

# Ab Initio Quantum-Mechanical Study of the Stability of Cyclic $\alpha$ -Acetoxy-*N*-nitrosamines: Amine $N \rightarrow NO$ Dative Bonding in $\alpha$ -Hydroxy-*N*-nitrosamines versus $N \rightarrow$ Carbocation Dative Bonding in *N*-Nitrosiminium Ions

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**Abstract:** The dissociations of  $\alpha$ -hydroxy-*N*-nitrosopyrrolidine, **1**, and  $\alpha$ -hydroxy-*N*-nitrosopiperidine, **2**, to form the nitrosiminium ions, **3** and **4**, respectively, have been studied as models for the  $S_N1$  process of the corresponding  $\alpha$ -acetoxy-*N*-nitrosamines. In excellent agreement with experiments, the ionization of the pyrrolidine derivative is found to be more endothermic at *ab initio* levels up to MP4(SDTQ)/6-31G\*\*//RHF/6-31G\* and including corrections for thermal motions. This finding is explained with more efficient  $N \rightarrow NO$   $\pi$ -dative bonding in **1** compared to **2** while ring size effects in **3** and **4** are rather small. The activation barriers to NN-rotation provide quantitative measures of the strengths of the  $N \rightarrow NO$   $\pi$ -dative bonding in **1–4** and the transition-state structures **1-TS–4-TS** for the rotation about the NN bonds in **1–4** were determined. Electron density analyses (NBO) and electrostatic field analysis (CHELPG, MKS) were performed to assess the extent of  $N \rightarrow NO$   $\pi$ -dative bonding in  $\alpha$ -hydroxy-*N*-nitrosamines and the electronic relaxation associated with the competition between amine  $N \rightarrow NO$  and  $N \rightarrow$ carbocation  $\pi$ -dative bonding in *N*-nitrosiminium ions. The comparative analysis of the structural and electronic relaxation associated with ionization in the presence (**1–4**) or absence (**1-TS–4-TS**) of the possibility for  $N \rightarrow NO$   $\pi$ -dative bonding demonstrate in a compelling fashion that  $\sigma$ -polarizations are responsible for most of the electron density relaxation.

## Introduction

$\alpha$ -Acetoxy-*N*-nitrosamines are latent  $\alpha$ -hydroxynitrosamines and the latter are believed to be formed by metabolic cytochrome P450 mediated oxidation of nitrosamines.<sup>1</sup> The elucidation of the mechanism of the decomposition of  $\alpha$ -acetoxy-*N*-nitrosamines presents a central issue. For acyclic  $\alpha$ -acetoxy-*N*-nitrosamines, it is thought that *N*-nitrosiminium ions are formed in an  $S_N1$  process.<sup>2</sup> Cyclic  $\alpha$ -acetoxy-*N*-nitrosamines have been studied less, even though they play an important role in the chemistry and toxicology of nitrosamines, and of nitrosopyrrolidine and nitrosopiperidine in particular,<sup>3,4</sup> and nucleophilic attack on the acetyl group's carbonyl carbon was discussed.<sup>5</sup> Fishbein et al.<sup>6</sup> have studied the kinetics of  $\alpha$ -acetoxy-*N*-nitrosopyrrolidine and  $\alpha$ -acetoxy-*N*-nitrosopiperidine, and they were found to decompose via the formation of *N*-nitrosiminium

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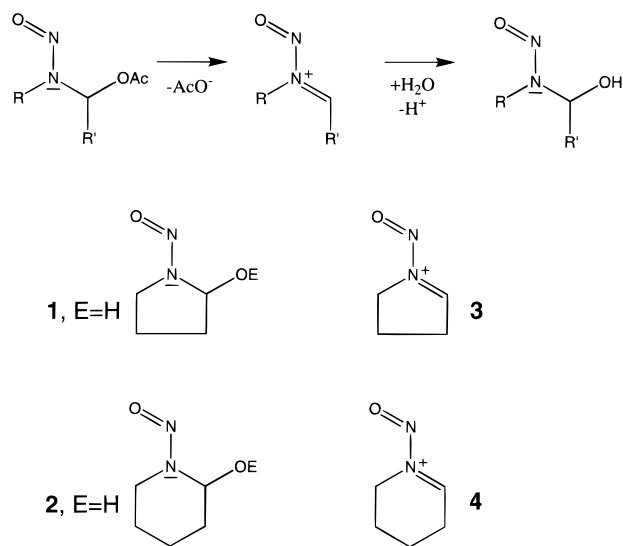
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**Scheme 1.** Conversion of  $\alpha$ -Acetoxy-*N*-nitrosamines into  $\alpha$ -Hydroxy-*N*-nitrosamines by Way of *N*-Nitrosiminium Ions



ions at physiological pH (Scheme 1). The reactivities of the  $\alpha$ -acetoxy-*N*-nitrosamines were found to be remarkably different for the two cyclic systems. Activation enthalpies of  $\Delta H^\ddagger = 21.8 \pm 3.4$  and  $17.8 \pm 0.8$  kcal/mol were determined for the five- and six-membered rings systems. The activation entropies were found to be  $\Delta S^\ddagger = -4.8 \pm 1.1$  and  $-8.2 \pm 1.2$  cal/deg mol, respectively. The activation barriers differ by 4.0 kcal/mol, and the piperidine derivative decomposes with a rate 100 times faster compared to the pyrrolidine derivative.

**Table 1.** Total Energies and Results of Vibrational Analysis

molecule	RHF	VZPE	$E_{\text{thermal}}$	MP2	MP3	MP4(SDTQ)
<b>1</b>	-414.661 997	0.142 369	0.150 417	-415.859 005	-415.886 026	-415.952 760
<b>2</b>	-453.696 268	0.173 482	0.182 427	-455.026 203	-455.062533	-455.136205
<b>3</b>	-338.966 406	0.124 122	0.131 240	-339.960 822	-339.989857	-340.050047
<b>4</b>	-378.012 581	0.155 615	0.163 481	-379.141 361	-379.178 688	-379.246 174
<b>1-TS</b>	-414.625 872	0.141 377	0.148 912	-415.818 161	-415.850 383	-415.914 070
<b>2-TS</b>	-453.668 092	0.172 915	0.181 094	-454.993 323	-455.034 528	-455.104 918
<b>3-TS</b>	-338.951 850	0.123 195	0.129 917	-339.950 065	-339.978 434	-340.040 005
<b>4-TS</b>	-377.997 173	0.154 699	0.162 176	-379.128 454	-379.165 855	-379.233 942

<sup>a</sup> All energies in atomic units. <sup>b</sup> Vibrational zero-point energies (VZPE) are given as computed. <sup>c</sup> Thermal energies ( $E_{\text{thermal}}$ ) are given as computed for standard conditions.

In the present study we are investigating the unimolecular dissociations of  $\alpha$ -hydroxy-*N*-nitrosopyrrolidine, **1**, and of  $\alpha$ -hydroxy-*N*-nitrosopiperidine, **2**, that lead to the corresponding nitrosiminium ions, **3** and **4**, respectively, as shown in Scheme 1 for E = H. We stress at this point that the actual decomposition reaction of the  $\alpha$ -hydroxy-*N*-nitrosamines are not likely to follow the  $S_{\text{N}}1$  process.<sup>7</sup> Instead, we are studying these reactions as models for the  $S_{\text{N}}1$  process of the  $\alpha$ -acetoxy-*N*-nitrosamines that occurs at physiological pH. The ionization of the pyrrolidine derivative is found to require more energy, and we seek to provide an explanation for this intrinsic difference in the unimolecular dissociation of the  $\alpha$ -hydroxy-*N*-nitrosamines. The transition-state structures for the rotation about the NN bonds in **1–4**, the structures **1-TS–4-TS** were determined. The activation barriers to NN-rotation provide quantitative measures of the strengths of the N $\rightarrow$ NO  $\pi$ -dative bonding in the neutral molecules and in the nitrosiminium cations. That is, we employ the structures **1-TS–4-TS** to model the dissociation energies of the nitrosamines in the absence of the N $\rightarrow$ NO  $\pi$ -dative bonding. In addition to the exploration of the potential energy surface, we have performed electron density analyses and electric field analyses to assess the extent of N $\rightarrow$ NO  $\pi$ -dative bonding in  $\alpha$ -hydroxy-*N*-nitrosamines and to investigate the outcome of the competition between amine N $\rightarrow$ NO and N $\rightarrow$ carbocation  $\pi$ -dative bonding in *N*-nitrosiminium ions. The comparative analysis of the structural and electronic relaxation associated with ionization in the presence or absence of N $\rightarrow$ NO  $\pi$ -dative bonding demonstrate in a compelling fashion that  $\sigma$ -polarizations are responsible for most of the electron density relaxation.<sup>8</sup>

## Computational Methods

Structures were completely optimized at the restricted Hartree–Fock (RHF) level of theory and using gradient methods embedded in the quantum-mechanical program Gaussian94.<sup>9</sup> All calculations employed the 6-31G\* basis set.<sup>10</sup> This basis set allows for a flexible description of the valence electrons as the result of its split-valence nature. The polarization functions on all heavy atoms are known to be important for the description of polar bonds and they help to adequately describe electron lone pairs as well. This level of ab initio theory is referred to

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(8) Glaser, R.; Horan, C. J.; Lewis, M.; Zollinger, H. *J. Org. Chem.* **1999**, *64*, 902, and references therein.

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**Table 2.** Relative Energies and Activation Barriers

parameter	RHF	VZPE	$E_{\text{thermal}}$	MP2	MP3	MP4
$\Delta E_{\text{diss}}(\mathbf{1-3}) - (\mathbf{2-4})$	-7.47	0.22	0.13	-8.37	-7.73	-7.96
$\Delta E_{\text{diss}}(\mathbf{1-TS-3-TS}) - (\mathbf{2-TS-4-TS})$	-1.95	-0.02	0.04	-2.03	-2.06	-1.94
$\Delta E_{\text{act}}(\mathbf{1,1-TS})$	22.67	-0.57	-0.86	25.63	22.37	24.28
$\Delta E_{\text{act}}(\mathbf{2,2-TS})$	17.68	-0.33	-0.76	18.85	16.05	17.93
$\Delta E_{\text{act}}(\mathbf{2-1})$	-4.99	0.24	0.10	-6.78	-6.31	-6.34
$\Delta E_{\text{act}}(\mathbf{3,3-TS})$	9.13	-0.53	-0.76	6.75	7.17	6.30
$\Delta E_{\text{act}}(\mathbf{4,4-TS})$	9.67	-0.53	-0.75	8.10	8.05	7.68
$\Delta E_{\text{act}}(\mathbf{4-3})$	0.53	0.01	0.01	1.35	0.88	1.37

<sup>a</sup> All energies in kilocalories per mol. <sup>b</sup> Vibrational zero-point energies (VZPE) and thermal energies ( $E_{\text{thermal}}$ ) are scaled. <sup>c</sup>  $\Delta H_{\text{act}} = \Delta E + \Delta \text{VZPE}$  or, even better,  $\Delta H_{\text{act}} = \Delta E + \Delta E_{\text{thermal}}$ .

as RHF/6-31G\*. Vibrational analyses were carried out analytically for all stationary structures to ensure that each gradient optimization indeed located a true stationary structure. Energies are summarized in Table 1. The results of the vibrational analysis also were employed to compute vibrational zero-point energies, VZPE, as well as thermal energies  $E_{\text{thermal}}$  that contain all thermal energy contributions (translational, rotational, and vibrational). Pertinent relative energies are summarized in Table 2. The results of the vibrational analysis are reported as computed in Table 1 but the values were scaled when applied to the computation of relative energies. The scale factor 0.8928 was used for frequencies and the factor 0.9135 was used for the VZPE data and  $E_{\text{thermal}}$  values.<sup>11</sup>

Hartree–Fock calculations neglect large parts of electron correlation. The effects of this neglect are most profound in cases where bonds are greatly reorganized and the assumption of cancellation of error might not be warranted. Here we will be studying electronic relaxations associated with complete bond dissociations and with rotations that cause the breaking of  $\pi$ -bonds and, hence, the consideration of electron correlation effects seemed necessary. We have employed Møller–Plesset perturbation theory at the second- and third-order levels, MP2 and MP3, and up to full fourth-order, MP4(SDTQ), that is, singles, doubles, triples, and quadruple excitations all are taken into account.<sup>12</sup> The perturbation calculations were carried out using the frozen-core approximation and all calculations employed the 6-31G\* basis set and were based on the RHF/6-31G\* structures.

Electronic structures were analyzed with the natural bond order method<sup>13</sup> (NBO). In the NBO method, the molecular orbitals are transformed into a set of maximally localized molecular orbitals. The “natural populations” of these “natural orbitals” produce charges that are in agreement with expectations based on ionization energies of atoms and they usually parallel the atomic charges determined with the more costly “atoms in molecules” method.<sup>14</sup> In the context of

(11) Pople, J. A.; Scott, A. P.; Wong, M. W.; Radom, L. *Isr. J. Chem.* **1993**, *33*, 345.

(12) (a) MP4(SDT): Pople, J. A.; Head-Gordon, M.; Raghavachari, Krishnan *Int. J. Quantum Chem.* **1988**, *22*, 377. (b) Curtiss, L. A.; Raghavachari, K.; Pople, J. A. *J. Chem. Phys.* **1995**, *103*, 4192, and references therein.

(13) NBO Method: (a) Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *NBO Version 3.1*. (b) Glendening, E. D.; Weinhold, F. *J. Comput. Chem.* **1998**, *19*, 628, and references therein.

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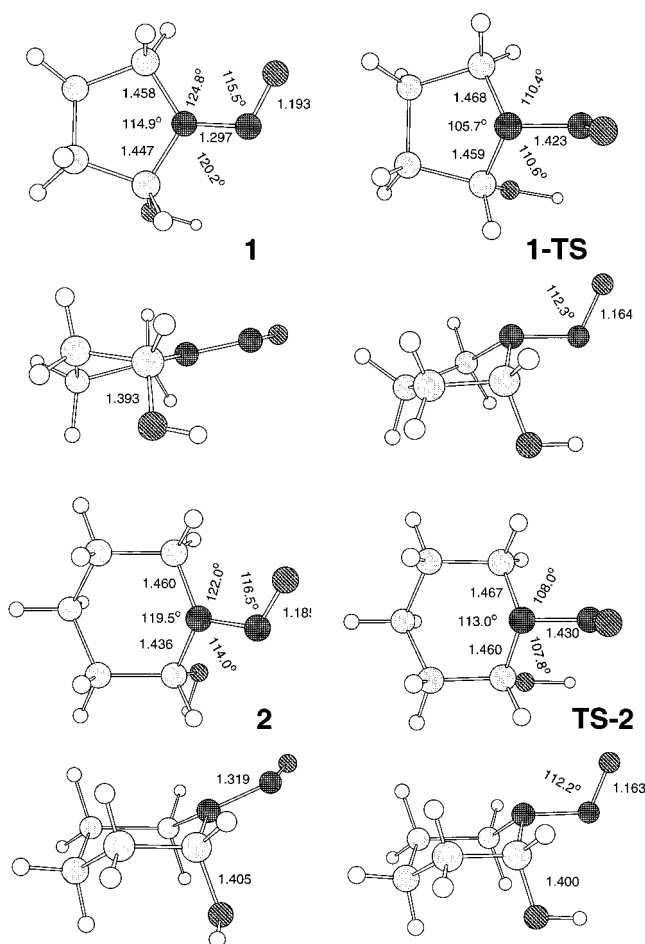
chemical questions of intermolecular interaction, the electrostatic potential of a molecule plays a critical role and there are several ways to derive atomic charges such that they reproduce the electrostatic field. We computed two sets of electrostatic-potential derived charges based on the CHELPG method<sup>15</sup> as well as the Merz–Kollman–Singh (MKS) method.<sup>16</sup> The methods mostly differ in the definition of the areas and the method of discretization for which the electrostatic potential is computed.<sup>17</sup> All of the electronic structure analysis were carried out at the MP2(fc)/6-31G\*/RHF/6-31G\* level.

## Results and Discussion

### $\alpha$ -Hydroxy-*N*-nitrosamines and *N*-Nitrosiminium Ions.

The parent nitrosammonia, H<sub>2</sub>N–NO, is of special interest in atmospheric chemistry and it has been studied in very much detail.<sup>18</sup> *Ab initio* calculations of *N*-nitrosamines are scarce and they were investigated only at rather modest computational levels. *N*-nitrosomethylamine and *N*-dimethylnitrosamine were studied at the RHF/6-31G\*/RHF/3-21G level,<sup>19</sup> and, more recently, the results of photoelectron spectroscopic studies of dialkylnitrosamines (R = methyl, ethyl, propyl) were reported and RHF/6-31G\* data were employed for the assignments of the spectra.<sup>20</sup> Thompson et al. reported theoretical studies of nitrosamine chemistry at the RHF level with split-valence basis sets.<sup>21</sup> Calculations on dimethylnitrosamine and its metabolite hydroxydimethylnitrosamine were reported,<sup>21a</sup> and methylnitrosamine and the decomposition of hydroxymethylnitrosamine were studied in detail.<sup>21b</sup> Sapse et al.<sup>22</sup> studied dimethylnitrosamine, their isomeric hydroxydimethylnitrosamines and their ester conjugates using RHF/6-31G\* structures and with MP2/6-31G\*/RHF/6-31G\* energy calculations. In particular, several nitrosiminium ions were considered in this study, albeit at the much lower level RHF/3-21G, and the energy difference between *E*- and *Z*-isomers was found to be very small. The authors also studied nucleophilic addition reactions to nitrosiminium ions.<sup>23</sup> With the level chosen for our present study, MP4(SDTQ)/6-31G\*/RHF/6-31G\* and including vibrational analysis, we are exceeding greatly any of the previously employed theoretical levels even though the molecules we are interested in are larger.

The optimized structures of  $\alpha$ -hydroxy-*N*-nitrosopyrrolidine, **1**, and of  $\alpha$ -hydroxy-*N*-nitrosopiperidine, **2**, are shown in Figure 1. In both cases we optimized the structure in which the nitroso O-atom and the hydroxyl group are on opposite sides of the N–N bond. We are interested in learning about the intrinsic differences of the energies associated with the formations of the respective *N*-nitrosiminium ions. With the choice of configuration made, we ensure that unwanted hydrogen-bonding



**Figure 1.** Structures of  $\alpha$ -hydroxy-*N*-nitrosopyrrolidine, **1**, and of  $\alpha$ -hydroxy-*N*-nitrosopiperidine, **2**, are shown to the left. The structures shown on the right are the transition state structures for rotation about the N–N bonds.

interactions do not complicate the interpretation.<sup>21a</sup> Furthermore, in both structures the hydroxyl groups are in positions that are best described as axial. These are the structures that can reasonably well be expected to undergo unimolecular dissociation with the least activation because of optimal orbital alignment.

The structures of *N*-nitrosiminium ions **3** and **4** derived from **1** and **2**, respectively, are shown in Figure 2. In the spirit described for the neutral compounds, for **3** and **4** we considered the geometrical isomers that contain trans-configured four-center  $\pi$ -systems. The NN bond lengths in **3** and **4** are 1.441 and 1.457 Å, respectively. In an earlier report it was stressed that the NN bonds in nitrosiminium ions are very long (>1.58 Å) and the conclusion was put forth that nitrosiminium ions should be considered as ion–molecule complexes between NO<sup>+</sup> and an imine.<sup>22</sup> Our results show that the long NN bonds found earlier are artifacts of the RHF/3-21G level used in that work. Our electron density analysis will clarify the charge distribution (vide infra). The C–N bond lengths in the iminium ions are 1.273 and 1.275 Å and these values can be compared to results of X-ray structure analysis of iminium salts. Knop et al.<sup>24</sup> reviewed available X-ray structures of iminium salts and found a range of CN distances 1.264–1.302 Å with a mean of 1.283 Å and indicative of a C=N double bond. More recently reported solid-state structures of iminium ions also fall into this range.<sup>25,26</sup>

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(21) (a) Shancke, A.; Thompson, C. *Int. J. Quantum Chem.* **1982**, *21*, 431. (b) Reynolds, C. A.; Thompson, C. *J. Mol. Struct. (THEOCHEM)* **1986**, *138*, 131. (c) Bonaccorsi, R.; Tomasi, J.; Reynolds, C. A.; Thompson, C. *J. Comput. Chem.* **1988**, *9*, 779.

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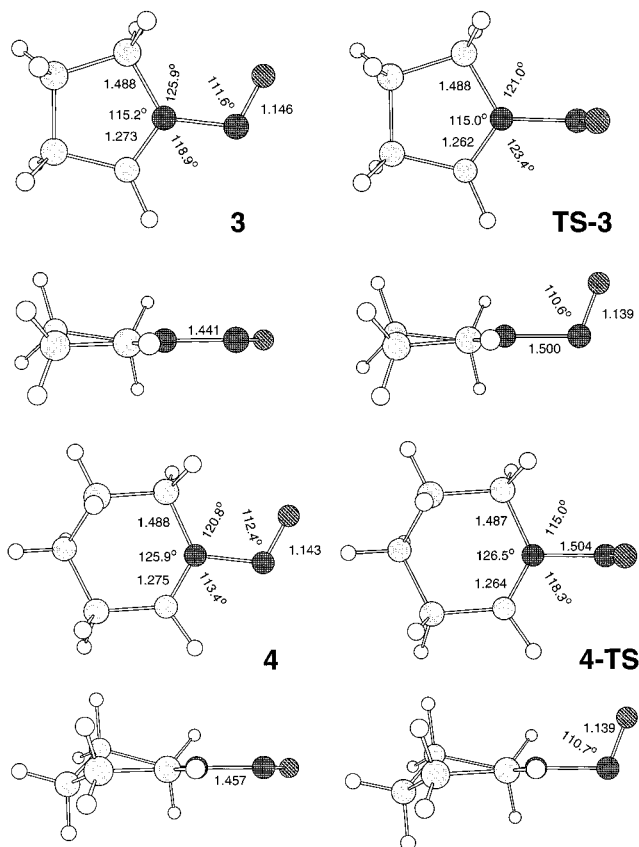
**Table 3.** Structural Parameters

parameter	5-ring			6-ring			neutrals	cations
	1	3	$\Delta(3-1)$	2	4	$\Delta(4-2)$	$\Delta(2-1)$	$\Delta(4-3)$
N–O	1.193	1.146	–0.047	1.185	1.143	–0.042	–0.008	–0.003
N–N	1.297	1.441	0.144	1.319	1.457	0.138	0.022	0.016
(HO)HC–N	1.447	1.273	–0.174	1.436	1.275	–0.161	–0.011	0.002
H <sub>2</sub> C–N	1.458	1.488	0.030	1.460	1.488	0.028	0.002	0
N–N–O	115.5	111.6	–3.9	116.5	112.4	–4.1	1.0	0.8
(HO)HC–N–N	120.2	118.9	–1.3	114.0	113.4	–0.6	–6.2	–5.5
H <sub>2</sub> C–N–N	124.6	125.9	1.3	122.0	120.8	–1.2	–2.6	–5.1

parameter	5-ring			6-ring			neutrals	cations
	1-TS	3-TS	$\Delta(3-1)_{TS}$	2-TS	4-TS	$\Delta(4-2)_{TS}$	$\Delta(2-1)_{TS}$	$\Delta(4-3)_{TS}$
N–O	1.164	1.139	–0.025	1.163	1.139	–0.024	–0.001	0.000
N–N	1.423	1.500	0.077	1.430	1.504	0.074	0.007	0.004
(HO)HC–N	1.459	1.262	–0.197	1.460	1.264	–0.196	0.001	0.002
H <sub>2</sub> C–N	1.468	1.488	0.020	1.467	1.487	0.020	–0.001	–0.001
N–N–O	112.3	110.6	–1.7	112.2	110.7	–1.5	–0.1	0.1
(HO)HC–N–N	110.6	123.4	12.8	107.6	118.3	10.7	–3.0	–5.1
H <sub>2</sub> C–N–N	110.4	121.0	10.6	108.0	115.0	7.0	–2.4	–6.0

<sup>a</sup> Bond lengths are in angstroms, and bond angles, in degrees.



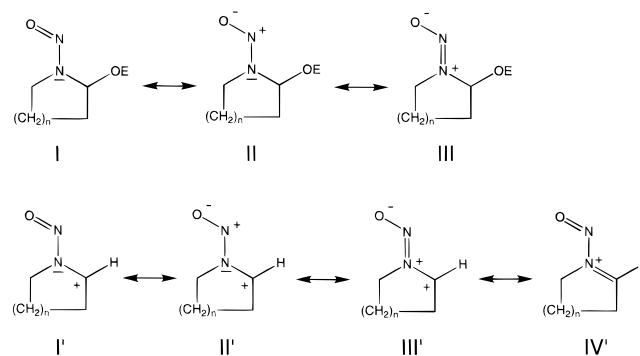
**Figure 2.** Structures of the nitrosiminium ions **3** and **4** derived from  $\alpha$ -hydroxy-*N*-nitrosopyrrolidine, **1**, and  $\alpha$ -hydroxy-*N*-nitrosopiperidine, **4**, are shown to the left. The structures shown on the right are the transition-state structures for rotation about the N–N bonds in the *N*-nitrosiminium ions.

**Structural Relaxation upon Ionization and Valence Bonds Descriptions.** Some of the more important structural parameters are tabulated in Table 3 together with the changes of these values associated with bond cleavage,  $\Delta(3-1)$  and  $\Delta(4-2)$ . The values  $\Delta(2-1)$  and  $\Delta(4-3)$  allow for an assessment of the ring-size effects on the neutral molecules and the cations, respectively.

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**Scheme 2.** Resonance Forms Used in the VB Description of *N*-Nitrosamines (**I–III**) and of *N*-Nitrosiminium Ions (**I'–IV'**)



Ring-size affects the endocyclic angles but the changes of these angles upon ionization are almost the same. Changes of bond lengths due to ionization are a magnitude larger than are differences among the nitrosamines or the iminium ions. The main structural changes associated with ionization are an elongation of the N–N bond length and a shortening of the N–C bond length. The latter effect is more pronounced and both effects are more pronounced for the smaller ring.

The structural trends can be understood qualitatively in terms of valence bond theory and considering the resonance forms shown in Scheme 2. The nitroso group is the *N*-analogue of the carbonyl group, O=N– vs O=C<, and the O=N– polarity is accounted for by consideration of resonance forms **I** and **II**. The amino *N*-atom in the nitrosamines is nearly planar and may engage in N→NO  $\pi$ -dative bonding as indicated by resonance form **III**. In the cations, the delocalization of the amine *N*-lone pair toward the electron-depleted *N*-atom of the NO group, **I'–III'**, would seem to present less of an option since such dative bonding would place positive charge next to a carbocationic center. Contributions from **III'** should therefore be less significant and N→C  $\pi$ -dative bonding, **IV'**, should occur instead. The stabilization of the positive charge in iminium ions is known to be very effective. Iminium salts not only exist in solids (vide supra) but Mayr et al.<sup>27</sup> have recently provided NMR spectroscopic evidence that iminium ion pairs exist even in polar solvents.

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**Table 4.** Population Analysis

mol.	method	O	(O)N	(ON)N	(N)-CH	NO	NCH	$\Sigma$
<b>1</b>	NPA	-0.384	0.184	-0.265	0.493	-0.200	0.228	0.028
	CHELPG	-0.221	-0.228	0.311	0.143	-0.449	0.454	0.005
	MKS	-0.221	-0.261	0.410	0.142	-0.482	0.552	0.070
<b>2</b>	NPA	-0.364	0.205	-0.279	0.502	-0.159	0.223	0.064
	CHELPG	-0.192	-0.173	0.125	0.374	-0.365	0.499	0.134
	MKS	-0.187	-0.193	0.193	0.261	-0.380	0.454	0.074
<b>3</b>	NPA	-0.132	0.334	-0.212	0.574	0.202	0.362	0.564
	CHELPG	0.045	-0.031	0.308	0.241	0.014	0.549	0.563
	MKS	0.042	-0.053	0.397	0.242	-0.011	0.639	0.628
<b>4</b>	NPA	-0.132	0.329	-0.213	0.559	0.197	0.346	0.543
	CHELPG	0.040	-0.026	0.351	0.187	0.014	0.538	0.552
	MKS	0.039	-0.043	0.444	0.137	-0.004	0.581	0.577
<b>1-TS</b>	NPA	-0.209	0.252	-0.456	0.270	0.043	-0.186	-0.143
	CHELPG	-0.096	0.061	-0.358	0.274	-0.035	-0.084	-0.119
	MKS	-0.091	0.043	-0.297	0.293	-0.048	-0.004	-0.052
<b>2-TS</b>	NPA	-0.206	0.252	-0.457	0.467	0.046	0.010	0.056
	CHELPG	-0.079	0.013	-0.337	0.233	-0.066	-0.104	-0.170
	MKS	-0.065	-0.016	-0.285	0.212	-0.081	-0.073	-0.154
<b>3-TS</b>	NPA	-0.098	0.372	-0.214	0.503	0.274	0.289	0.563
	CHELPG	0.073	0.052	0.100	0.251	0.125	0.351	0.476
	MKS	0.080	0.039	0.148	0.259	0.119	0.407	0.526
<b>4-TS</b>	NPA	-0.104	0.367	-0.208	0.488	0.263	0.280	0.543
	CHELPG	0.071	0.047	0.018	0.316	0.118	0.334	0.452
	MKS	0.077	0.033	0.064	0.294	0.110	0.358	0.468

**Ring-Size Dependence of the Dissociation Energy.** The energy  $\Delta E_{\text{diss}} = (1-3) - (2-4)$  is the difference in the dissociation energies of **1** and **2**. The  $\Delta E_{\text{diss}}$  values show the dissociation to be more endothermic for **1** than for **2** at all levels and at the highest level  $\Delta E_{\text{diss}}$  is  $-7.96$  kcal/mol. Inclusion of corrections for thermal motions has only a very small effect.

The computations reproduce the preferential formation of the *N*-nitrosiminium ion of the six-membered ring compared to the five-membered ring. Calculations and experiment even agree relatively well on the magnitude of this preference. The consideration of the transition-state structures for rotation about the *N*-*N* bonds in **1**-**4** allows one to determine the cause for the more facile formation of the six-membered ring nitrosiminium ion.

**Rotational Transition State Structures and Rotational Barriers of  $\alpha$ -Hydroxy-*N*-nitrosamines and of *N*-Nitrosiminium Ions.** The rotations about the *N*-*N* bond in nitrosamines and in nitrosiminium ions are hindered as the result of *N*→*NO*  $\pi$ -dative bonding (Scheme 2). One way to quantify the strengths of these dative bonds is by way of the activation barrier to rotation. Calculations and measurements of the rotational barriers of some symmetrical nitrosamines<sup>28</sup> gave barriers of 19–23 kcal/mol which equals about one-third of the energy of a *N*=*N*  $\pi$ -bond.<sup>29</sup> The only previous report of rotational barriers in nitrosiminium ions (6–8 kcal/mol) is based on RHF/3-21G energy data computed for nonoptimized structures.<sup>22</sup>

The rotation about the *N*-*N* bond in the nitrosamines may follow two pathways. The rotation may be such that the nitroso *O*-atom either approaches or avoids a close approach of the hydroxyl substituent. The latter path is the one desired in the present study since we are interested in that rotational transition state structure that will allow for the best estimate of the double-bond character of the *NN* bond in **1** and **2**. These transition state structures **1-TS** ( $i252$   $\text{cm}^{-1}$ ) and **2-TS** ( $i187$   $\text{cm}^{-1}$ ) were located, and they are shown to the right in Figure 1. Structures

**1-TS** and **2-TS** contain pyramidal amine *N*-atoms and the *N*-lone pair is axial and points away from the hydroxyl group. We have also located transition state structures in which the *N*-lone pair is pointed in the opposite direction; they are slightly higher in energy and their discussion is omitted for brevity. In both structures **1-TS** and **2-TS**, the hydroxyl *H*-atom is oriented in a way that brings this *H*-atom in best contact with the *N*-lone pair but the *H*⋯*N* distances remain 2.498 (**1-TS**) and 2.365 Å (**2-TS**) and too long for a strong *H*-bond.

The transition state structures for the rotations about the *N*-*N* bonds in the cations are shown in Figure 2 as **3-TS** ( $i158$   $\text{cm}^{-1}$ ) and **4-TS** ( $i167$   $\text{cm}^{-1}$ ). The structural changes associated with rotation are relatively minor except for the angular changes at the iminium *N*-atom. In **3** and **4**, the *C*=*N*-*N* angle is significantly less than the *C*-*N*-*N* angle while these angles become more equal in the transition state structures.

The activation barriers are found to be relatively insensitive to the choice of the theoretical level. The activation barriers computed at the highest level are 24.3 and 17.9 kcal/mol for the neutral five- and six-membered rings systems, respectively. The barriers both are reduced slightly if thermal motions are considered. Why is the barrier about 6.3 kcal/mol less for the six-membered ring system? Apparently the *N*-lone pair in the piperidine derivative does not mind localization in the transition-state structure as much as in the case of the pyrrolidine or the *N*-lone pair is less prone to delocalize in the minimum structure of the six-ring compared to the five-ring. Consideration of ring strain in the pyrrolidine suggests the latter effect. Enhanced delocalization of the *N*-lone pair favors *N*-*sp*<sup>2</sup> hybridization, relieves ring strain, and provides an incentive for higher *N*→*NO*  $\pi$ -dative bonding in **1**.

The activation barriers computed for the cations are much lower than for the neutral species, and they differ much less from each other. In the cations, the delocalization of the amine *N*-lone pair toward the electron-depleted *N*-atom of the *NO* group is less of an option since such dative bonding would place positive charge right next to a carbocationic center. Contributions from **III'** should be less significant and *N*→*C*  $\pi$ -dative bonding, **IV'**, should occur instead. The rotational barriers of **3** and **4** are less than one-third of the barriers found for the neutral

(28) (a) *N*-Nitrosodimethylamine: Harris, R. K.; Spragg, R. A. *Chem. Commun.* **1967**, 362. (b) *N*-Nitrosodiethylamine: Lunazzi, L.; Cerioni, G. *J. Am. Chem. Soc.* **1976**, 98, 7884. (c) *N*-Nitrosodiphenylamine: Forlani, L.; Lunazzi, L. *Tetrahedron Lett.* **1979**, 1451.

(29) MNDO study of rotational barriers: Dai, Q.; Fu, X. *J. Mol. Struct. (THEOCHEM)* **1993**, 280, 117.

systems **1** and **2**. In the case of the cations, both ring sizes are perfectly able to accommodate the endocyclic double bond and the rotational barrier for the six-ring is only 1.4 kcal/mol higher than for the five-ring system.

The computed rotational barriers thus reveal the origin of the lower reactivity of  $\alpha$ -hydroxy-*N*-nitrosopyrrolidine, **1**, as compared to  $\alpha$ -hydroxy-*N*-nitrosopiperidine, **2**. The amino N-lone pair is engaged more in N $\rightarrow$ NO  $\pi$ -dative bonding in **1** than in **2**. This extrastabilization of 6.3 kcal/mol of **1** needs to be overcome in the formation of **3**. This effect accounts for most of the difference in the ionization energies ( $\sim 80\%$ ). The difference in the dissociation energies of **1** and **2** in the absence of N $\rightarrow$ NO  $\pi$ -dative bonding is given by the energy  $\Delta E_{\text{diss}} = (\mathbf{1-TS} - \mathbf{3-TS}) - (\mathbf{2-TS} - \mathbf{4-TS})$  and this energy is merely  $-1.94$  kcal/mol (Table 2).

**Structural Relaxation in the Presence and Absence of N $\rightarrow$ NO  $\pi$ -Dative Bonding.** The data presented in Table 3 allow for a comparison of the structural effects of ionization at the  $\alpha$ -position in the presence (**1-4**) or absence (**1-TS-4-TS**) of N $\rightarrow$ NO  $\pi$ -dative bonding. As with the minima, the main structural changes associated with the ionization in the absence of N $\rightarrow$ NO  $\pi$ -dative bonding are an elongation of the N-N bond length and a shortening of the N-C bond length. The N-N bond length elongations are about one-half of the respective bond length changes in the true ionization reactions. The shortenings of the N-C bonds are about 15% more pronounced in the hypothetical reaction of the rotameric transition state structures. These data show that the N-N bond lengthens upon ionization at the  $\alpha$ -position irrespective as to whether there was any N $\rightarrow$ NO dative bonding to begin with! Note that the NN bond elongation in going from **1-TS** to **3-TS** (or from **2-TS** to **4-TS**) is moderated by the simultaneously occurring N-rehybridization. One would then have to conclude that *at least* half of the N-N elongation associated with the ionizations of **1** and **2** have causes other than the cleavage of N $\rightarrow$ NO  $\pi$ -dative bonding! It is also noteworthy that the C-N bonds in the cations that do not allow for N $\rightarrow$ NO  $\pi$ -dative bonding (**3-TS** and **4-TS**) are only about 0.011 Å shorter than in the cations that do allow for N $\rightarrow$ NO  $\pi$ -dative bonding (**3** and **4**). This observation demonstrates in a compelling fashion that amine N $\rightarrow$ NO dative bonding is much less significant compared to N $\rightarrow$ carbocation dative bonding in *N*-nitrosiminium ions.

**Electronic Structure Analysis.** Pertinent results of the three types of electronic structure analyses (NBO, CHELPG, MKS) are summarized in Table 4. We give the charges of the heteroatoms and of the  $\alpha$ -CH groups and we also provide the charges of the NO group and the NCH fragments and the total charge of the ONNCH fragment.

Irrespective of the method employed to determine the charges, a few general statements can be made. First, the total charge of the ONNCH fragment in the *N*-nitrosamines **1** and **2** is slightly positive. There is the expected electron accumulation on the heteroatom group ONN but the hydroxyl group's electron

density withdrawal is larger. Ionization generates the ions **3** and **4** with ONNCH fragment charges that are significantly less than unity, they vary in the range 0.50–0.65. Hence a rather significant part of the positive charge is distributed onto the hydrocarbon fragments by way of  $\sigma$ -polarization. This important fact is entirely neglected in discussions that are limited to the consideration of the  $\pi$ -pushing resonance forms shown in Scheme 2. Second, all methods agree that ionization at the  $\alpha$ -position is accompanied by a large reduction of the electron density of the NO group and this is true in the presence and in the absence of N $\rightarrow$ NO conjugation. Third, all methods show that the ionization at the  $\alpha$ -position is accompanied by a larger reduction of the electron density of the NO group for the five-membered ring system than for the six-membered ring system. The electron density depletion of the NCH fragment is only about one-third of the depletion of the NO group. These results corroborate that polarizations in the  $\sigma$ -system are highly important and that the ionization of the five-ring system requires more electron density withdrawal from the NO group.

Even though there are these same trends in all three methods, one does have to realize that the NBO analysis and the electrostatic methods differ greatly in the way they describe the polarization patterns. For the nitrosamines, for example, the NBO analysis shows strong charge alterations O(-)-N(+)-N(-)-CH(+) while the CHELPG and MKS analyses would indicate a charge distribution of the type O(-)-N(-)-N(+)-CH(+). For bonding issues, clearly the former method is to be preferred. Only the NBO method correctly reflects the known polarity of the NO group, for example. We shall therefore consider the NBO charges in detail for the ionization of **1** and **2**. The NO charge is more negative in **1** ( $-0.200$ ) than in **2** ( $-0.159$ ) and the NO charge changes more during the ionization of **1** ( $0.402$ ) than the ionization of **2** ( $0.356$ ). We can assess the effects of conjugation of the NO group again by inspection of the charge relaxation of the hypothetical ionization reactions of the transition-state structures. It can be seen that the NO charges are much less in **1-TS** ( $0.043$ ) and **2-TS** ( $0.046$ ), that they are about the same, and that the NO charge changes during the ionization of **1-TS** ( $0.231$ ) and **2-TS** ( $0.217$ ) to form ions **3-TS** and **4-TS**, respectively, are smaller and more comparable to each other. These findings show that ionization causes a flow of electron density from the NO group to the developing carbocationic center and that the charge flow is larger if the NO group is in a conformation suitable for conjugation.

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