Theoretical Investigation of the Proton-Induced Decomposition of 4,5-Dihydro-1,2,3-triazole To Form the Aziridinium Ion: Instability of the (2-Aminoethyl)diazonium Ion

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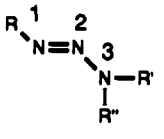
Abstract: Ab initio molecular orbital calculations within the Hartree–Fock approximation were used to investigate 4,5-dihydro-1,2,3-triazole (1,2,3-triazoline) and related compounds. Moller–Plesset perturbation theory was used to investigate the effects of electron correlation on the energy of some configurations. The proton affinities for the various protonation sites of 1,2,3-triazoline were obtained. The order of preference for protonation was found to be $N_3 > N_1 \gg N_2$. No local minima were found in the region of the N_1-protonated 1,2,3-triazoline at the 3-21G basis set level. Instead the molecule dissociated by an N_1–N_2 heterolysis pathway. This finding prompted additional investigation of the decomposition process and its intermediates, ultimately leading to the global minimum for this pathway. Searches along the partial potential energy hypersurface for the reaction reveal that certain rotational conformers of the (2-aminoethyl)diazonium ion, the product of the heterolysis, were stable intermediates (the number of intermediates found depended on the basis set used). The diazonium ion in the antiperiplanar conformation was not stable and collapsed to the aziridinium ion with the expulsion of molecular nitrogen. Similar calculations were performed on the neutral and N_1-protonated forms of 1-methyl-4,5-dihydro-1,2,3-triazole (1-methyltriazoline) and 1,4,5,6-tetrahydro-1,2,3-triazine (triazinine). These molecules also decomposed upon protonation. The instability of the (2-aminoethyl)diazonium ion led to an investigation of several other substituted diazonium ions including the (2-chloroethyl)diazonium ion, the (2-hydroxyethyl)diazonium ion and the (2-sulfhydrylethyl)diazonium ion. All were found to converge to stable structures in the antiperiplanar conformation.

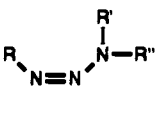
Introduction

Considerable experimental work on triazenes and related compounds has been carried out in our laboratory, including the study of both simple alkyl-substituted and acyl-substituted compounds. Recently these studies have been augmented by theoretical methods. Alkyltriazenes are known to decompose by an acid-catalyzed mechanism in aqueous buffer.[1,2] Alkyldiazonium ions are believed to be the intermediates in the decomposition, where the final stable products are alkylamines and alcohols. Alkyldiazonium ions are produced during the metabolism of various nitrogen-containing carcinogens.[3] Moreover, alkyldiazonium ions are also the important reactive electrophilic species produced by chemotherapeutic agents such as the (2-haloethyl)nitrosoureas.[4]

In an earlier publication, we discussed the results of a theoretical study of the protonation of triazene, 1-methyltriazene, and 1,3-dimethyltriazene.[5] Our results generally agreed with and complemented the earlier study of Nguyen and co-workers.[6] One of the findings in the earlier work was that alkyltriazenes can exist in the *E* and *Z* configurations, although the *E* configuration is the one that is commonly encountered. The inversion barrier is believed to be large (>40 kcal/mol), with the *E* form being more stable by as much as 5–10 kcal/mol.



(E)-Triazene



(Z)-Triazene

It was shown that the order of preference for protonation sites, based on calculated proton affinities, was $N_1 > N_3 \gg N_2$ for the parent, 1-methyl-, and 1,3-dimethyltriazenes. Also, it was shown that even though protonation at N_3 leads to the experimentally observed products from decomposition of triazenes in aqueous buffer, protonation at N_1 was preferred by as much as 10 kcal/mol. Although equilibrium favors the N_1-protonated from, N_3 protonation results in subsequent irreversible decomposition.[2] Another significant finding, and the one most relevant to this work, was the fact that certain *Z* conformations of the various acyclic alkyltriazenes studied were unstable toward protonation at N_3 (the saturated nitrogen); that is, several of the (*Z*)-triazenes were found to have no local minima in the region of the N_3-protonated structure. Dissociation by an N_2-N_3 heterolysis pathway was observed when attempts were made to attach a proton to N_3. Optimization led to products that correspond to the N_3-alkylamine and the corresponding alkyldiazonium ion. Although the results seem significant, the consequences of these findings were not discussed.

Acyclic (*Z*)-triazenes are not known as stable molecules. However, *triazolines* can be regarded as cyclic (*Z*)-*triazenes*. Since triazenes in the *Z* conformation showed synchronous N_2–N_3 bond cleavage upon protonation at the saturated nitrogen, we predicted that triazolines would also undergo concerted decomposition upon protonation.

Little is known experimentally about simple alkyltriazolines. However, extensive experimental work has been done on more complicated triazoline systems, including those substituted with aryl and acyl groups.[7] Several simple 1-alkyltriazolines, including 1-methyltriazoline, have recently been synthesized in our labo-

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(1) Smith, R. H., Jr.; Denlinger, C. L.; Kupper, R.; Mehl, A. F.; Michejda, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 3726.

(2) Smith, R. H., Jr.; Wladkowski, B. D.; Mehl, A. F.; Cleveland, M. J.; Rudrow, E. A.; Chmurny, G. N.; Michejda, C. J. *J. Org. Chem.* **1989**, *54*, 1036.

(3) Dipple, A.; Weisburger, E. C.; Michejda, C. J. Metabolism of Chemical Carcinogens. In *Mechanisms of Cellular Transformations*; Grunberger, D., Goff, S., Eds.; Plenum Press: New York, 1987; pp 1–32.

(4) Sieh, D. H.; Andrews, A. W.; Michejda, C. J. *Mutat. Res.* **1980**, *73*, 227. Malaveille, C.; Kolar, G. F.; Bartsch, H. *Mutat. Res.* **1976**, *36*, 1. Kolar, G. F.; Fahrig, R.; Vogel, E. *Chem.-Biol. Interact.* **1974**, *9*, 365. Preussmann, R.; Invankovic, S.; Landschutz, C.; Gurmy, J.; Flohr, E.; Griesbach, U. *Z. Krebsforsch. Klin. Onkol.* **1974**, *81*, 285.

(5) Schmiedekamp, A.; Smith, R. H., Jr.; Michejda, C. J. *J. Org. Chem.* **1988**, *53*, 3433.

(6) Nguyen, M. T.; Hoesch, L. *Helv. Chim. Acta* **1986**, *69*, 1627. Nguyen, M. T.; Kaneti, J.; Hoesch, L.; Dreiding, A. S. *Helv. Chim. Acta* **1984**, *67*, 1918.

(7) Scheiner, P. In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1970; p 327.

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Table I. Total Energies Calculated for Neutral and Protonated 4,5-Dihydro-1,2,3-triazole, 1-Methyl-4,5-dihydro-1,2,3-triazole, and 1,4,5,6-Tetrahydro-1,2,3-triazine

		energy (hartrees)				
structure	symmetry	SCF 3-21G	SCF 6-31G*	MP2 6-31G*	MP3 6-31G*	MP4(SDTQ) 6-31G*
1	C_1	−240.538 91	−241.918 832	−242.659 354	−242.681 168	−242.722 110
2	C_1	−279.355 91	−280.951 644			
3	C_1	−279.351 69	−280.943 554			
4	C_1	(−240.902 88)[a]	−242.258 281	−242.996 573	−243.021 115	−243.063 505
5	C_1	−240.875 11	−242.248 118	−242.981 686	−243.006 938	−243.047 585
6	C_{2v}	−240.916 74	−242.286 193	−243.016 744	−243.041 478	−243.080 972
7	C_1	(−279.720 77)[a]	−281.300 788			
8	C_1	(−279.713 64)[a]				

[a] Unstable structure.

ratory by a modification of the procedure developed by Gaudiano and co-workers.[8] Experimental studies to complement the present theoretical results are being carried out.

Theoretical studies on triazolines have been limited to the study of Zacheslavskii et al.,[9] who investigated the potential surface for the reaction of ethylene with hydrazoic acid to form the parent triazoline (4,5-dihydro-1,2,3-triazole) using MINDO/2 semiemperical methods.

We report here an ab initio theoretical study of the protonation of 4,5-dihydro-1,2,3-triazole (1,2,3-triazoline). The goal of this work was to explore the most likely decomposition pathways for this interesting class of compounds. An extensive investigation to explore all possible reaction pathways and to obtain geometries and energetics to an exceedingly high level of accuracy was not our aim. The results of this study provide valuable data on sites of reaction and energetics of the key intermediates formed during the reaction. These data will then be very useful in the analysis of the much more complicated liquid-phase decomposition process.

Calculations

Hartree–Fock ab initio calculations were performed by using a variety of standard double-ζ quality (including 3-21G, 3-21G*, and 6-31G*) basis sets. Moller-Plesset perturbation theory (including MP2, MP3, and MP4(SDTQ) within the frozen core approximation) was used to study the effects of electron correlation on the energetics of these systems. The GAUSSIAN series of programs were used throughout, including GAUSSIAN-82,[10a] GAUSSIAN-88,[10b] and GAUSSIAN-90[10c] adapted to run on the Cray XMP-2 computer at FCRDC. The Berny optimization sequence[11] was used in the exploration of the hypersurface to find the saddle points and energy minima. The optimized geometries and SCF energies were obtained for 4,5-dihydro-1,2,3-triazole (triazoline), **1**, 1-methyl-4,5-dihydro-1,2,3-triazole (1-methyltriazoline), **2**, and the six-membered ring 1,4,5,6-tetrahydro-1,2,3-triazine (triazinine), **3**. The N_1-, N_2-, and N_3-protonated species of triazoline (molecules **4**, **5**, and **6**, respectively), the N_1-protonated species of 1-methyltriazoline, **7**, and the N_1-protonated species of triazinine, **8**, were also investigated (see Figure 1). A dynamical investigation of the N_1-proton-induced decomposition of triazoline and comparison of stabilities of several (2-X-ethyl)diazonium ions in the antiperiplanar configuration are presented. These ions included (2-aminoethyl)diazonium ion, **9**, [2-(*N*-methylamino)ethyl]diazonium ion, **10**, (2-chloroethyl)diazonium ion, **11**, (2-hydroxyethyl)diazonium ion, **12**, and (2-sulfhydrylethyl)diazonium ion, **13** (see structures in Table V).

Results and Discussion

A. Neutral Structures. The optimized structures of **1** and **2** are very similar with respect to the ring geometry. In both cases, the ring is puckered, the C–H hydrogens are slightly eclipsed, and N_1 is pseudo-sp^3-hybridized. The inversion barrier at N_1 was not found, which suggests that the height of the barrier between the two enantiomeric forms (Figure 2) must be low.

It is likely that triazinine, **3**, has multiple local minima, but only one was detected in this investigation. The minimized structure had all hydrogens staggered and the ring was in a pseudochair conformation. Interestingly, **3** lies higher in energy than its structural isomer, **2**, but only by 2.6 kcal/mol at the SCF 3-21G level and 5.1 kcal/mol at the SCF 6-31G* level (Table I). A partial list of the optimized geometrical parameters for these molecules is given in Table II.

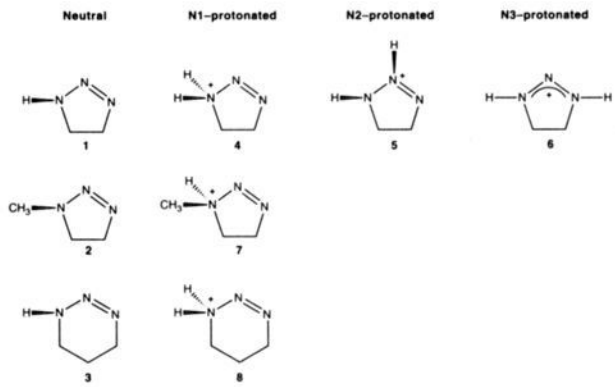
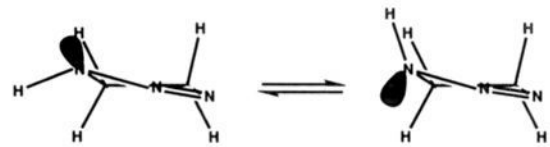


Figure 1. Neutral and protonated structures that were investigated by computational methods at various levels of ab initio theory.



1,2,3-triazoline (structure **1**)

Figure 2.

B. Protonated Structures. The actual proton transfer reaction step, which may involve one or more bound complexes, and which may be an important topic in its own right, is not discussed in the present work. We restrict ourselves to the study of the protonated species and their subsequent decomposition. It is this aspect of the reaction that is most relevant to the experimental study of triazoline decomposition. In order to avoid specifying a particular protonating agent, the optimizations of the various protonated triazolines were started with a proton attached to the individual sites of interest on the neutral structures (which had previously been optimized at a given level of theory). The initial geometry was chosen with a proton–neutral bond distance of 1.0 Å and a trajectory that minimized repulsive interactions.

The N_2-protonated triazoline, **5**, optimized to a structure with little change to the ring geometry (see Table I). Protonation of the parent triazoline at N_3 led to a completely planar structure with C_{2v} symmetry, **6**. Attempts to optmize on a local minimum in the region of the N_1-protonated structure were unsuccessful using a 3-21G basis set; however, a minimum was found for the N_1-protonated parent triazoline, **4**, and N_1-methyltriazoline, **7**, by using a larger basis set, 6-31G*. These structures featured considerably elongated N_1–N_2 bond lengths. No local minima were found for the N_1-protonated triazinine, **8**, by using either a 3-21G or a 6-31G* basis set. At the 3-21G basis set level, optimization of **4** led to an inflection point on the potential surface.

(8) Gaudiano, G.; Ticozzi, C.; Umani-Ronchi, A.; Bravo, P. *Gazz. Chim. Ital.* **1967**, *97* (10), 1411.
(9) Zacheslavskii, S. A.; Mel'nikov, V. V.; Gidaspov, B. V. *Zh. Org. Khim.* **1979**, *15*, 677.
(10) Binkley, J. S.; Whiteside, R. A.; Raghavachari, K.; Seeger, R.; Defrees, D. J.; Schlegel, H. B.; Frisch, M. J.; Pople, J. A.; Kahn, L. R. *Gaussian 82*; Carnegie-Mellon University: Pittsburgh, 1982.
(11) Schlegel, H. B. *J. Chem. Phys.* **1982**, *77*, 3678.

Table II. Optimized Geometrical Parameters for Neutral and Protonated Triazoline, N_3-Methyltriazoline, and Triazinine

	bond length (Å)						bond angle (deg)					
compound	N_1–N_2	N_2–N_3	N_3–C	N_1–C	C_1–C_2	R–N_n	$\angle N_1N_2N_3$	$\angle CN_1N_2$	$\angle CN_3N_2$	$\angle CCN_1$	$\angle CCN_3$	$\angle RN_nN_m$
1, R = H												
SCF 3-21G	1.437	1.229	1.514	1.481	1.544	1.000	111.9	108.5	111.3	99.5	103.6	111.8
SCF 6-31G*	1.375	1.213	1.471	1.455	1.526	0.998	112.8	108.1	110.5	98.8	103.1	110.1
2, R = CH_3												
SCF 3-21G	1.434	1.230	1.514	1.477	1.540	1.459	112.3	107.8	111.0	107.8	103.2	113.5
SCF 6-31G*	1.372	1.214	1.471	1.452	1.523	1.444	113.3	107.8	110.3	99.3	102.9	113.7
3, R = H												
SCF 3-21G	1.407	1.234	1.499	1.461	1.531	0.996	120.8	122.1	121.2	114.9	106.1	110.0
SCF 6-31G*	1.363	1.216	1.467	1.447	1.524	0.996	121.6	119.7	122.3	106.3	115.8	107.9
4, R = H^+ [a,b]												
5, R = H^+												
SCF 3-21G	1.425	1.220	1.514	1.502	1.552	1.012	117.62	104.45	108.44	101.57	103.99	121.51
SCF 6-31G*	1.366	1.202	1.470	1.474	1.538	1.011	119.13	104.22	107.44	100.62	103.94	120.40
6, R = H^+												
SCF 3-21G	1.280	1.280	1.500	1.500	1.558	1.002	110.5	114.3	114.3	100.5	100.5	118.3
SCF 6-31G*	1.254	1.254	1.473	1.473	1.542	1.000	110.57	114.52	114.49	100.15	100.15	117.80
7, R = CH_3												
SCF 3-21G[a]	1.638	1.185	1.495	1.504	1.561	1.520	107.61	105.35	118.92	103.51	104.50	106.83
SCF 6-31G*	1.523	1.188	1.460	1.487	1.533	1.482	109.66	106.03	116.00	101.78	104.24	108.90
8, R = H^+												
SCF 3-21G[a]	1.580	1.190	1.512	1.523	1.531	1.019	115.30	116.55	125.58	106.03	111.93	103.94

[a] Unstable structure. [b] Equivalent to structure b, Table IV.

Table III. Proton Affinities Calculated for the Various Protonation Sites of 4,5-Dihydro-1,2,3-triazole

	proton affinity (kcal/mol)				
protonation site	SCF 3-21G	SCF 3-21G*	MP2 6-31G*	MP3 6-31G*	MP4(SDTQ) 6-31G*
N_1	227.6[a]	213.0	211.6	213.3	214.2
N_2	211.0	206.6	202.3	204.4	204.2
N_3	237.1	230.5	224.3	226.1	225.2

[a] Unstable structure; N_1–N_2 bond distance constrained to be 1.85 Å in order to get an appropriate proton affinity.

At this level of theory, the N_1–N_2 bond was found to be considerably elongated and increased charge development was found on N_3. This suggests that structure **4** is a useful reference point along the reaction coordinate leading to N_1–N_2 heterolysis.

The proton affinities for protonation at the various sites on triazoline are presented in Table III. The ordering of preference for protonation is the same as for the simple acyclic triazenes, namely, $N_3 > N_1 \gg N_2$ (the numbering system changes in going from the open chain triazene to the cyclic triazoline).[5,6] It is difficult to discuss the accuracy of the proton affinities obtained in this study since no experimental results are available; however, the experimental ordering of the preference for protonation site is unlikely to be different from the theoretical values. It must be remembered, however, that the energy obtained for N_1 protonation is that of a nonstationary point (for the case of triazoline with the 3-21G basis set and triazinine with both basis sets) since the molecule is unstable toward dissociation. Thus, the ordering for proton affinity does not take into consideration the dynamical nature of the potential energy surface. Energies and geometrical parameters for the various protonated species are given in Tables I and II.

The potential energy surface before and after the dissociative transition state for the parent triazoline was explored further by using the Berny optimization scheme. In order to reduce the computational effort, the calculations were carried out at the 3-21G basis set level and the 6-31G* basis set was then used at selected points on the surface to obtain more reliable geometries and energetics.

The Berny optimization scheme follows the pathway of steepest descent, which does not necessarily follow the exact reaction coordinate (minimum energy pathway) throughout the optimization procedure. This makes it difficult to follow the exact reaction coordinate for such a complex multidimensional surface. However, useful qualitative information can be gained from the general shape of the surface explored via the steepest descent algorithm. An interpretation of the findings obtained from the optimization process is illustrated in Figure 3.

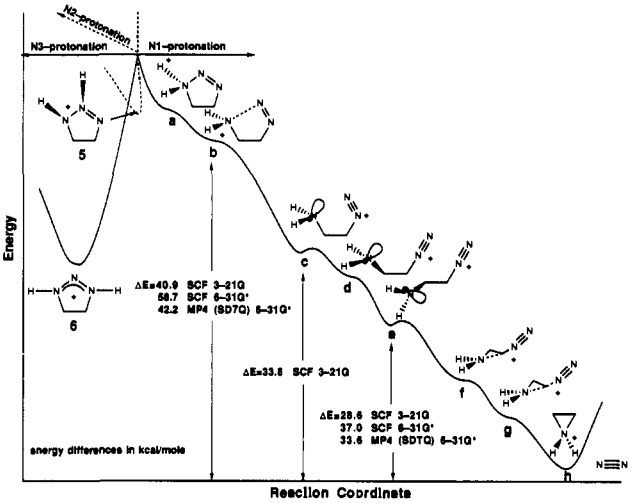


Figure 3. Partial potential energy hypersurface for the protonation of triazoline. This is a largely qualitative depiction that is designed to show the relative positions of the various species on the hypersurface.

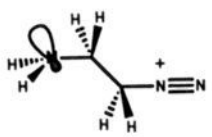
There is a slight inflection prior to the dissociative structure **4** possibly due to hydrogen–hydrogen interactions at long range. This is represented by structure a in Figure 3 in which the N_1–proton distance was found to be 1.07 Å. Structure a was obtained by a partial optimization of the parent triazoline with a proton placed at a nominal distance from N_1. Subsequently, full optimization was performed (in order to simulate the proper proton trajectory). Once past structure **4** (designated as b in Figure 3), the incipient (2-aminoethyl)diazonium ion converges to the synperiplanar structure c. Rotation of the C-C bond creates another inflection point, structure d. Further rotation about the C–C bond produces a conformational isomer, structure e. Once past the second rotation barrier, the diazonium ion reaches the antiperiplanar conformation and collapses past two more inflection points, structures f and g, to form the aziridinium ion with the displacement of molecular nitrogen, structure h. The geometrical parameters and energies at the SCF 3-21G and SCF 6-31G* levels are given in Table IV, and a representation of the decomposition process is given in Figure 3. The figure indicates the partial potential hypersurface for all three protonation sites along some multidimensional reaction pathway. It is interesting to note that while protonation at N_3 is most favorable, the progression along the reaction coordinate resulting from N_1 protonation eventually

Table IV. Geometrical Parameter for Structures along the Proton-Induced Decomposition Pathway of 1,2,3-Triazoline

		bond length (Å)						bond angle (deg)				
compound	energy[a]	N_1–N_2	N_2–N_3	N_3–C	C–C	C–N_1	H–N_1	∠NNN	∠N_2N_3C	∠N_3CC	∠CCN_1	∠CN_1N_2
a	(−240.873 57)[b]	1.439	1.229	1.514	1.544	1.481	1.0268	111.9	111.3	103.6	99.5	108.5
b	(−240.902 88)[b,c]	1.85	1.1413	1.4917	1.5833	1.4776	1.0109	101.71	125.35	103.95	106.50	102.49
	−242.258 28[d]	1.5616	1.1806	1.4576	1.5413	1.4845	1.0101	108.18	117.65	104.98	102.03	106.80
c	−240.916 45	3.0309	1.0769	1.5333	1.5823	1.4540	1.0025		177.01	106.93	110.74	91.60
d	(−240.916 80)[b]	3.1347	1.0771	1.5403	1.5846	1.4466	1.0059		177.96	105.67	110.66	89.12
e	−240.921 30	3.2581	1.0776	1.5648	1.5403	1.4569	1.0041		176.76	105.03	107.81	81.31
	−242.292 89[d]	3.3663	1.0723	1.5385	1.5296	1.4404	1.0017		179.32	106.66	108.90	77.88
f	(−240.923 51)[b]	5.0351	1.0816	2.2734	1.4537	1.4426	1.0005		176.04	106.79	78.55	26.52
g	(−240.960 70)[b]	5.1719	1.0822	2.6217	1.4596	1.4874	1.0055		176.51	99.51	66.95	38.24
h	−240.966 81	∞	1.0830	∞	1.4752	1.5329	1.0082				57.49[e]	
	−242.351 90[d]	∞	1.0784	∞	1.4600	1.4879	1.0046				58.76[e]	

[a] Energy in hartrees. [b] Inflection point structure. [c] constrained geometry; N_1–N_2 = 1.85 Å. [d] SCF 6-31G* energy and geometry. [e] ∠CN_1C.

Table V. Optimized Geometrical Parameters for (2-Aminoethyl)-, [2-(*N*-Methylamino)ethyl]-, (2-Chloroethyl)-, (2-Hydroxyethyl)-, and (2-Sulfhydrylethyl)diazonium Ions Obtained at the 3-21G Basis Set Level



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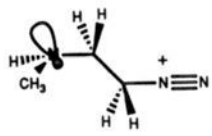

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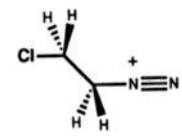

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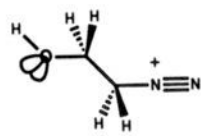

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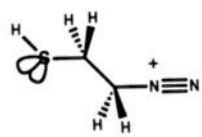

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			bond length (Å)				bond angle (deg)			dihedral angle (deg)	
compound	point group	energy (hartrees)	N_1–N_2	N_2–C	C–C	C–R	∠N_1N_2C	∠N_2CC	∠CCR	∠N_1N_2CC	∠N_2CCR
9	C_s	(−240.923 51)[a,b]									
10	C_1	(−279.734 76)[b]	1.0808	1.9069	1.4894	1.4433	148.32	108.10	91.23	0.14	182.41
11	C_s	−643.002 78	1.0790	1.5974	1.5310	1.7847	179.74	107.56	104.65	0.00	180.00
12	C_s	−260.624 69	1.0787	1.5767	1.5349	1.4282	179.87	109.60	96.03	180.0	0.00
13	C_s	−581.851 07	1.0789	1.5954	1.5307	1.8370	179.39	107.47	105.14	0.00	180.00

[a] See compound f, Table IV, for structure. [b] Unstable structure.

produces the lowest energy point on the hypersurface. Even though this pathway to the formation of aziridinium ion is reasonable, it must be appreciated that other pathways with lower energies leading to other products may exist; however, no other pathways were found in this study. Structures c and e were the only true local minima found on the potential surface between the initial N_1-protonated triazoline and the final aziridinium ion product, by using the 3-21G basis set. The barrier heights to these rotations were not fully investigated; however, it is apparent from the minima along the reaction pathway that these are rotational transition states and therefore would be quite small.

It could be argued that the shallowness of (or lack of) the potential well for these protonated triazenes and triazolines may be a result of an inadequate basis set. The propensity for the 3-21G basis to underestimate the geometries and energetics for strained ring systems is well documented.[12] The energetic information obtained from the 3-21G basis level calculations will be less reliable than from those obtained by using a higher basis set. However, we believe that the qualitative mechanistic conclusions derived from the SCF 3-21G basis set calculations are valid.

C. Substituted Diazonium Ions. The lack of stability of the (2-aminoethyl)diazonium ion in the antiperiplanar conformation raises an interesting question. How stable are other 2-heteroatom-substituted ethyldiazonium ions relative to ring closure and expulsion of molecular nitrogen? As a consequence, several such diazonium ions were investigated by using a 3-21G basis set (or 3-21G* basis set for second-row elements). All of the diazonium ion optimizations were started from the antiperiplanar conformation. Energy information and geometrical parameters for the various diazonium ions studied are presented in Table V.

Surprisingly, the only other diazonium ion that was unstable in the transoid, antiperiplanar orientation was the [1-(methylamino)ethyl]diazonium ion, which like the parent (2-aminoethyl)diazonium ion, optimized directly to the three-membered ring structure with the displacement of molecular nitrogen. In both cases, the optimization was started with the amino nitrogen lone pair anti to the C–C bond in order to minimize the propensity toward ring closure. Intramolecular displacement of N_2 still occurred, with inversion of the amino nitrogen being part of the reaction coordinate. The other diazonium ions investigated,

Reaction Coordinate

including (2-chloroethyl)-, (2-hydroxyethyl)-, and (2-sulfhydrylethyl)diazonium ion, were stable and each optimized to a local minimum in the antiperiplanar orientation by using a 3-21G (3-21G* for the second-row elements, Cl and S) basis set. The transition states to ring formation were not explored, so the energy barriers for such processes are unknown at this time. However, the mere existence of a local minimum for these three diazonium ions is surprising enough given the fact that their amino analogues are unstable. The (2-chloroethyl)diazonium ion was examined in the past by using computational methods. Sapse and co-workers[13] studied the possible intermediates leading to the observed products of decomposition of (2-haloethyl)nitrosoureas. One intermediate, the (2-chloroethyl)diazonium ion, was found to be stable, and rigorous computation produced pertinent energetic information in good agreement with our study. Other intermediates studied by Sapse and co-workers included the (2-haloethyl)diazo hydroxides. Interestingly, evidence from these calculations pointed to collapse of these diazo hydroxides to form 1,2,3-oxadiazolines. Even though the transition state was not

(12) Hehre, W. J.; Radom, L.; Schleyer, R.; Pople, J. A. *Ab initio Molecular Orbital Theory*; Wiley-Interscience: New York, 1986; Table 6.69, p 293.

(13) Sapse, A.-M.; Allen, E. B.; Lown, J. W. *J. Am. Chem. Soc.* **1988**, *110*, 5671.

actually explored, Sapse and co-workers suggested "the formation of the 1,2,3-oxadiazoline intermediate to be geometrically and energetically feasible". These finidings are very similar to the reverse of the process reported here and strongly reinforce our conclusions. Experimental data also support the independent existence of the (2-chloroethyl)diazonium ion.[14]

The stability of the (2-sulfhydrylethyl)diazonium ion was particularly surprising due to the well-known propensity of sulfur moieties in a β position to a good leaving group to form the thiridinium ion.[15]

Rodriquez and Hopkinson discussed the stability of 2-substituted ethyl carbocations relative to their three-membered ring counterparts.[16] The 2-amino-, 2-hydroxy-, and 2-sulfhydrylethyl carbocations were studied. In all three cases, the three-membered ring structures were found to be more stable than the open chain carbocation analogues. The aziridinium ion is more stable by 46.1 kcal/mol, the oxiridinium ion is more stable by 14.0 kcal/mol, and the thiridinium ion is more stable by 32.0 kcal/mol, relative to the respective open chained counterparts, at the 6-31G* basis set level. From Figure 3, one can see that the aziridinium ion plus nitrogen lies lower in energy than its open chain counterpart (structures e, d, and f) by a large value, >30 kcal/mol (in accord with the results of Rodriquez and Hopkinson, who show that the aziridinium ion is the most stable of the heterocycles, relative to their respective open chain counterparts). It appears that ring formation in the case of the (2-aminoethyl)diazonium ion is related to the enhanced stability of the aziridinium ring as compared to that of the oxygen and sulfur analogues.

The consequences of the instability of (2-aminoethyl)diazonium ions may be quite significant. It is likely that the electrophilic intermediate involved in triazoline decomposition is the aziridinium ion, rather than the diazonium ion. It follows, therefore, that the interaction with certain types of nucleophiles such as DNA would be quite different for triazolines than for the corresponding triazenes. This would have profound effect, for example, on the design of chemotherapeutic agents based on these structures. This property could also be used to advantage in synthetic applications. Since triazolines are relatively stable in the presence of nucleophiles,[6] while aziridinium ions are highly reactive under those conditions,[17,18] triazolines could be used as masked aziridinium moieties. Experiments along these lines are being carried out in our laboratory.

Conclusion

4,5-Dihydro-1,2,3-triazole, 1-methyl-4,5-dihydro-1,2,3-triazole, and 1,4,5,6-tetrahydro-1,2,3-triazine were investigated via Hartree-Fock ab initio molecular orbital calculations at the 3-21G and 6-31G* basis set levels. Moller–Plesset perturbation theory was used to investigate the effects of correlation on the energetics of these systems.

4,5-Dihydro-1,2,3-triazoline was found to be unstable once protonated at N_1. Exploration of the potential surface reveals that the aziridinium ion plus nitrogen are the eventual stable products. Other diazonium ions were investigated to further explore the propensity of 2-substituted diazonium ions to collapse and displace molecular nitrogen. Of the diazonium ions studied, only the (2-aminoethyl)diazonium ion and [2-(methylamino)-ethyl]diazonium ion were found to have no barrier to ring formation at the 3-21G basis set level.

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(14) Lown, J. W. In *Synthesis and Properties of New Antileukemic 2-Haloethylnitrosoureas Based on an Analysis of the Reactions with DNA*; Bardos, T. J., Kalman, I. I., Eds.; Elsevier: New York, 1982; p 61.

(15) Smit, W. A.; Zefirov, N. S.; Bodrikov, I. V.; Krimer, M. Z. *Acc. Chem. Res.* **1979**, *12*, 282.

(16) Rodriquez, C. F.; Hopkinson, A. C. *J. Mol. Struct.*: THEOCHEM **1987**, *152*, 69.

(17) Dermer, O. C.; Ham, G. E. *Ethylenimines and Other Aziridines*; Academic Press: New York, 1969.

(18) Rieber, N.; Bohm, H. *J. Heterocycl. Chem.* **1981**, *18*, 1.