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# ON THE MECHANISM OF THE DIAZIRINE EXCHANGE REACTION WITH AZIDE ANION

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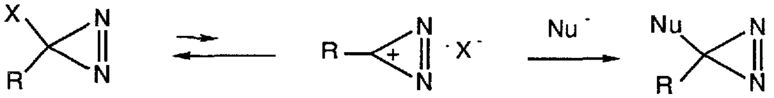
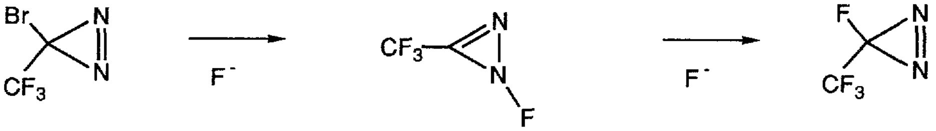
*Summary*: Treatment of isotopically labeled bromophenyldiazirine containing one $^{15}N$ atom with azide ion produces benzonitrile which contains 50% $^{15}N$. This suggests that N-azidodiazirines are intermediates in the reaction. *Ab initio* calculations predict that N-azidodiazirines will have a very low barrier to decomposition to nitrile and two molecules of nitrogen.

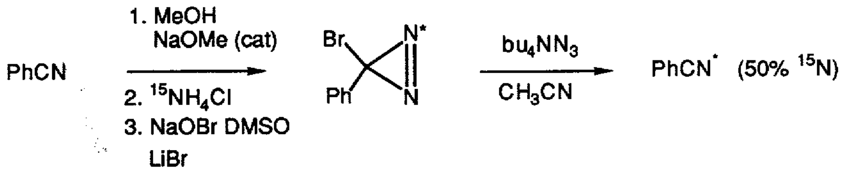
The diazirine exchange reaction which was pioneered by Moss and coworkers is a valuable synthetic method for the preparation of various novel diazirines.[1] In this reaction, a halodiazirine is treated with a strong nucleophile and the halogen atom is eventually replaced by the nucleophile. There is theoretical[2] and experimental[3] evidence which suggests that the reaction proceeds through a tight ion pair intermediate which is captured by the externally added nucleophile.



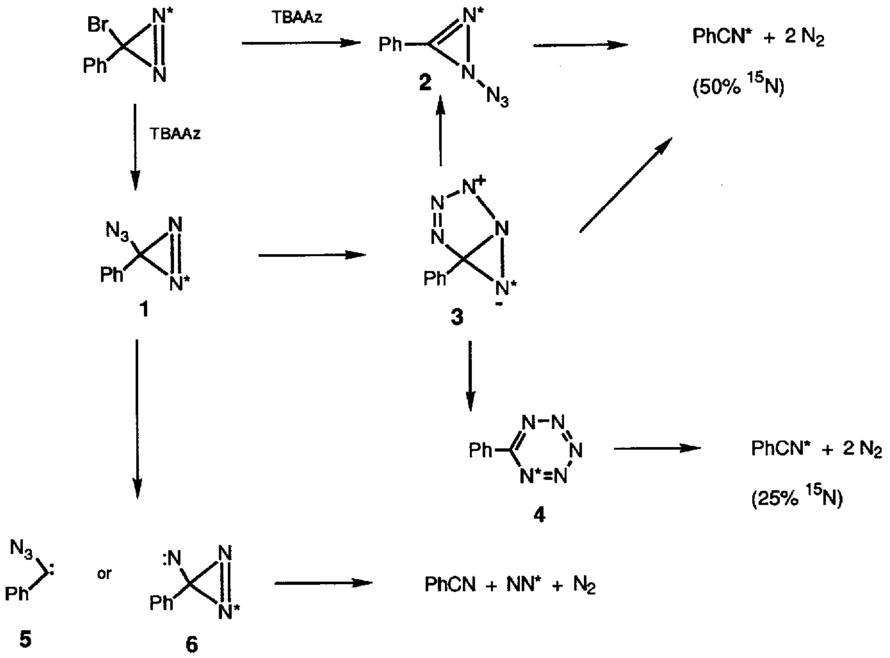
We have recently reported that treatment of bromotrifluoromethyldiazirine with fluoride ion generates fluorotrifluoromethyldiazirine in good yield under the standard diazirine exchange conditions.[4] Because one would have expected a tremendous rate deceleration for any reaction whose mechanism requires a cationic center adjacent to a trifluoromethyl group,[5] we proposed that the exchange reaction in this case proceeded by a double $S_N2'$ reaction. This mechanism was originally proposed by Graham.[6]



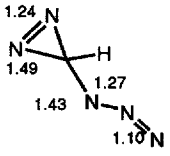
The mechanism of the diazirine exchange reaction has been explored in detail by Moss and coworkers using bromoaryldiazirines and azide anion as the nucleophile.[3] The reaction proceeds in good yield and produces nitrogen gas and an arylnitrile. In the tight ion pair mechanism, an azidodiazirine intermediate (**1**) would be formed which decomposes to two molecules of nitrogen and one molecule of nitrile. *Ab initio* calculations predicted that **1** should be a "high-energy, very unstable intermediate" and that there are several possible pathways to decomposition.[3] However, "neither the nitrenodiazirine nor the azidocarbene represent potential energy surface minima".[3] If the mechanism involves an initial $S_N2'$ reaction, an N-azidodiazirine (**2**) would be formed and this too would be expected to decompose to produce analogous products. The $S_N2'$ mechanism predicts that the nitrile nitrogen atom of the product would be derived from one of the original diazirine nitrogen atoms. Alternative mechanisms proceeding from **1** might not require that one of the diazirine nitrogen atoms were present in the nitrile product (see below). As a probe of the mechanism of the diazirine exchange reaction with azide ion, we have prepared the mono $^{15}N$ labeled bromophenyldiazirine and reacted it with tetrabutylammonium azide under Moss' conditions. The mono $^{15}N$ labeled benzamidine hydrochloride was prepared by reaction of benzonitrile with a catalytic amount of sodium methoxide in methanol followed by addition of one equivalent of $^{15}NH_4Cl$ ( 98 atom % $^{15}N$, Aldrich). Treatment of this material with sodium hypobromite in aqueous DMSO produced the bromophenyldiazirine which contained 50% $^{15}N$ by mass spectroscopy.[7] Mass spectrometric analysis of the benzonitrile produced from the reaction of this labeled material with azide ion indicates that it contains exactly 50% $^{15}N$.[7] This conclusively demonstrates that the nitrile nitrogen atom is derived from one of the diazirine nitrogen atoms.



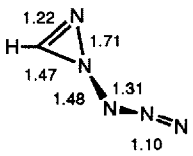
The various mechanistic alternatives may now be addressed. If the diazirine exchange reaction produces an azidodiazirine (**1**), there are several possible modes for decomposition. On the basis of our labeling study, the mechanisms proceeding through the nitrenodiazirine (**6**) and azidocarbene (**5**) may be dismissed since they would predict no incorporation of the $^{15}N$ label. This supports the earlier worker's conclusion that neither of these species is an intermediate.[3] A referee has suggested the possibility that **1** could lead to **3** (or an intermediate derived from **3**) and this could lead to labeled product. Ring expansion of **3** to the pentaazabenzene **4** and then decomposition would produce benzonitrile which contained 25% $^{15}N$. Consistent with previous calculations,[3] this eliminates **4** as an intermediate. Alternatively, **3** could rearrange to N-azidodiazirine (**2**) which would produce benzonitrile which contained 50% $^{15}N$ or it could lose both nitrogen molecules in concert and produce benzonitrile containing 50% $^{15}N$. The $S_N2'$ mechanism predicts that the exchange reaction produces the N-azidodiazirine (**2**) which could decompose either stepwise or concertedly to give benzonitrile containing 50% $^{15}N$.



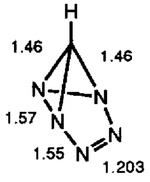
As a further guide, we have carried out *ab initio* calculations on the parent $CHN_5$ system using Gaussian 88.[8] We have located several minima at the HF/3-21G level of theory. These include the isomeric azidodiazirines **7** and **8** and the unusual tricyclic compound **9**. Compounds **7** and **9** maintained $C_s$ symmetry. Unlike the case for the decomposition of azidodiazirine **7**,[3] it was relatively easy to locate the transition structure **10** for decomposition of N-azidodiazirine **8** to hydrogen cyanide and two molecules of nitrogen. Reaction path following using the intrinsic reaction coordinate algorithm[8] confirmed that this transition structure led from **8** directly to hydrogen cyanide and two molecules of nitrogen without any other minima along the reaction path. Single point energy calculations were carried out at the HF/6-31G* level of theory on these stationary points. Partial bond lengths (Å) and the total and relative energies for these stationary points are shown below.



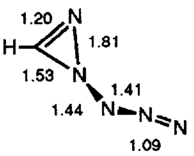
**7**



**8**



**9**



**10**

| | 7 | 8 | 9 | 10 |
|---|---|---|---|---|
| -E | 310.50845 | 310.43165 | 310.39637 | 310.41733 hartrees |
| rel E | -48. | 0.0 | 22. | 9. kcal/mol |

Our calculations predict that rearrangement of **1** to **2** should be endothermic by 48 kcal/mol. Since the decomposition of any intermediate must be less than the measured activation barrier of 18 kcal/mol,[3] this seems to exclude this pathway for the decomposition of **1**. Likewise, the tricyclic compound **9** is 70 kcal/mol higher in energy than **1**. We were not able to locate a transition structure resembling **3** which connects **1** to nitrile and nitrogen, but this does not exclude the possibility that one exists. On the other hand, **8** is calculated to decompose to nitrile and nitrogen gas with a barrier of less than 9 kcal/mol via transition structure **10**.

In conclusion, we have presented both experimental and theoretical evidence which supports the idea that the diazirine exchange reaction with azide ion proceeds via an $S_N2'$ mechanism to produce an N-azidodiazirine. This compound is calculated to decompose directly to nitrile and two molecules of nitrogen with a very small barrier. While our findings do not completely dismiss the alternative tight ion pair mechanism proceeding through the azidodiazirine **1**, we believe the requirement of a hypothetical intermediate such as **3** (or the corresponding biradical or ring-closed tricyclic compounds ) argues against it.

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