 40 kcal/mol. The results further indicate that this barrier can be lowered by ∼20 kcal/mol or more by heterolytic cleavage of R^2 to form the corresponding anion. Support for such a dramatic ionization-induced rate enhancement and corresponding transition state stabilization has been observed in the carbon-bound diazeniumdiolate resulting from NO addition to the anion derived from dimethylmalonate.[32] As in the case of **5**, deprotonation at the α position led to conjugation with the $N(O){=}NO$ fragment, which in turn was trapped as a cyclized *E* diazeniumdiolate derivative.

Conclusions

Our results demonstrate that diazeniumdiolates having *E* stereochemistry, as in structure **2**, can exist and in fact be isolated. The data also provide insight into the energetics of their interconversion with the corresponding *Z* isomers (**1**). While the barrier to direct thermal $Z \rightarrow E$ isomerization appears insurmountably high at ∼40 kcal/mol, the substantially lower activation energy in ions produced on ionizing the N−H bond of an $R^1HNN(O){=}NOR^3$ molecule may offer a convenient route to pairs of *Z* and *E* isomers of otherwise identical structure. Such a capability could be of considerable benefit in seeking to exploit the rich chemistry of the diazeniumdiolates for the design of improved drugs and medical devices. The *Z* and *E* forms should fit quite differently into enzymatic active sites, for example, and thus might be expected to be cleaved at significantly different rates to free the spontaneously NO-releasing $R^1R^2NN(O){=}NO^-$ or $R^1HNN(O){=}NO^-$ ion for concentration at the site of activation. Moreover, the freed ions might themselves be characterizable as distinct *Z* and *E* forms possessing useful differences in physicochemical properties, including their rates and possibly even mechanisms of hydrolysis to NO and related bioactive agents. We are currently engaged in efforts to generate acyclic *Z* and *E* pairs for individual study that we hope will shed light on the nature of the expected differences.

Acknowledgment. This project has been funded in part by the National Cancer Institute under Contract No. NO1-CO-12400. D.S.B. gratefully acknowledges support from NSERC in the form of a Discovery Grant. The X-ray crystallographic

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(31) Freundlich, H.; Bartels, R. *Z. Phys. Chem.* **1922**, *101*, 177−184. The rate constant actually given by Freundlich and Bartels was "rund 0.02", with no units specified. From the experimental description these authors supplied, we infer the units to be min^{-1}, hence the value we quote is $k = 3 \times 10^{-4}$ s^{-1}.

(32) Arulsamy, N.; Bohle, D. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2089−2091.

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Supporting Information Available: Crystal data and structure refinement for **6**, including bond lengths and angles, atomic coordinates and isotropic displacement parameters, anisotropic displacement parameters, hydrogen coordinates, and torsion angles; Cartesian coordinates and absolute energies of all optimized structures; and complete refs 23 and 24. This material is available free of charge via the Internet at http://pubs.acs.org.

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