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Vapor phase phototransposition of pyrazine deuterium labeling studies

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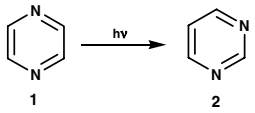
Abstract—2,5-Dideuteriopyrazine (**1**-2,5-d_2) and 2,6-dideuteriopyrazine (**1**-2,6-d_2) phototranspose in the vapor phase to mixtures of 4,6-dideuteriopyrimidine (**2**-4,6-d_2) and 2,5-dideuteriopyrimidine (**2**-2,5-d_2) or 4,5-dideuteropyrimidine (**2**-4,5-d_2) and 2,4-dideuteriopyrimidine (**2**-2,4-d_2), respectively. In each case, a trace quantity of a dideuteriopyridazine (**7**-d_2) photoproduct was also observed. These products are consistent with a diazaprefulvene mechanism involving, 2,6-bonding, one or two nitrogen migrations, and rearomatization.

Although the phototransposition of pyrazine **1** to pyrimidine **2** in the vapor phase was reported almost four decades ago,[1–3] little is known regarding the mechanism of this isomerization.[4] Two mechanistic pathways can be envisioned for this phototransposition. One pathway, shown in Scheme 1, involves the intermediacy of diazaprismane **4**.[5,6]



This species can cleave by pathway A or B to form Dewar-pyrimidines **5** and **6** which would rearomatize to form pyrimidine with the scrambling patterns shown in **2a** or **2b**.

A second plausible pathway, shown in Scheme 2, involves initial photochemical 2,6-bonding to form diazaprefulvene **1b**.[7] One nitrogen migration in either a clockwise or counter clockwise direction converts **1b** to diazaprefulvenes **1c** or **1d** which would rearomatize to pyrimidine with the scrambling patterns shown in **2c** and **2d**. In this pathway, a second nitrogen migration in either direction followed by rearomatization of **1e** or **1f** would lead to the formation of pyridazine with the scrambling patterns shown in **7e** and **7f**.[8] Thus, unlike the diazaprismane mechanism, which predicts only the formation of pyrimidine, the diazaprefulvene pathway allows for the formation of both pyrimidine and pyridazine as photoproducts.

In order to distinguish between these two mechanistic pathways, the vapor phase photochemistry of 2,5-dideuteriopyrazine (**1**-2,5-d_2)[9] and 2,6-dideuteriopyrazine (**1**-2,6-d_2)[11] has been studied. These reactants were selected because they would transpose to the isomeric dideuteriopyrimidines shown in Scheme 3 by the two mechanistic pathways.

In these studies, the dideuterated pyrazine, **1**-2,5-d_2 or **1**-2,6-d_2, was allowed to vaporize into an evacuated 3 L quartz vessel to a total pressure of 3.0 Torr. The vessel was irradiated at 254 nm in a Rayonet Photochemical Reactor equipped with 16 low pressure Hg lamps. After 15 min of irradiation, the resulting vapor was pumped out of the reaction vessel and condensed in an acetone-dry ice trap. The condensate was examined by gas chromatography, mass spectroscopy, and ^{1}H NMR.

Gas chromatographic analysis of the product mixture obtained by irradiation of 2,5-dideuteriopyrazine (**1**-2,5-d_2) revealed a small amount of unconsumed reactant and a very large peak with the same retention time as an authentic sample of pyrimidine. The mass spectrum of this major product exhibited a molecular ion at $m/z =$ 82, corresponding to the molecular weight of dideuteriopyrimidine. In addition, GC analysis also showed

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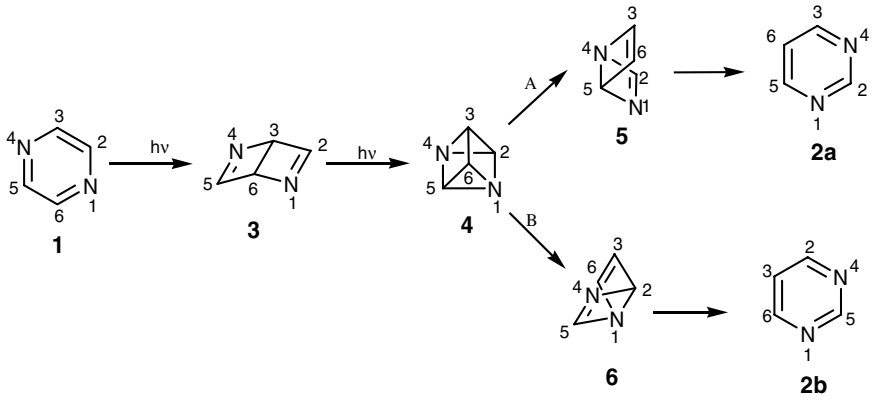
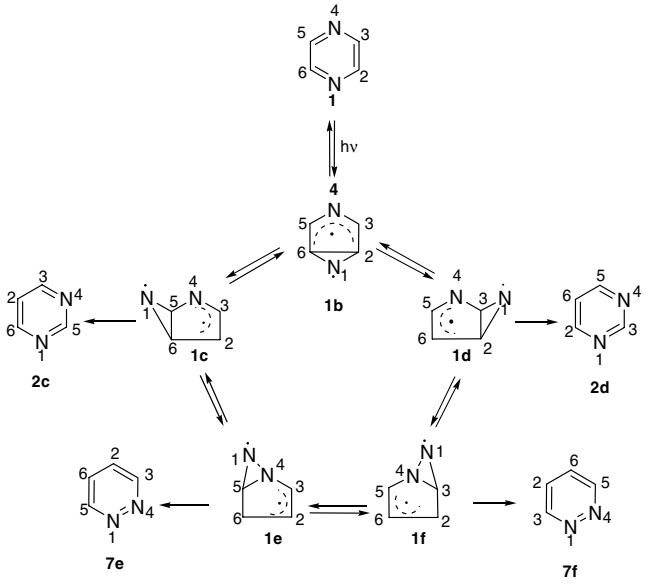


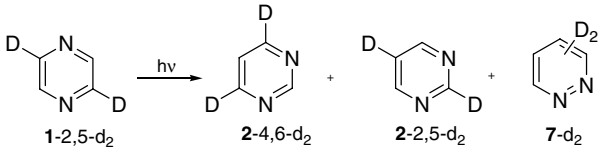
Scheme 1.



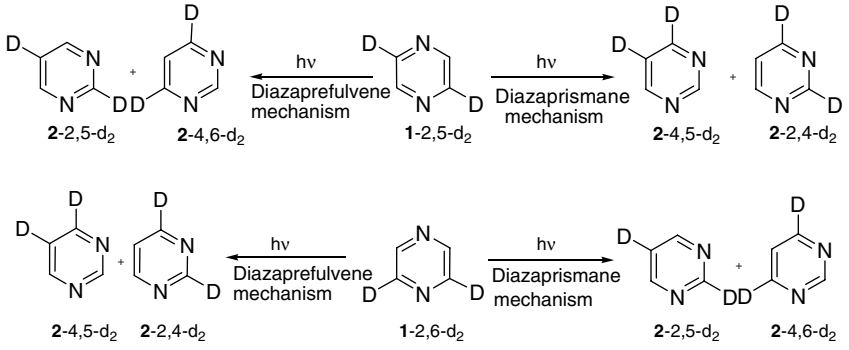
Scheme 2.

a trace quantity of another product identified as a dideuteriopyridazine isomer.

The product mixture was also analyzed by ^{1}H NMR spectroscopy. Figure 1 shows a portion of the ^{1}H NMR spectrum from δ 6.5–9.5 (a) before irradiation and (b) after irradiation for 15 min. Before irradiation the spectrum shows a singlet at δ 8.59 due to the equivalent H3 and H6 protons of **1**-2,5-d_2. After irradiation, the spectrum shows a small singlet at δ 8.59 due to unconsumed reactant and three new singlets at δ 9.23, 8.70, and 7.32 in an integrated ratio of 1:2:1 due to the formation of products. Since each photoproduct will bear two deuterium atoms and two protons, the appearance of these signals means that two different dideuteriopyrimidine isomers have been formed. Furthermore, since all of the signals are singlets, neither of the photoproducts can have hydrogen atoms on adjacent ring positions. By comparison with the known chemical shifts of pyrimidine ring protons, the 1H singlets at δ 9.23 and 7.32 were assigned to H2 and H5 of 4,6-dideuteriopyrimidine (**2**-4,6-d_2), while the 2H singlet at δ 8.70 was assigned to the equivalent ring protons at ring positions 4 and 6 of 2,5-dideuteriopyrimidine (**2**-2,5-d_2). The yield of the dideuteriopyridazine (7-d_2) was insufficient for detection by ^{1}H NMR spectroscopy. Accordingly, the positions of the deuterium atoms could not be determined. These results are summarized below.



2,6-Dideuteriopyrazine (**1**-2,6-d_2) vapor (3.0 Torr) was also irradiated for 15 min. Gas chromatographic and



Scheme 3.

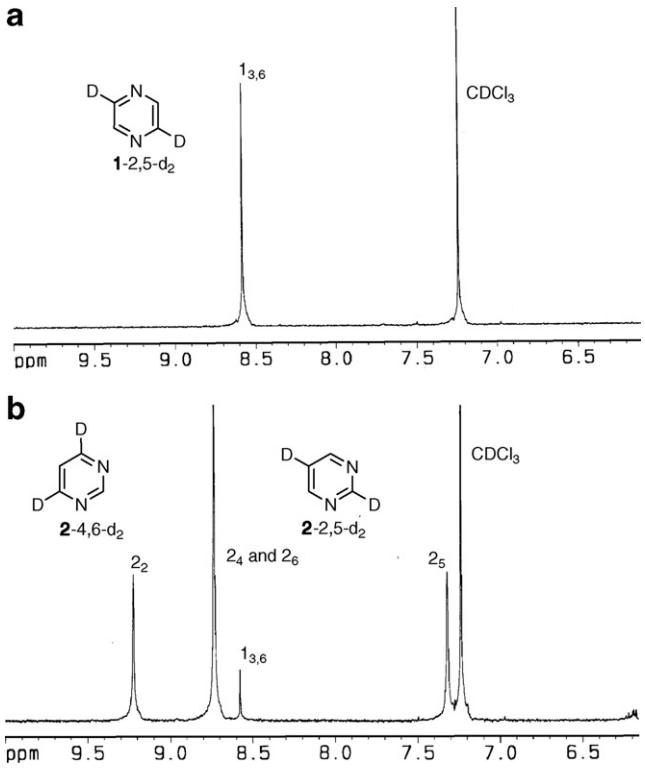


Figure 1. (a) 2,5-Dideuteriopyrazine before irradiation and (b) after irradiation for 15 min.

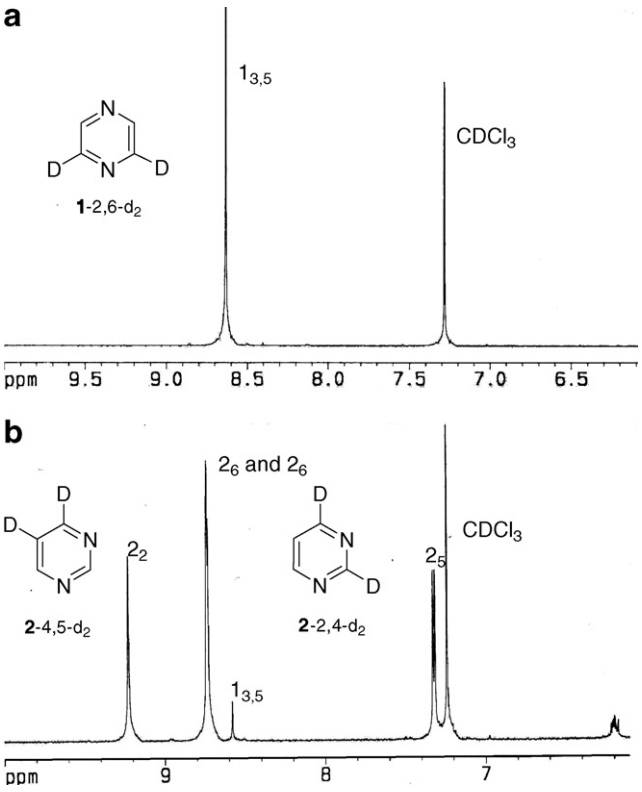
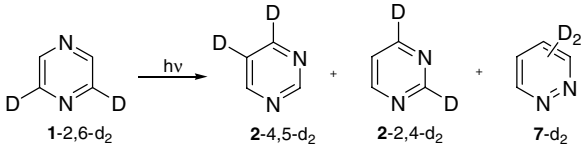


Figure 2. (a) 2,6-Dideuteriopyrazine before irradiation and (b) after irradiation for 15 min.

mass spectral analysis of the product mixture again revealed the presence of a small quantity of unconsumed reactant, a large yield of dideuteriopyrimidines, and a trace quantity of a dideuteriopyridazine isomer. The ^{1}H NMR spectrum before irradiation, shown in Figure 2a, shows a singlet at δ 8.54 for the equivalent H3 and H5 protons of the reactant **1**-2,6-d_2. After irradiation the spectrum shows a singlet at δ 9.23, a singlet at δ 8.74 overlapping with a doublet ($J = 4.5$ Hz) at δ 8.74, and a doublet ($J = 4.5$ Hz) at δ 7.32. The singlets at δ 9.23 and 8.74 were assigned to the H2 and H6 protons of 4,5-dideuteriopyrimidine (**2**-4,5-d_2) while the doublets at δ 8.74 and 7.32 were assigned to the H5 and H6 protons of 2,4-dideuteriopyrimidine (**2**-2,4-d_2).

As in the previous reaction, the yield of the dideuteriopyridazine (7-d_2) was insufficient for detection or identification by ^{1}H NMR. The results for this photoreaction are summarized below.



Comparison of the isomeric dideuteriopyrimidines obtained from **1**-2,5-d_2 and **1**-2,6-d_2 with those in Scheme 3, shows that in both cases the observed products are identical to those predicted by the diazaprefulvene mechanism but are different from those predicted by the diazaprismane pathway. The observation of dideuterated pyridazines from these reactions is also consistent with the diazaprefulvene mechanism. As shown in Scheme 2, these pyridazines would be formed via a second nitrogen migration from **1d** to **1f** or from **1c** to **1e**. This second nitrogen migration requires breaking a C–N bond and forming a weaker N–N bond. This second migration would thus be expected to be slower than the rearomatization of **1d** and **1c** to pyrimidines **2d** and **2c**. Accordingly, as observed, the yield of pyridazines is expected to be much smaller than the yield of pyrimidines.

References and notes

1. Lahmani, F.; Ivanoff, N.; Magat, M. C. R. *Acad. Sci. Paris* **1966**, *263*, 1005.
2. Lahmani, F.; Ivanoff, N. *Tetrahedron Lett.* **1967**, 3913.
3. For a review see: Lablache-Combier, A. In *CRC Handbook of Organic Photochemistry and Photobiology*; Horspool, W. M., Pill-Soon, S., Eds.; CRC Press: Boca Raton, 1995; p 1063.
4. Theoretical investigations concerning the photophysics and photochemistry of pyrazine have been carried out. See: (a) Sobolewski, A. L.; Woywod, C.; Domcke, W. *J. Chem. Phys.* **1993**, *98*, 5627; (b) Ferretti, A.; Lami, A.; Villani, G. *Chem. Phys.* **1995**, *196*, 447; (c) Ming-Der, S. *J. Phys. Chem. A* **2006**, *110*, 9420.
5. Prismanes have previously been suggested as intermediates in the photochemical isomerizations of aromatic and heteroaromatic compounds. See, for example (a) Wilzbach, K. E.; Kaplan, L. *J. Am. Chem. Soc.* **1965**, *87*, 4004; (b) Arnett, E. M.; Bollinger, J. M. *Tetrahedron Lett.* **1964**,

49; (c) Caplain, S.; Lablache-Combier, A. *J. Chem. Soc., Chem. Commun* **1970**, 1247.
6. Perfluoroalkyl substituted pyrdines are known to photoisomerize to perfluoroalkyl substituted prismanes which thermally rearomatize. See, for example: (a) Barlow, M. G.; Haszeldine, R.; Dingwall, J. G. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1542; (b) Chambers, R. D.; Middleton, R.; Corbally, R. P. *J. Chem. Soc., Chem. Commun.* **1975**, 731; (c) Chambers, R. D.; Middleton, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1500.
7. A similar biradical structure called prefulvene was first suggested to be an intermediate in the photisomerization of benzene. See: Byrce-Smith, D.; Longuet-Higgins, H. C. *J. Chem. Soc., Chem. Commun.* **1966**, *17*, 593.
8. A similar mechanism has been proposed to explain the vapor phase phototranspositions of deuterated pyridines. See: Pavlik, J. W.; Laohhasurayotin, S. *Tetrahedron Lett.* **2003**, *44*, 8109.
9. **1**-2,5-d_2 was synthesized from pyrazine-2,5-dicarboxylic acid by exchanging the carboxyl protons for deuterium followed by decarboxylation at 180 °C.[10]
10. Califano, S.; Adembri, G.; Sbrana, G. *Spectrochim. Acta* **1964**, *20*, 385.
11. **1**-2-6-d_2 was synthesized by conversion of pyrazine to pyrazine N-oxide,[12] base catalyzed exchange of the protons at ring positions 2 and 6 for deuterium,[13,14] followed by reduction of the N-oxide with phosphorous trichloride.[15]
12. Koelsch, C. F.; Gumprecht, W. H. *J. Org. Chem.* **1958**, *23*, 1603.
13. Kawazue, Y.; Onishi, M.; Yoshioka, Y. *Chem. Pharm. Bull.* **1964**, *12*, 1384.
14. Zoltewicz, J. A.; Kaufman, G. M. *J. Org. Chem.* **1969**, *34*, 1405.
15. Azzam, R.; Borggraeve, W. D.; Compernolle, F.; Hoornaert, G. J. *Tetrahedron Lett.* **2004**, *45*, 1885.