Stereospecific Hydrogen Rearrangement of a 1,4 Cation Radical

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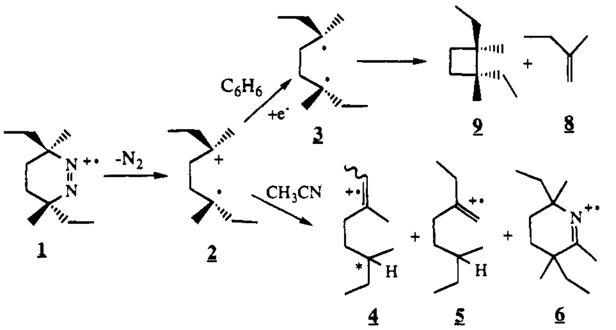
Received February 13, 1995

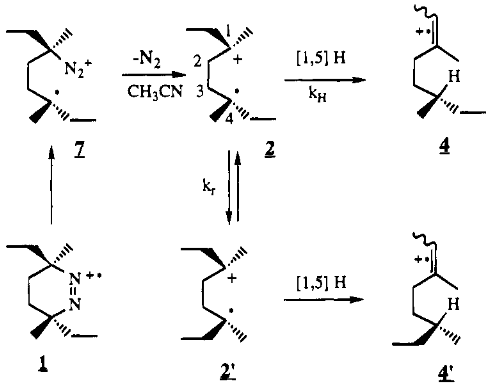
We recently reported[1a] that the photooxidative decomposition of *meso*- and *dl*-3,6-diethyl-3,6-dimethyl-1,2-diazacyclohexene (**1**) in benzene yielded 1,2-diethyl-1,2-dimethylcyclobutanes (**9**) stereospecifically (Scheme 1).[2] The reaction involved the initial loss of nitrogen from the azo cation radical to form the 1,4 cation radical **2**. Under the reaction conditions, **2** is reduced to the 1,4 biradical **3**, which then either ring closes or cleaves to yield 2-methylbutene (**8**). The stereospecificity of the reaction is due to the fast combined rates of reduction and ring closure relative to C−C bond rotation. However, if **1** is oxidized in polar solvents where ion pair separation occurs, the subsequent reduction of **2** is slow and a 1,5 hydrogen rearrangement occurs to afford the isomeric cation radicals of olefins **4** and **5**. In an effort to determine the relative lifetime of **2** under these conditions, we now report mechanistic details of this reaction using stereochemically and isotopically labeled substrates. In this regard, we have found that the hydrogen transfer occurs stereospecifically and with high regioselectivity, which suggests that although the reaction is exceedingly fast, it is highly selective.

Our initial stereochemical studies were designed to probe the relative rates of the 1,5 rearrangement of **2** and C−C bond rotation using enantiomerically enriched **1** (Scheme 2). If the rate of C−C bond rotation of **2** to form **2′**, k_r, is competitive with rearrangement, k_H, then the rearrangement olefin should be a mixture of enantiomers **4** and **4′**. Optically active (+)-**1** was obtained by the resolution of the precursor 3,6-dimethyl-3,6-diaminooctane with L-tartaric acid.[3,4] The absolute configuration of the diamine was determined to be 3(*R*),6(*R*) by X-ray crystallography of the diamine−D-tartrate complex.[5] Irradiation (λ > 420 nm) of dicyanoanthracene (0.5 mM) in a degassed acetonitrile solution containing cosensitizer biphenyl (0.2 M) and (+)-**1** (0.01 M) at 20 °C affords a mixture of *trans*- and *cis*-3,6-dimethyl-2-octene (**4**, 79%), 2-ethyl-5-methyl-1-heptene (**5**, 5%), and 3,6-diethyl-2,3,6-trimethyl-1-dehydropiperidine (**6**,16%).[6] For analysis, the isomeric product olefins were converted to the corresponding ketones by ozonolysis. The major ketone, 5-methyl-2-heptanone, was isolated and purified by preparative GC, and its optical rotation was compared to that of independently synthesized ketone of known optical purity and absolute configuration.[7,8] We find that decomposition of (+)-**1** yields **4** with ≥95% ee in CH_3CN and with *retention* of configuration.[10]

Scheme 1



Scheme 2



Several mechanistic questions about the rearrangement should be addressed. Formation of **4** could result from the stereospecific rearrangement of the diazonium radical intermediate, **7**, a possible precursor to **2**. However, this reaction would be expected to proceed with inversion of configuration at the asymmetric center, which is not observed experimentally. Conversely, nucleophilic displacement of N_2 in **7** by CH_3CN, followed by rearrangement, would result in the observed retention of configuration. However, the reaction also proceeds with retention in less nucleophilic solvents, CH_2Cl_2 and $(CF_3)_2CHOH$ albeit with less stereospecificity, 85 and 60% ee, respectively. The lower stereospecificity in these solvents may be due in part to competitive formation of the

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[1] (a) Zona, T. A.; Goodman, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 4925. (b) Zona, T. A.; Goodman, J. L. *Tetrahedron Lett.* **1992**, *33*, 6093

[2] For previous work on the oxidation of azoalkanes, see: (a) Engel, P. S.; Robertson, D. M.; Scholz, J. N.; Shine, H. J. *J. Org. Chem.* **1992**, *57*, 6178 and references therein. (b) Bae, D. H.; Engel, P. S.; Hoque, A.; Keys, D. E.; Lee, W.; Shaw, R. W.; Shine, H. J. *J. Am. Chem. Soc.* **1985**, *107*, 2561. (c) Engel, P. S.; Kitamura, A.; Keys, D. E. *J. Org. Chem.* **1987**, *52*, 5015. (d) Mendicino, M. E.; Blackstock, S. C. *J. Am. Chem. Soc.* **1991**, *113*, 713. (e) Adam, W.; Grabowski, S.; Miranda, M. A.; Rubenacker, M. *J. Chem. Soc., Chem.Commun.* **1988**, 142. (f) Adam, W.; Dorr, M. *J. Am. Chem. Soc.* **1987**, *109*, 1570. (g) Shine, H. J.; Bae, D. H.; Hoque, A. K. M. M.; Kajstura, A.; Lee, W. K.; Shaw, R. W.; Soroka, M.; Engel, P. S.; Keys, D. E. *Phosphorus Sulfur* **1985**, *23*, 111. (h) Adam, W.; Walter, H.; Chen, G.-F., Williams, F. *J. Am. Chem. Soc.* **1992**, *114*, 3007.

[3] *Optical Resolution Procedures for Chemical Compounds*; Newman, P., Ed.; Manhattan Press: Riverdale, NY, 1978; Vol. 1, p 542.

[4] The di-Mosher amide derivative was 86% *R,R*; 9% *R,S*; and 5% *S,S*, as determined by 500 MHz ^{1}H NMR analysis of the amide protons at 6.5−6.6 ppm. Product olefins derived from this mixture could have a maximum enantiomeric excess of 81%. The yield of the amide was typically >90%. The *d l:meso* ratio was checked for azo compound **1** by GC and NMR and found to be in good agreement, <3% difference, with that found for the amide derivative.

[5] Crystals of 3(*R*),6(*R*)-3,6-dimethyl-3,6-diaminooctane−D-tartaric acid belong to the orthorhombic space group $P2_12_12$ with a = 10.74(1) Å, b = 16.12(3) Å, c = 7.13(2) Å, V = 1234(6) Å^3, D_{calcd} = 1.368 g/cm^3, and Z = 4. Data were collected at 233 K, and the structure was refined to R_f = 0.073, R_w = 0.082 for 696 reflections with $I > 3.00\sigma(I)$.

[6] All analytical reactions were degassed by four successive freeze−pump−thaw cycles. Preparative reactions were degassed by bubbling argon through the solution for approximately 1 h prior to irradiation. Yields were determined by capillary gas chromatography relative to an internal standard and were the average of at least three runs.

[7] Rossi, R.; Salvadori, P. A. *Synthesis* **1979**, 209. Our synthesis of 5-methyl-2-heptanone is a variation on the literature construction of 6-methyl-3-octanone. We alkylated diethyl malonate with (*S*)-2-methylbromobutane followed by saponification and decarboxylation. In contrast to the literature route, we converted the resulting acid to the Weinreb amide[9] and reduced this with methylmagnesium bromide to the desired ketone.

[8] The enantiomeric excess of the ketone was assumed to be undiminished in conversion from the starting bromide; $[\alpha]^{21}{}_D$ +4.31° (*c* 5.2, $CHCl_3$). The enantiomeric excess of the bromide was determined by conversion to the corresponding alcohol and then to the Mosher Ester. ^{1}H NMR analysis of the the Mosher esters derived from both chiral and racemic alcohols indicates the bromide is 93.4% ee.

[9] Nahm S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

[10] The product olefins do not isomerize nor lose optical activity under the reaction conditions. The ratio of products is independent of irradiation time.

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transoid conformation of **2** by rotation about the C_2-C_3 bond. In CH_3CN, this conformer may be selectively trapped by the solvent to form imine **6**.[11]

The intermediacy of the 1,4 cation radical **2** in the formation of olefins **4** and **5** and cyclic imine **6** is supported by several experimental observations. First, irradiation of dicyanobenzene (0.005 M) in a degassed CH_3CN solution containing cosensitizer benzene (1.5 M) and 2-methylbutene (0.35 M) affords olefins **4** and **5** and imine **6**, as was observed from oxidation of **1**.[12] Presumably, oxidation of 2-methylbutene is followed by nucleophilic addition by another olefin to form the putative intermediate **2**, which then yields products. Importantly, this method of generation of **2** does not involve the loss of nitrogen. Second, deuterium substitution at the ethyl methylene position of **1** results in a decrease in the **4**:**6** ratio by 17%.[13] These results suggest that both **4** and **6** are formed in part from a common intermediate, presumably the 1,4 cation radical **2**.[14] If so, the rearrangement of **2** is quite fast, $>10^8$ s^{-1}, as modeled by the lifetime of the *tert*-butyl cation in CH_3CN, which is thought to be quite short, <10 ns.[15]

It is of interest to compare the chemistry of the reactive intermediates **2** and **3**. Thermolysis or photolysis of the azo compound **1** yields **3**, which affords the olefins **4** (5%) and **5** (10%), in addition to 2-methylbutene (**8**, 50%) and 1,2-diethyl-1,2-dimethylcyclobutane (**9**, 35%).[1,16] Although **2** and **3** are both short lived and differ only in oxidation state, their product distribution is quite different. This may reflect quite different energy surfaces for the two species (Table 1). The product yields from **3** do not reflect the overall reaction exothermicities and indicate a rather nonselective and indiscriminate intermediate. In contrast, the 1,4 cation radical **2** is much more discriminate. The reactions to form **8** and **9**, which are exothermic for **3**, are endothermic for **2** and consequently do not occur under the reaction conditions. In addition, the relative olefin regioselectivities exhibited by the two species are quite different. The **4**:**5** olefin ratios from the 1,4 cation radical **2** and from the biradical **3** are 15.8 and 0.5, respectively. The rearrangements of **3** to form **4** and **5** are highly exothermic, and the difference, $\Delta\Delta H$, is small, 3.5 kcal/mol. In contrast, the reaction enthalpies for the formation of **4** and **5** from **2** are much smaller, and importantly the difference is significantly larger, $\Delta\Delta H = 10.5$ kcal/mol.

Table 1. Calculated Heats of Formation and Reaction Enthalpies (kcal/mol)

X	$\Delta H_f(X)^a$	$\Delta H_f(X^{\bullet+})^a$	$\Delta H_r(\mathbf{3} \rightarrow X)^b$	$\Delta H_r(\mathbf{2} \rightarrow X^+)^b$
4	−39.6	156.0	−59.7	−23.2
5	−36.1	166.5	−56.2	−12.7
8	−6.8	199.0	−33.7	+13.0
9	−27.9	190.0	−48.0	+10.8

[a] AM1 values.[17] [b] Calculated using $\Delta H_f(\mathbf{3}) = 20.1$ kcal/mol and $\Delta H_f(\mathbf{2}) = 179.2$ kcal/mol.[18]

In conclusion, we have found that optically active **1** yields **4** stereospecifically via the 1,4 cation radical **2**. The rate of rearrangement of **2** is significantly faster than C−C bond rotation but is competetive with CH_3CN trapping to form **6**. In addition, **2** exhibits high chemo- and regioselectivity, in contrast with the 1,4 biradical **3**. This suggests that the chemistry of biradicals can be greatly altered by oxidation (or reduction) because of large changes in the reaction enthalpies.

Acknowledgment. This work was generously supported by the National Science Foundation (CHE-9312429 and CHE-9057092) and the Alfred P. Sloan Foundation. We thank Prof. J. P. Dinnocenzo for helpful discussions and Prof. R. K. Boeckman for his help with the X-ray crystallography.

Supplementary Material Available: Experimental details, characterization data, and structural details, including an ORTEP diagram, for the diamine−D-tartrate complex (19 pages); listing of observed and calculated structure factors (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(11) Although the cyclic imine **6** could arise from an initial reaction of the solvent CH_3CN with the azo cation radical of **1** or **7**, followed by loss of nitrogen and ring closure, we believe it is formed primarily from the Ritter reaction of the 1,4 cation radical **2** with CH_3CN, followed by ring closure. Previous studies have failed to detect any CH_3CN dependence of the azo cation radical lifetime in CH_2Cl_2.[1b]

(12) At short irradiation times and low conversion, the ratio of products (**4** + **5**):**6** from 2-methyl-1-butene is 0.74, which is different from that obtained from **1**. If the dimerization of 2-methyl-1-butene occurs predominantly to yield the transoid conformation of **2**, and it selectively reacts with CH_3CN, then the (**4** + **5**):**6** ratio might be expected to be lower than that obtained from **1**.

(13) Deuterium incorporation was accomplished by ethyl-d_5-magnesium bromide reduction of 2,5-hexanedione to afford the deuterated diol, which was converted to the diamine. 300 MHz ^{1}H NMR of **1**-d_{10} indicated >95% deuterium incorporation at the ethyl methylene position.

(14) Alternatively, **2** can rearrange to **4** in competition with formation of transoid **2**, which is trapped by CH_3CN to form **6**.

(15) (a) McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.; Steenken, S. *J. Am. Chem. Soc.* **1989**, *111*, 3966. (b) A reasonable model compound for the *tert*-butyl cation, the 1-phenylcyclohexyl cation, is not observed in CH_3CN, which suggests a lifetime of <10 ns, see: Cozens, F. L.; McClelland, R. A.; Steenken, S. *J. Am. Chem. Soc.* **1993**, *115*, 5050.

(16) Bartlett, P. D.; Porter, N. A. *J. Am. Chem. Soc.* **1968**, *90*, 5317.

(17) AM1 values obtained using Spartan, V. 3.1; Wavefunction Inc.: Irvine, CA, 1994.

(18) $\Delta H_f(\mathbf{3})$ was determined using the AM1 value of $\Delta H_f = -65.3$ kcal/mol for 3,6-dimethyloctane and a C−H bond dissociation energy of 94.8 kcal/mol.[19] $\Delta H_f(\mathbf{2})$ was obtained using $\Delta H_f(\mathbf{3})$ and the ionization potential of 6.9 eV for $(CH_3)_3C^{\bullet}$.[20]

(19) Doering, W. v. E. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 5279.

(20) *Gas Phase Ion and Neutral Thermochemistry*; American Institute of Physics, Inc.: New York, 1988; Vol. 17, Suppl. 1.