The 5-Hydroxy-1,2,3-oxadiazolinium Ion: Neighboring Group Interaction between *N*-Nitroso and Aldehyde Carbonyl

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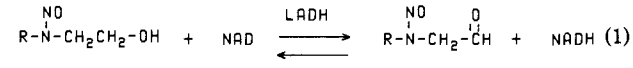
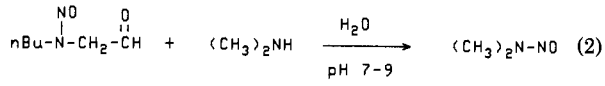
Abstract: A set of MNDO calculations performed to explore possible neighboring group interaction between the *N*-nitroso group and a β-aldehyde carbonyl demonstrated the formation of the stable 5-hydroxy-3-methyl-1,2,3-oxadiazolinium cation **6** from the protonated aldehyde. This prediction was experimentally verified and the structure of **6** confirmed by X-ray methods and NMR. MNDO predicts that the ring will spontaneously open upon deprotonation. The MNDO derived stable conformations of methyl- and ethyl(2-hydroxyethyl)nitrosamine and methyl- and ethyl(2-oxoethyl)nitrosamine are given. MNDO was more successful in predicting the *Z*:*E* isomer ratios of the ethanol nitrosamines than of the ethanal nitrosamines.

α-Nitrosamino aldehydes are highly reactive compounds.[1-4] Because they can be produced from the alcohol dehydrogenase-mediated oxidation of the parent alcohols (eq 1), they could be

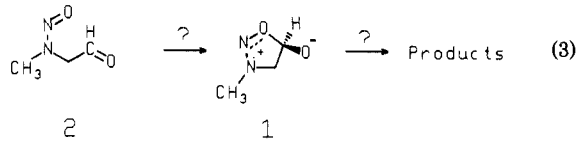


significant in the carcinogenesis and mutagenic properties of these substances.[2-8] In the course of a fundamental investigation into the properties of α-nitrosamino aldehydes, we discovered two unusual chemical characteristics of these compounds. In the first case they enter into transnitrosation reactions with great ease. The nitroso group of an α-nitrosamino aldehyde can be transferred either to a secondary or a primary amine without catalysis[1-3] (eq 2). The reaction occurs rapidly in benzene and more slowly in



aqueous solution. In the second case, α-nitrosamino aldehydes have been shown to decompose spontaneously in aqueous and organic solvents to produce a product mixture that is characteristic of those obtained from the decomposition of diazonium ions. An aryl diazonium ion has been trapped in the decomposition of an appropriate α-nitrosamino aldehyde[1] (Scheme I).

In rationalizing the unusual behavior of these α-nitrosamino aldehydes, we have considered the possible role of a 1,2,3-oxadiazolinium intermediate **1** (eq 3). Examination of the NMR data for a set of β-functional nitrosamines reveals an unusual distribution of *Z*-*E* isomers for compounds that have a carbonyl group in the β-position[4] (see Table I). *Z*-*E* isomer ratios in unsymmetrical nitrosamines are known to be predominantly influenced by steric factors. The oxygen preferentially orients itself away from the larger *N* substituent.



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For example, methyl(2-hydroxyethyl)nitrosamine exists 83% in the *E* form. In contrast, the corresponding aldehyde exists predominantly in the *Z* form (54%). The interesting change in the *Z*-*E* preference accompanying the change in oxidation state of the β-functional group of these nitrosamines is even more pronounced in the case of the butyl nitrosamines (see Table I). The ^{13}C NMR chemical shifts for the aldehyde carbons in the *Z* and *E* isomers of methyl(2-oxoethyl)nitrosamine are found at 194 and 196 ppm.[2] While these shifts are somewhat upfield for aldehydes, their similar magnitude rules out significant ground state covalent interaction between the nitroso oxygen and the carbonyl carbon in the solvents investigated (D_2O, C_6D_6, $CDCl_3$). Nevertheless, the possibility of intramolecular interaction between the carbonyl carbon and the nitroso oxygen has been considered as a possible kinetic factor in the unusual characteristics of these compounds.

In order to explore further the possible interaction between the nitroso oxygen and the carbonyl carbon, we have performed a set of MNDO calculations (1) to establish whether the *Z*-*E* isomer ratios in nitrosamino alcohols and nitrosamino aldehydes can be modeled and (2) to determine whether these calculations predict any bonding between the *N*-nitroso and carbonyl functions. We report here the theoretical prediction and experimental verification of the formation of the 5-hydroxy-1,2,3-oxadiazolinium cation from carbonyl oxygen protonated α-nitrosamino aldehyde.

Scheme I

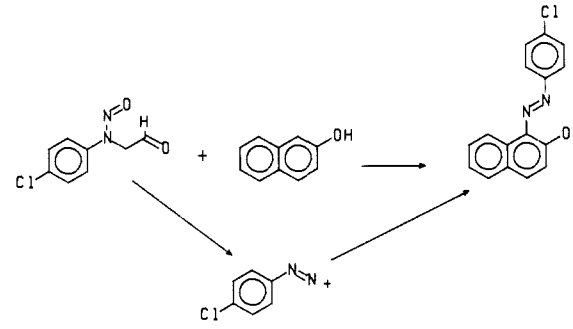
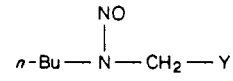


Table I. *Z*/*E* Ratios for Butyl β-Oxidized Nitrosamines



Substituent	*Z*/*E* Ratio
$-CH_2OH$	58:42
$-CHO$	90:10
$-COC_3$	85:15
$-CO_2H$	80:20
$-CO_2CH_3$	77:23

MNDO Calculations and Nitrosamine *Z*-*E* Ratios

The calculations reported here were done in two steps. First, a general survey of the configuration space was performed with

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(2) Loeppky, R. N.; Tomasik, W.; Kerrick, B. E. *Carcinogenesis* **1987**, *8*, 941.
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(7) Chung, R. L.; Hecht, S. S. *Carcinogenesis* **1985**, *6*, 1671-1673.
(8) Airoldi, L.; Bonfanti, M.; Fanelli, R.; Bove, B.; Benfenati, E.; Gariboldi, P. *Chem-Biol. Interact.* **1984**, *51*, 103-113.

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Table II. MNDO Computed Conformer ΔH_f, Populations, and Dipole Moments of (2-Hydroxyethyl)nitrosamines

ethyl(2-hydroxyethyl)nitrosamine				methyl(2-hydroxyethyl)nitrosamine			
isomer[a]	ΔH_f, kcal/mol	conform, %	dipole moment, D	isomer	ΔH_f, kcal/mol	conform, %	dipole moment, D
3Za	−55.45	22.9	2.43	**2Za**	−50.41	23.5	2.35
3Zc	−54.84	8.1	2.66	**2Zc**	−49.85	9.0	2.60
3Zar	−54.70	6.5	2.35	**2Zb**	−49.70	7.0	3.90
3Zb	−54.65	5.9	3.97	**2Ea**	−50.66	35.6	3.02
3Zcr	−54.20	2.8	2.74	**2Ec**	−50.04	12.4	2.66
3Zbr	−54.06	2.2	3.99	**2Eb**	−50.04	12.4	4.21
3Ea	−55.45	23.0	2.91				
3Ec	−54.95	9.8	2.49				
3Eb	−54.79	7.5	4.14				
3Ear	−54.61	5.6	2.90				
3Ecr	−54.32	3.4	2.35				
3Ebr	−54.10	2.3	4.15				

[a] Number and letter designations refer to structure numbers and conformer letters in Figure 1. The **r** designation refers to the conformers generated by a 180° rotation around the ethyl C–N bond.

Table III. MNDO Computed Conformer ΔH_f, Populations, and Dipole Moments of (2-Oxoethyl)nitrosamines

ethyl(2-oxoethyl)nitrosamine				methyl(2-oxoethyl)nitrosamine			
isomer[a]	ΔH_f, kcal/mol	conform, %	dipole moment, D	isomer	ΔH_f, kcal/mol	conform, %	dipole moment, D
5Zd	−35.14	35.2	3.73	**4Zd**	−30.08	44.0	3.65
5Zdr	−34.61	14.4	3.86	**4Ze**	−29.15	9.1	3.99
5Zf	−34.18	7.0	4.03	**4Ed**	−29.71	23.5	3.90
5Zfr	−33.83	3.8	4.04	**4Ef**	−29.51	16.9	2.18
5Ed	−34.74	17.9	3.92	**4Ee**	−28.95	6.5	3.54
5Ef	−34.50	12.1	2.32				
5Ee	−34.06	5.7	3.52				
5Eer	−33.85	4.0	3.70				

[a] Number and letter designations refer to structure numbers and conformer letters in Figure 2. The **r** designation refers to the conformers generated by a 180° rotation around the ethyl C–N bond.

a MNDO program adapted for use on a microcomputer.[9] To simplify the optimization process in this initial investigation, the nitrosamine skeleton was fixed in a planar configuration. Then, when we had obtained a good idea of which structures were most likely to be stable and to contribute significantly to the thermal configuration distribution, we began a systematic reoptimization, making no assumptions concerning skeletal planarity or molecular symmetry. This second step utilized a more sophisticated program[10] which, in addition, yielded eigenvalues of the Hessian matrix associated with the converged geometry. For all structures reported here, the resulting Hessian matrices were found to have only positive eigenvalues, and so these structures indeed may be deemed true local minima.

Although it was originally parametrized for H, B, C, N, O, and F and later for a number of the other elements, MNDO does not include any NO compounds in its reference set of molecules.[11] As a result, the uncertainty associated with NO bond lengths and RNO bond angles in the optimized structure could be slightly greater than these same parameters in a typical hydrocarbon. Nevertheless, both structural parameters[12] and ΔH_f[13] for dimethylnitrosamine were calculated as a check and found to be in excellent agreement with the experimental data[12,13] (ΔH_f = −0.8 ± 2 (exptl), 2.1 kcal/mol (calcd).

Calculations were performed for all of the evident stable conformations of both the *Z* and *E* isomers of methyl(2-hydroxyethyl)nitrosamine (**2**), ethyl(2-hydroxyethyl)nitrosamine (**3**), methyl(2-oxoethyl)nitrosamine (**4**), and ethyl(2-oxoethyl)nitrosamine (**5**). In each case, heats of formation and other relevant properties were calculated in order to obtain the likely minimum energy conformations. The structure of the most stable conformation of each compound is given in Figure 1, and the structure of the other significant rotamers of each is also depicted (Figure 2). The calculated heats of formation and dipole moments

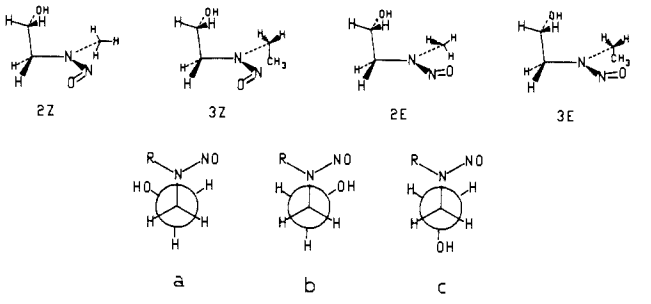

Figure 1. The most stable conformers of each of the (2-hydroxyethyl)-nitrosamines are given in the top row. The O–N–N and the two attached carbons are coplanar. The 2-hydroxyethyl and ethyl C–C bonds are perpendicular to this plane as shown. Minor conformers exist (see Table II) where the ethyl group is rotated 180° from that shown above. The stable rotamers with respect to the 2-hydroxyethyl C–C bond are given in the second row.

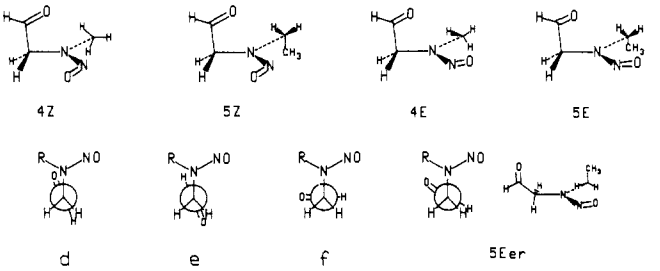

Figure 2. The most stable conformers of each of the (2-oxoethyl)-nitrosamines are given in the top row. The O–N–N and the two attached carbons are coplanar. The 2-oxoethyl and ethyl C–C bonds are perpendicular to this plane as shown. Minor conformers exist (see Table III) where the ethyl group is rotated 180° from that shown above. In the case of **5Er** the C–O C–N dihedral angle is 45°, while the C–C N–N dihedral angle is 55°. The stable rotamers with respect to the 2-oxoethyl C–C bond are given in the second row.

for these conformers are presented in Tables II and III. It can be seen that the stable conformers are similar for all of the compounds, although the *Z* or *E* orientation of the nitroso function

(9) Thiel, W. *QCPE* **1978**, *19*, 353.
(10) Dewar, M.J. S.; Stewart, J. J. P. *QCPE Bull.* **1987**, *7*, 85.
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(12) Krebs, B.; Mandt, J. *Chem. Ber.* **1975**, *108*, 1130.
(13) Korsunski, B. L.; Pepekin, V. I.; Lebedev, Y. A.; Apin, A. Y. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1967**, (*3*), 525.

affects aldehyde conformations somewhat as is discussed below. The dihedral angle between the C1–C2 bond and the NNO plane is very close to 90° for both the alcohols and the aldehydes. The C–C bond of the ethyl group prefers a similar orientation, except that it is perpendicularly directed toward the opposite face of the molecule (dihedral angle 270°).

The lowest energy conformers (**2Z**, **2E**, **3Z**, **3E**) of the alcohols with respect to the ethanol moiety are identical. The OH group is gauche to the C–N bond (see Figure 2). This arrangement is known to be (from both ab initio calculations[14] and experimental determinations[15]) the most stable conformer for 1-propanol and related β-substituted ethanols which have more polar substituents at this position. This conformational preference in propanol (compared to that where the OH and CH_3 are anti) has been related to intramolecular dipolar attraction[14] which arises from the induction of a dipole in the C2–C3 bond. In our case this dipole already exists. It is interesting that MNDO predicts the anti conformation of 1-propanol to be slightly more stable than the gauche in contrast to ab initio results. The energy differences between these conformers is small in all cases. Experimental observations fail to show any intramolecular hydrogen bonding in (2-hydroxyethyl)nitrosamines and our MNDO calculations also do not demonstrate this interaction.

The conformational preference for each of the (2-oxoethyl)-nitrosamines with respect to the ethanal moiety is similar for each compound (see Figure 2), and the lowest energy conformer (type **d**) is close to what is found for propanal.[14] In propanal, the carbonyl oxygen eclipses the C–CH_3 bond, while in **4** and **5** it is the C–N bond that is nearly eclipsed (**4** and **5Z**, ~8°; **4** and **5E**, ~25°). Preference for this conformer in propanal is thought to result from a combination of avoidance of H eclipsed repulsion (ethane-like barrier) and a O=C C—CH_3 dipolar attraction resulting from a carbonyl induced dipole in the C–C bond.[14] (This attractive interaction has also been described in MO terms as a mixing of the C–C (here C–N) σ and σ* orbitals under the influence of the C=O electric field, which gives it an angular dependence and explains the preference for the next more energetic conformer (type **e**)). The preference for conformer **d** among the nitrosamino aldehydes can easily be rationalized by means of attractive dipolar interactions because of the opposing polarities of the C—N and C=O bonds (N is δ+ due to the delocalization of the unshared pair by N=O).

While conformer types **d** and **e** are the only minima found for propanal, our calculations show an additional conformer **f** in the nitrosamino aldehydes. (It should be noted that, in contrast to our experience with the (2-hydroxyethyl)nitrosamines, considerable difficulty was encountered in optimizing the structures of the corresponding aldehydes due to the presence of broad minima in the potential hypersurfaces with respect to changes in dihedral angle of the carbonyl.) The stability of **f** is determined by the orientation of the nitroso group. It is not a stable conformer in the case of **4Z** or **5Z**. In the case of **5Z**, rotation of the methyl group to the front face of the molecule (dihedral angle 90°) also produces a change in the dihedral angles of the ethanal moiety, as is shown in Figure 1. The carbonyl dihedral angle increases to 45° and the C1–C2–N–N dihedral angle contracts to 55°, and no other stable conformers are found for **5Z** (rotated).

The **Z–E** isomerization barrier for nitrosamines is high and has been determined for a number of compounds.[16] As is the case for amides (nitrosamines are amides of nitrous acid), this barrier is attributed to π-electron delocalization of the amine nitrogen unshared pair. The *Z*/*E* isomer ratios for unsymmetrical nitrosamines can easily be determined by NMR or HPLC. The isomeric ratios of nitrosamino alcohols and aldehydes, determined for completely equilibrated samples in several solvents by ^1H NMR, are given in Table IV. The alcohol *Z*–*E* ratios are not remarkable as they reflect the general observation that this ratio is governed principally by the steric bulk of the N-bound substituents. The aldehydes, on the other hand, show a clear preference for the *Z* isomer and this preference is enhanced in solvents of high dielectric constant.

Table IV. Percent *Z* Isomer for β-Oxidized Nitrosamines

	experimental, in several solvents				theory	
compd	C_6D_6	$CDCl_3$	CD_3CN	D_2O	all[a]	H.D.[b]
2	28	28	28	17	39	13
3	51	54	45	44	48	45
4	54	57	53	81	53	64
5	86	87	88	91	60	69

[a] Calculated for all conformers in Tables II and III. [b] Calculated for only those conformers having dipole moments above 3 D.

The *Z*–*E* isomer ratios were calculated from the MNDO computed heats of formation for each particular conformer, and these data were used to establish each conformer's relative population at 25 °C in the set (relative to the lowest energy conformer). Summing of the percent contributions of the *Z* or *E* conformers then produces the isomer ratio. The results are given in Table IV. Comparison of the data in the "all" column with the experimental data shows that the calculation method enables a theoretical prediction of the major isomer but falls short of predicting the quantitative *Z*–*E* ratios. Since the experimental data for the alcohols and aldehydes clearly show a change in the *Z*–*E* ratio with solvent change, which in the case of **5** particularly results in an increased preference for the *Z* isomer with increased solvent dielectric constant (although other factors could certainly be involved), we considered the idea that solvents of higher dielectric constant might promote the preferential population of conformers with higher dipole moments. Using the calculated dipole moments of every conformer studied, we calculated the average dipole moment for the *Z* and *E* isomers of each of the four nitrosamines. For both ethyl- and methyl(2-hydroxyethyl)nitrosamine, the average dipole moment is greater for the *E* isomer than it is for the *Z* isomer, while the opposite is true for the (2-oxoethyl)nitrosamines. Reference to Table IV shows that the *E* alcohols and the *Z* aldehydes are preferred in the higher dielectric constant medium, D_2O.

Since a solvent with a large dielectric constant obviously can better solvate a molecule with a large dipole moment, we ignored those conformers whose dipole moments were below a critical value (arbitrarily chosen as 3.0 D) and recalculated the equilibrium ratio in order to quantify the effect of a high dielectric solvent. The resulting isomeric ratio for methyl(2-hydroxyethyl)nitrosamine is 13:87; the ratios for the other three compounds are reported in Table IV under the column marked "H.D." along with the experimental results. Perhaps fortuitously, the newly calculated ratios for the (2-hydroxyethyl)nitrosamines are in much better agreement with the experimental data for D_2O. The recalcualted ratios for the aldehydes have shifted toward the experimental observations, but fall far short of a quantitative prediction. Since the aldehydes have, on the average, higher dipole moments than their corresponding alcohols, upward manipulation of the critical dipole moment was attempted, but it did not lead to improved predictions.

Although our improved calculation of the equilibrium ratio of isomers, based on a drastically simplified model of solvent effects, has yielded a better prediction of the ratio of *Z* to *E* isomers in a high dielectric solvent for both ethyl- and methylethanalnitrosamine and an excellent prediction of *Z*:*E* for both ethyl- and methyl(2-hydroxyethyl)nitrosamine, it is apparent that there are intramolecular attractive forces in the nitrosamino aldehydes that are not well modeled by MNDO and for which our simplified model of solvent effects cannot compensate.

MNDO Calculations and the 1,2,3-Oxadiazolinium Cation

As was indicated in the introductory section, a goal of this work was to determine whether there is an attractive interaction between the nitroso oxygen and the carbonyl carbon of the α-nitrosamino

(14) Wiberg, K. B.; Martin, E. J. *J. Am. Chem. Soc.* **1985**, *107*, 5035.
(15) Abdurahmavov, A. V.; Rahimam, R. A.; Imanov, L. M. *Phys. Lett. A* **1970**, *32*, 123.
(16) Loeppky, R. N.; Hazlitt, L. G. *J. Org. Chem.* **1982**, *47*, 4841.
(17) Koeppke, S. R.; Kupper, R.; Michejda, C. J. *J. Org. Chem.* **1979**, *44*, 2718.

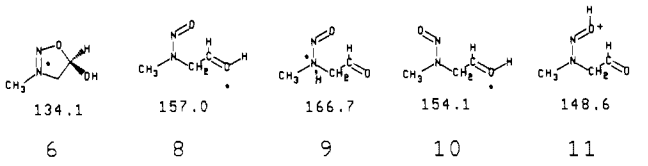
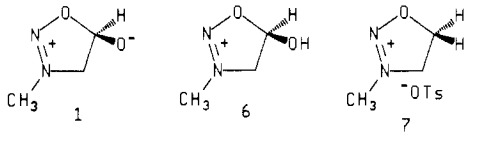


Figure 3. The structure and heat of formation (kcal/mol) of isomeric protonated forms of methyl(2-oxoethyl)nitrosamine are given. Note that the oxadiazolinium ion is 21 kcal/mol more stable than any other isomer.

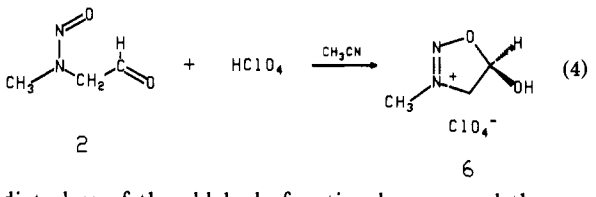
aldehyde which would produce the "dihydrosydnone" **1**. Kinetically significant production of **1** might destabilize the aldehydes and account for their unusual chemical properties. In order to test this point further, we explored the MNDO generation of **1**. Merely putting the carbonyl carbon and nitroso oxygen atoms within bonding distance at the start of a calculation is an insufficient impetus for bonding. In fact, even when the input parameters are arranged so as to explicitly connect carbon and oxygen at the start of a calculation, geometry optimization opens the ring to generate one of the *Z* isomers. In addition, an examination of the bond order matrix for methyl(2-oxoethyl)-nitrosamine, which gives atomic orbital overlap coefficients between every pair of atoms in the molecule, reveals no net bonding between carbon and oxygen. We conclude, therefore, that the neutral compound cannot form a stable structure containing the pentagonal arrangement found in **1**.



Intuitively, one might expect neighboring group interaction between the nitroso oxygen and the carbonyl carbon if the carbonyl oxygen atom is protonated. Michejda and co-workers have shown neighboring group participation in the solvolysis of the tosylate of **2** to give **7**.[17] Reactions of this type are thought to have possible biological significance through sulfate conjugates of **2** (as modeled by the tosylate) and in the chemistry of chemotherapeutic β-chloroethylnitrosoureas. By using the same format described above, our calculations show that the cyclic 5-hydroxy-1,2,3-oxadiazolinium ion **6** is 23 kcal/mol more stable than the protonated open chain form **8**. Because nitrosamines are known to protonate at more than one site, we also calculated the energies for the nitroso oxygen-protonated and amino nitrogen-protonated forms **8–11** (see Figure 3). The 5-hydroxyoxadiazolinium ion **6** is 14 kcal/mol more stable than any of these other forms. The formation of a similar ring through bonding carbonyl oxygen of the *E* isomer of **11** with the nitroso nitrogen fails to occur.

The Synthesis and Structural Characterization of the 5-Hydroxyoxadiazolinium Cation

Because the MNDO calculation showed the 5-hydroxyoxadiazolinium ion to be so much more stable than any of the other protonated forms an experimental investigation of this point was made. Methyl(2-oxoethyl)nitrosamine was dissolved in CD_3CN and 1 equiv of 70% perchloric acid was added to this solution (eq 4). The resulting ^1H NMR spectrum showed the



(4)

immediate loss of the aldehyde functional group and the appearance of new peaks (vida infra). Experimentation of this type led to the formation of a solid that was carefully recrystallized from acetonitrile and isolated in an inert atmosphere. An X-ray crystallographic analysis of this material clearly shows that it has the structure of 3-methyl-5-hydroxy-1,2,3-oxadiazolinium perchlorate (see Figure 4).

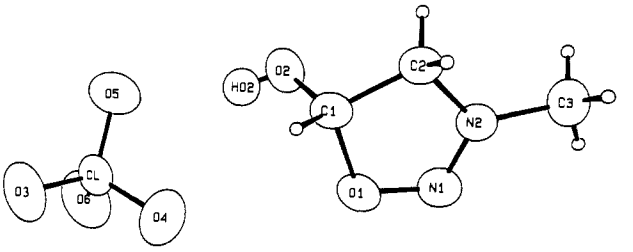


Figure 4. The structure of 5-hydroxy-3-methyloxadiazolinium perchlorate as determined from an X-ray crystallographic determination. Bond distances and angles are given in Table V.

Table V. Bond Distances and Angles for 5-Hydroxy-3-methyloxadiazolinium Perchlorate

	distance, Å			
bond	calcd	exptl	diff	% diff
C2–N2	1.509	1.464	0.045	3.07
N2–N1	1.280	1.238	0.042	3.39
N1–O1	1.252	1.319	−0.067	−5.08
O1–C1	1.494	1.515	−0.021	−1.39
C1–C2	1.575	1.496	0.079	5.28
N2–C3	1.506	1.459	0.047	3.22
C1–HCl	1.123	0.980	0.143	14.59
C1–O2	1.364	1.348	0.016	1.19
O2–HO2	0.952	0.750	0.202	26.93
angle	calcd, deg	exptl, deg	diff	% diff
C2–N2–N1	113.3	114.5	−1.2	−1.05
N2–N1–O1	112.4	111.0	1.4	1.26
N1–O1–C1	114.0	109.8	4.2	3.83
O1–C1–C2	100.7	100.9	−0.2	−0.20
C1–C2–N2	99.5	102.0	−2.5	−2.45
C3–N2–C2	124.9	124.8	0.1	0.08
O2–C1–C2	111.9	111.4	0.5	0.45
HO2–O2–C1	114.7	108.0	6.7	6.20

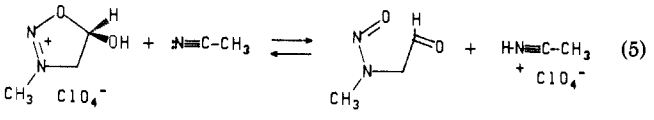
The key feature to be determined in this structure study was the existence of a carbon–oxygen single bond between the carbonyl carbon and the nitroso oxygen. The C–O distance of 1.515 Å is clearly well within the covalent bond radial distance and just slightly longer than a normal C–O bond. It also compares favorably with the structural parameters calculated by the MNDO program (see Table V). This distance is much shorter than the O(NO)–C(CO) distance of 3.259 Å computed for the *Z* aldehyde. The geometrical array of atoms bonded to the former carbonyl carbon is clearly tetrahedral. The "tetrahedral deformation" of the former carbonyl carbon from the plane defined by its attached C, H, and O, as measured by the angle which the C–O bond makes with the plane in a right triangle having as its other side the normal of the carbon to the plane, is 12.7°. The X-ray data clearly show, then, that there is a covalent bond between the nitroso oxygen and the aldehyde carbon resulting in the 5-hydroxyoxadiazolinium structure. The solution structure of this salt is more ambiguous.

We anticipated that the generation of the 5-hydroxyoxadiazolinium ion could easily be detected by the appearance of a characteristic ABX pattern for the ring protons in its ^1H NMR spectrum. This is not the case. The 300-MHz NMR spectrum of a CD_3CN solution of **6** reveals these hydrogens as a doublet (δ 4.586, J = 5.99 Hz) and a triplet (δ 6.960 Hz, J = 5.99 Hz). There is long-range coupling of the methylene to the *N*-methyl group (J = 1.1 Hz) which is indicative of the degree of resolution. Several plausible explanations have been considered for the lack of an ABX pattern and the observation of the apparent A_2X pattern for these protons: (1) lack of ring formation in solution; (2) accidental magnetic equivalence of the methylene hydrogens and comparable coupling constants to the methine H; or (3) fast chemical exchange between the ring opened and closed forms. We favor the last option. Examination of the ^{13}C spectra of **4**, **6**, and related compounds clearly shows a significant change in bonding for the former carbonyl carbon in **6**, which appears at δ 111.51. The *Z* aldehyde (δ(C=O), 193.643) and its corresponding hydrate (δ($C(OH)_2$, 86.83) both appear in solution as

slowly exchanging *Z*–*E* isomers, while the spectrum of **6** shows only a single isomer with a carbon chemical shift intermediate between these extremes. The observations of Olah's group on the ^{1}H chemical shifts and coupling constants of protonated aldehydes show $\delta > 9.5$ and small coupling constants to the adjacent methylene ($J < 1.1$ Hz).[18] In super acid the aldehyde proton is clearly coupled to the O–H, but we see no such coupling. The chemical shift of the *N*-methyl also reveals a change in its environment. The carbon is shifted 2–4 ppm downfield from the corresponding gem diol or aldehyde and its protons are similarly shifted 0.3 ppm downfield. These shifts are in good agreement with those of O-protonated and O-alkylated nitrosamines.[19] The NMR spectral data argue for bonding alterations at both the *N*-nitroso function and the carbonyl.

Specialized 2-D NMR experiments suggest that the methylene hydrogens are not strictly magnetically equivalent although they could be accidentally degenerate (experimentally equivalent within the resolution characteristics of the instrument). The 2-D NMR experiment employed the pulse sequence for selective indirect *J* spectroscopy described by Rutar and Wong for the selective determination of geminal coupling constants between magnetically distinct protons.[20] If the protons at C-2 are magnetically equivalent a single sharp peak should be observed while nonequivalent protons will give rise to a sharp doublet from which $^2J_{HH}$ can be determined. Application of this experiment to *6* resulted in a broad peak containing some fine structure that was enhanced in going from 25 to −40 °C. These results are typical of cases where the chemical shifts of the methylene protons are nearly but not strictly degenerate. The apparent A_2X pattern then could result from nearly equivalent shifts for the methylene protons and nearly equivalent coupling constants to the X proton (C-1 H). However, a process that results in the fast exchange of the methylene protons' environment would appear to provide a more reasonable explanation of the data in hand at this time.

Our interpretation of our NMR data must account for the lack of coupling of the ABX type, the failure to observe OH–CH coupling at the methine, and the nature of the various chemical shifts. The process depicted in eq 5 provides a good model by



(5)

which the NMR data can be rationalized. It is reasonable to assume that the equilibrium shown exists in the weakly basic solvent CH_3CN and that it is rapid on the NMR time scale. The chemical shift data suggest that the equilibrium is significantly shifted to the left. Ring opening and closing will necessarily exchange the positions of the two methylene hydrogens resulting in their identical chemical shift. This process also explains the lack of OH–CH coupling. It is not easily determined how the 2-D NMR method would respond to a chemically exchanging system. Neither the ^{13}C nor the ^{1}H NMR spectra of **6** in CD_3CN showed significant line broadening at −40 °C although the methine proton was significantly broadened in deuterioacetone. We have not been successful in finding a solvent without a weakly basic atom that would still dissolve **6**.

Conclusion

Perhaps not surprisingly, MNDO calculations fail to reveal any interaction between the carbonyl carbon and the *N*-nitroso oxygen in the unprotonated aldehyde. The calculations predicted the formation of a stable 5-hydroxy-3-methyl-1,2,3-oxadiazolinium cation from carbonyl oxygen protonation of (*Z*)-methyl(2-oxoethyl)nitrosamine. The fact that we were able to prepare 5-hydroxy-3-methyl-1,2,3-oxadiazolinium perchlorate and definitively demonstrate its structure through X-ray diffraction is not only a nice verification of the theoretical approach but it also opens the door to chemical investigations of similar compounds. These experiments are not only of intrinsic fundamental chemical interest but should go far toward answering questions about the intermediacy of the oxadiazolinium ion in several processes of importance in cancer research. The chemical properties of hydroxy and alkoxy 1,2,3-oxadiazolinium ions are under current investigation.

Conformer populations calculated from MNDO-determined heats of formation predict the major *Z*–*E* isomer in the case of two nitrosamino alcohols and the related pair of aldehydes but do not accurately predict the quantitative experimental *Z*–*E* ratio. Restriction of the set to the conformers with higher dipole moments was quite successful in quantitatively predicting the alcohol isomer ratios but failed to predict the overwhelming *Z* preference exhibited in the aldehydes. Factors not modeled well by MNDO must be responsible.

Table VI. Table of Positional Parameters and Their Estimated Standard Deviations[a]

atom	*x*	*y*	*z*	*B*, Å^2
Cl	0.16661 (7)	0.11579 (5)	0.20775 (5)	3.26 (1)
N1	0.3552 (2)	−0.0120 (2)	0.7782 (2)	3.50 (4)
C3	0.3339 (3)	−0.1748 (3)	0.9462 (2)	4.05 (5)
O3	0.2495 (3)	0.1123 (2)	0.0817 (2)	5.85 (5)
O4	0.2923 (3)	0.1201 (2)	0.3268 (2)	5.83 (5)
O5	0.0658 (3)	0.0032 (2)	0.2221 (2)	6.57 (5)
O6	0.0620 (3)	0.2265 (2)	0.2103 (2)	6.17 (5)
C1	0.3030 (3)	−0.1108 (2)	0.5586 (2)	3.07 (4)
O1	0.3523 (2)	0.0104 (1)	0.6410 (2)	3.77 (3)
N2	0.3373 (2)	−0.1277 (2)	0.8016 (2)	2.75 (4)
C2	0.3208 (3)	−0.2084 (2)	0.6747 (2)	2.88 (4)
O2	0.1380 (2)	−0.0998 (2)	0.5020 (2)	4.10 (4)

[a] Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as: $(4/3)[a^2\beta(1,1) + b^2\beta(2,2) + c^2\beta(3,3) + ab(\cos\gamma)\beta(1,2) + ac(\cos\beta)\beta(1,3) + bc(\cos\alpha)\beta(2,3)]$.

Experimental Section

Instrumentation. High-resolution ^{13}C and ^{1}H NMR spectra were taken on a Nicolet 300-MHz spectrometer. UV spectra were taken on a Perkin-Elmer 576 ST spectrometer. IR spectra were recorded on a Nicolet FTIR (20DXB) spectrometer. X-ray crystallographic analysis was performed as described below.

Materials. Caution: Nitrosamines are known potent animal carcinogens and should be treated accordingly. A representative safety protocol can be obtained from the authors. **Explosion Hazard**: During the writing of this manuscript an experiment with **6** and aniline resulted in an unpredictable and violent explosion. We presume that the perchlorate counterion was responsible. The preparation of alternative salts is under investigation. The perchlorate **6** should only be prepared and used in quantities <1 g.

Methyl(2-hydroxyethyl)nitrosamine, ethyl(2-oxoethyl)nitrosamine, *N*-methyl-*N*-nitroso-2,2-dimethoxyethanamine, and methyl(2-oxoethyl)nitrosamine are known compounds and were prepared by the cited methods. Acetonitrile was HPLC grade. Acetic acid and 70% perchloric acid were analytical grade.

The Synthesis of 5-Hydroxy-3-methyl-1,2,3-oxadiazolinium Perchlorate (6). Perchloric acid (0.45 mL, 5.2 mmol) was added slowly to a stirred and cooled (5 °C) solution of **4** (0.45 g, 4.4 mmol) in 10 mL of acetic acid. Mixing was continued for 1 h at 5 °C. White crystals formed and were collected by filtration under N_2, washed with acetic acid (5 mL) and dry ether (2 × 5 mL), and dried on the filter under a stream of N_2. Recrystallization from acetonitrile (2 days, −20 °C) gave white crystals, 0.70 g (78%). The perchlorate **6** can also be prepared from the acetal (*N*-methyl-*N*-nitroso-2,2-dimethoxyethanamine) in 75% yield by using the same reaction conditions except that the reaction time is extended to 15 h.

^{1}H NMR (CD_3CN) δ 6.96 (t, J = 5.9 Hz, 1 H), 5.8 (b, 1 H), 4.59 (dq, J = 5.9, 1.2 Hz, 2 H (coupling to methyl)), 4.16 (t, J = 1.2 Hz, 3 H). ^{13}C NMR (CD_3CN) δ 111.82, 64.43, 43.26. IR (cm^{-1}, fluorolube) 3410, 1562, 1468, 1436. UV (CH_3CN) max 221 nm (ϵ, 5044).

X-ray Diffraction. Intensity data were collected at 295 (1) K on an Enraf-Nonius CAD4 diffractometer with use of monochromatized Mo Kα radiation (0.7107 Å) in the θ–2θ mode with a scan width of $\theta = 0.7 + 0.35 \tan\theta$ out to $2\theta = 45°$. The structure was solved by direct methods

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(MULTAN) and refined by full-matrix least-squares (SDP). Hydrogens were located on difference Fourier maps and/or placed in chemically reasonable positions (not refined). **Crystal and Refinement Data** ($C_3H_7ClN_2O_6$): M = 202.6, monoclinic, $P2_1/n$; a = 7.802 (2) Å, b = 10.434 (3) Å, c = 9.480 (2) Å, β = 95.79 (2)°; Z = 4; V = 767.8 Å, D_x = 1.751 (2) g cm^{-3}. Of 2889 measured reflections, 1003 were unique (Rint = 0.029); $F(000)$ = 416, R = 0.028, R_w = 0.043 for 873 reflections with $I > 2\sigma(I)$. Final atomic coordinates are given in Table VI (also see the supplementary material paragraph). Relevant bond distances and angles are included in Table V.

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Supplementary Material Available: Tables including hydrogen atom positions and anisotropic thermal parameters (1 page); listing of observed and calculated structure factors (5 pages). Ordering information is given on any current masthead page.

An EXAFS Study of Co-Mn/SiO_2 Bimetallic Solvated Metal Atom Dispersed (SMAD) Catalysts

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Abstract: Supported cobalt-manganese catalysts prepared by solvated metal atom dispersion (SMAD) were studied by X-ray absorption spectroscopy (EXAFS). The manganese was found to be in the oxidized state, while the cobalt is in both the metallic and oxidized state. Manganese allows an appreciable increase in metallic cobalt present. The XAS results indicate that the most active Co-Mn/SiO_2 catalyst has the largest amount of metallic cobalt and that there is some carbon coordinated to the cobalt atoms. These results are consistent with catalytic data and suggest that Mn scavanges oxygen moieties (which are present in limited amounts) and allows Co to remain metallic. Other possible aiding functions of Mn are also discussed.

In recent years we have reported numerous examples of the synthesis and activities of unusual catalysts prepared by solvated metal atom dispersion (SMAD).[1-6] By this process, metal atoms are solvated at low temperatures in toluene or some other appropriate solvent, and upon warming metal atom clustering begins. This nucleation process (cluster growth) competes with a reaction channel where the growing clusters react with the host solvent. These growing clusters incorporate carbonaceous fragments and are stabilized as amorphous "pseudoorganometallic" powders. These carbonaceous fragments aid in the catalytic reaction and apparently provide a better means of attachment of the metal particles to catalyst support surfaces. Final cluster/particle size can be controlled by length of time of aging at low temperatures, dilution, type of solvent, and by the surface properties of the support used to capture the clusters.

In 1984 we reported the first examples of bimetallic catalysts prepared by the SMAD procedure.[7,8] Of primary interest are the Co-Mn/SiO_2 catalysts. Addition of an equimolar amount of Mn-Co/SiO_2 SMAD catalysts increased the catalytic activity for hydrogenation and hydrogenolysis reactions by 100-fold. A large amount of data on catalytic activity/selectivity showed that the Mn addition greatly affected the activities of Co but not selectivities. Mn itself was catalytically inactive. Extensive chemisorption studies showed that addition of Mn caused an increase in Co dispersion by only 2-fold. Therefore, we tentatively proposed that Mn, in addition to aiding dispersion, also favorably affected catalysis by Co by an electronic effect.

These interesting results prompted us to use extended X-ray absorption fine structure (EXAFS) spectroscopy to obtain information on the local structure surrounding the Co atom from the analysis of the Co and Mn K-edge spectra. The application of EXAFS to the study of catalytic systems and small metal clusters has had considerable impact in the understanding of the structure of these systems.[9-11]

Measurements of EXAFS are particularly valuable for very highly dispersed catalysts. From an analysis of EXAFS data, one can determine the number of neighboring atoms of a particular kind at a particular distance from a given type of absorber atom. By determining EXAFS for each element of interest in a complex material, it is possible to obtain information on the environments of the different types of atoms present. In this paper we report the results of EXAFS studies on the bimetallic SMAD Co-Mn-SiO_2 catalysts.

Experimental Section

Materials. Metals were obtained from Matheson, Coleman, and Bell (Mn) and Cerac, Inc. (Co). The catalyst support was Davison SiO_2 (300 m^2/gm). The support was calcined at 773 K for 3 h in flowing dry air

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