1,2-Azoxy Rearrangement and Fragmentation of β-Azoxy Radicals

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Our interest in carbon-centered radicals β to an azo group[1] led us to study the analogous β-azoxy radicals.[2] Azoxy compounds possessing biological activity are becoming increasingly common,[3] yet little is known about the radical chemistry of the azoxy group.[4] Presently, we report completely different chemical reactions for isomeric β-azoxy radicals differing in the location of oxygen.

Thermolysis of peresters **1**[5] and **2**[5] in C_6D_6 at 120.1 °C proceeded with rate constants of 2.27×10^{-4} s^{-1} and 2.31×10^{-4} s^{-1}, respectively. These values are close to that for the simple perester *tert*-butyl 3,3-dimethylperbutanoate ($k = 2.73 \times 10^{-4}$ s^{-1}), indicating that O–O bond homolysis is the rate-determining step for all three compounds.[12] A detailed product study of **1** and **2** revealed a striking difference in their chemical behavior; namely, **1** yields ~80% N_2O and isobutene while **2** produces neither of these fragments (cf. Table 1). Thus the carboxyl radical **3** from **1** must lose CO_2, isobutene, and N_2O. The first two of these steps occur sequentially, as evidenced by the formation of 3% carboxylic acid **6** and 0.29% 2,2'-dimethyl-2,2'-azoxypropane (**7**) when 0.685 M 1,4-cyclohexadiene (CHD) was present. (Scheme 1). The β-scission rate of **4** is calculated as $k_\beta [\text{CHD}][\text{N}_2\text{O}]/[\text{7}]$ = 2.21×10^6 M^{-1} s^{-1}[13] $\times$ 0.685 M $\times$ 79/0.29 = 4.1×10^8 s^{-1}, which is nearly as fast as fragmentation of β-azo radicals.[1] Since

† Author to whom inquiries about the X-ray crystal structure should be addressed.

(1) Engel, P. S.; Chen, Y.-Q.; Wang, C.-R. *J. Am. Chem. Soc.* **1991**, *113*, 4355.

(2) This work was presented in part at the 205th National Meeting of the American Chemical Society, Denver, CO, March 28–April 2, 1993, Paper No. 99.

(3) Parry, R. J.; Li, Y.; Lii, F.-L. *J. Am. Chem. Soc.* **1992**, *114*, 10062 and references cited therein.

(4) Koga, G.; Koga, N.; Anselme, J.-P. In *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*; Patai, S., Ed.; Wiley: New York, 1975; Part 2, p 922.

(5) Peresters **1**, **2**, and **14** were prepared from the corresponding azoxyacids by treatment with carbonyl diimidazole and *tert*-butyl hydroperoxide.[6] These azoxy acid precursors to **2** and **14** were synthesized using Kovacic's method[7] from the appropriate amino acids[8,9] while the azoxy acid corresponding to **1** came from oxidative hydrolysis of the pyrazolidinone, whose phenyl analog is known.[10] The structure of the *tert*-butyl azoxy acid was established by X-ray crystallography.[11] The azoxy peresters were purified by chromatography on Florisil, eluting with 15% EtOAc in hexane. The ^{1}H NMR spectra of samples used for thermolysis showed less than 1% of unexplained impurities (i.e., peaks not due to silicone grease, water, or residual solvent protons). ^{1}H NMR (250 MHz, C_6D_6): **1** δ 1.15 (9H, s), 1.39 (9H, s), 1.41 (6H, s), 2.52 (2H, s); **2** δ 1.15 (9H, s), 1.37 (9H, s), 1.42 (6H, s), 2.78 (2H, s); **14** δ 1.13 (9H, s), 1.17 (6H, s), 1.30 (9H, s), 3.61 (2H, s).

(6) Staab, H. A.; Rohr, W.; Graf, F. *Chem. Ber.* **1965**, *98*, 1122.

(7) Sullivan, F. R.; Luck, E.; Kovacic, P. *J. Org. Chem.* **1974**, *39*, 2967. Nelson, V.; Serianz, A.; Kovacic, P. *J. Org. Chem.* **1976**, *41*, 1751.

(8) Slimmer, M. D. *Chem. Ber.* **1902**, 400.

(9) Eisenbach, C. D.; Lenz, R. W. *Macromolecules* **1976**, *9*, 227.

(10) Prentice, B. *Justus Liebigs Ann. Chem.* **1896**, *292*, 272. Prentice, B. *J. Chem. Soc.* **1904**, *85*, 1667.

(11) Crystal data are as follows: triclinic, space group $P\bar{1}$, $a = 8.226(2)$ Å, $b = 12.526(2)$ Å, $c = 6.042(2)$ Å, $\alpha = 93.93(2)°$, $\beta = 108.16(2)°$, $\gamma = 72.31(1)°$, $Z = 2$, $D_{calcd} = 1.19$ g cm^{-3}. Intensity data were collected on a Rigaku AFC-5S diffractometer with graphite-monochromated Mo Kα radiation in the $2\theta \leq 55°$ range. The structure was solved with the direct methods program NITHRIL in the TEXSAN (v 2.0) Structure Analysis Package (Molecular Structure Corporation). Refinement converged with R = 0.047, R_w = 0.055 for 1955 (2764 collected) independent reflections with $I > 3\sigma(I)$.

(12) For a recent review of peresters, see: Sawaki, Y. In *Organic Peroxides*; Ando, W., Ed.; Wiley: New York, 1993.

(13) This trapping rate at 120 °C was calculated from the measured rate of primary radicals with CHD at 50 °C[14] and the same activation energy (5.5 kcal/mol) as found for methyl plus CHD.[15]

Table 1. Percent Yield of Thermolysis Products of **1** and **2** in C_6D_6

product	1	1 + CHD[a]	2	2 + CHD[b]
N_2	4	5	15	3
N_2O	80	79	0	0
CO_2	91	91	85	80
CH_4	15	6	14	11
C_4H_8[c]	76	84	0	0
C_4H_{10}[d]	42	79	0	0
acetone	58	1	66	21
t-BuOH	7	101	13	59
acid[e]	0	3	16	14
ether[f]	9	9	12	10
PhMe	21	0	11	0
ΣN_2[g]	93	96	43	56
ΣCO_2[h]	91	94	101	94

[a] 0.685 M 1,4-cyclohexadiene. [b] 0.33 M 1,4-cyclohexadiene. [c] Isobutene. [d] Isobutane. [e] The carboxylic acid from **1** is **6** while the acid from **2** is **12**. [f] The ether from **1** is **8** while the one from **2** is **13**. [g] Nitrogen balance = $N_2 + N_2O$ + acid + ether. [h] CO_2 balance = CO_2 + acid.

Scheme 1. Thermolysis of **1**
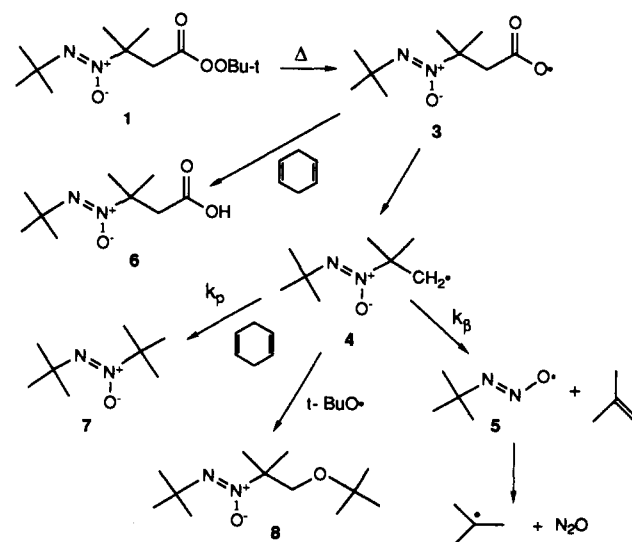
CHD might not trap **5** and since the hydrogen abstraction product would be an unstable aliphatic diazo hydroxide, we cannot distinguish stepwise from concerted fragmentation of **4**. The other noteworthy product is ether **8**, whose yield is unaffected by adding CHD and which must therefore arise in the solvent cage. Acyloxy radicals are known to decarboxylate fast enough[16] that **4** would be present in the solvent cage with *t*-BuO·.

In the case of azoxy perester **2**, the high CO_2 yield coupled with the absence of N_2O and isobutene imply that **9** decarboxylates but **10** does not fragment (Scheme 2). Formation of ether **13** occurs as in **1** (see above) while acid **12**, which is present even without added CHD, presumably arises from reaction of **9** with some hydrogen donor. Inclusion of CHD in the thermolysis solution produced the expected **7** along with a new product shown by authentic synthesis[17] to be **16** (Scheme 3). This result suggests that **10** cyclizes to **17**, which reopens to the more stable tertiary radical **15**. To verify this hypothesis, **14**[5] was thermolyzed under similar conditions, leading to **16** along with a small amount of **7**.

In view of the great current interest in free radical rearrangements,[18,19] we determined the interconversion rate of **10** and **15**
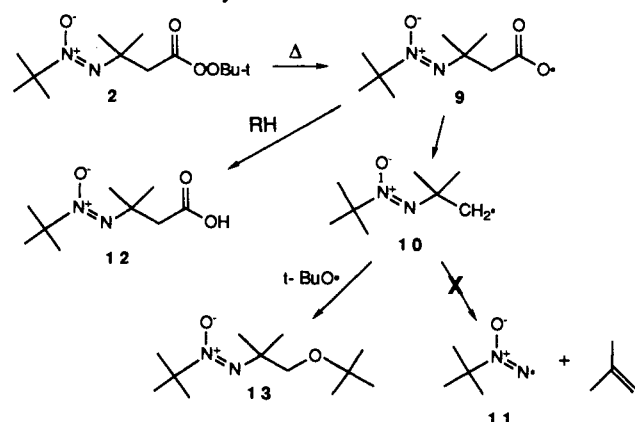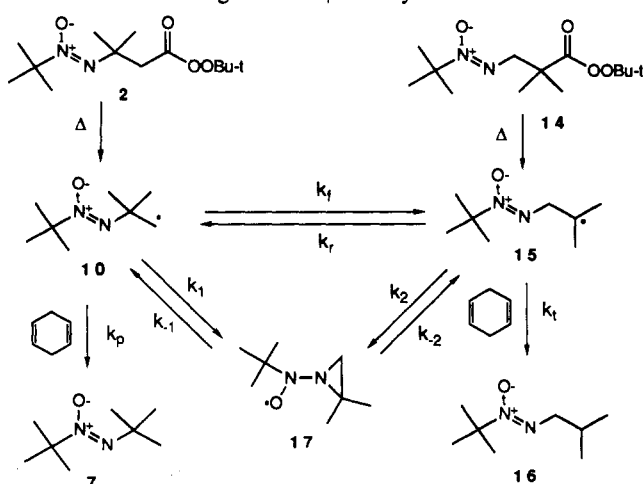
(14) Newcomb, M.; Park, S. U. *J. Am. Chem. Soc.* **1986**, *108*, 4132.

(15) Hawari, J. A.; Engel, P. S.; Griller, D. *Int. J. Chem. Kinet.* **1985**, *17*, 1215.

(16) Hilborn, J. W.; Pincock, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 2683.

(17) From 2-methyl-2-nitrosopropane and isobutylamine by Kovacic's method.[7] The material purified by preparative GC exhibited the following ^{1}H NMR spectrum (250 MHz, C_6D_6): δ 0.92 (6H, d, J = 6.7 Hz), 1.36 (9H, s), 2.03 (1H, nonet), 3.22 (2H, d, J = 6.6 Hz).

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Scheme 2. Thermolysis of **2**

**Scheme 3.** Rearrangement of β-Azoxy Radicals

from the product distribution on 120 °C thermolysis of **2** and **14** at various CHD concentrations.[20] The N_2 balance (Table 1) increased at higher [CHD], reaching 80% for **2** and 81% for **14** in neat CHD. The rate of diversion of radicals to high molecular weight materials enters only the intercept of the kinetic equations based on Scheme 3. Starting from **2**, a plot of **7**/**16** versus [CHD] gives a slope of k_p/k_f where k_p is the aforementioned trapping rate.[13] In the reverse direction, from **14**, a plot of **16**/**7** versus [CHD] gives a slope of k_t/k_r where k_t, the trapping rate for tertiary radicals, is 8.3×10^4 M^{-1} s^{-1}.[14,15] Both plots were pleasingly linear and led to the values $k_f = 1.5 \times 10^7$ s^{-1} and $k_r = 1.5 \times 10^3$ s^{-1}. The much greater magnitude of k_f than k_r is due to the Thorpe–Ingold effect invoked in analogous radicals,[21] but the rearrangement of **10** to **15** is a factor of 3.6 slower than the rate calculated at 120 °C for the analogous β-olefinic radical, 2,2-dimethyl-3-butenyl.[21] The interconversion of **10** and **15** resembles the rearrangement[23] of **18**, where radical attack also

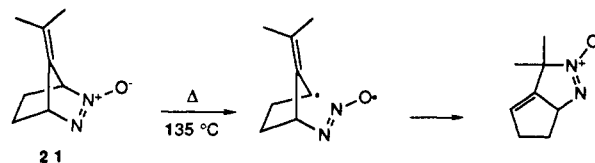occurs on nitrogen. Although ring closure of **10** and **15** is similar
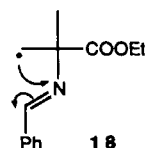
to the intermolecular "spin trapping" of radicals by nitrones,[22] preliminary attempts to detect the presumed intermediate nitroxyl radical **17** by ESR were without success. However, **2** is not a particularly appealing precursor for photochemical generation of **17** because the azoxy chromophore absorbs more strongly than the perester.

The above determination of k_f allows us to answer the longstanding question of whether β-azo radical **19** exists in the cyclized form.[24] In view of the tertiary radical center in **19** and the presumably smaller endothermicity of **10** $\rightarrow$ **17** than **19** $\rightarrow$ **20**, it is not likely that cyclization (k_c) of **19** is faster than that of **10** (k_1). The latter rate should be no more than $\sim$20% faster
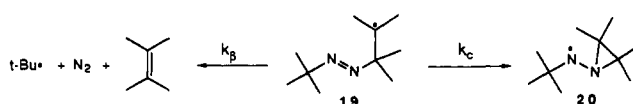
than k_f since **17**, like its carbon analog,[21] will surely proceed to **15** considerably faster than it reverts to **10**. Thus k_c will be <1.8 $\times 10^7$ s^{-1} at 120 °C while k_β is 2.5×10^9 s^{-1} at 153 °C.[1] The different temperatures used for these determinations are not very important in view of the low activation energies for rearrangement, leading us to conclude that k_β is about 100 times faster than k_c. Thus β-azo radical **19** will undergo β-scission long before it cyclizes.

Extrusion of N_2O from a closed shell molecule is much more endothermic than loss of nitrogen[25] and is therefore far less common. The presence of a radical center β to the azoxy group has the potential to facilitate N_2O loss since the reaction enthalpy (ΔH_r) for **4** or **10** fragmenting to t-Bu•, N_2O, and isobutene is only 4.8 kcal/mol compared to $\Delta H_r = 68.5$ kcal/mol for **7** $\rightarrow$ **2** t-Bu• + N_2O.[26] Why, then, does only **4** produce N_2O? The reason is simply that β-scission of **4** leads to a resonance stabilized species **5** while the analogous process in **10** would afford the much poorer radical **11**.[27] An analogy is found in **21**, which cleaves exclusively in one direction.[28] With the fragmentation pathway blocked, **10** undergoes intramolecular radical attack on the azoxy group, a reaction that becomes apparent only upon addition of a radical scavenger.

(18) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; deMayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, Chapter 4.

(19) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151.

(20) Starting from **2**, the yield (%) of **7** and **16** in benzene at various CHD concentrations (M) was as follows ([CHD], yield of **7**, yield of **16**): 1.03, 8.4, 46; 4.90, 26, 34.5; 7.88, 34, 28; 10.5, 46, 30. Starting from **14** under the same conditions, the data were as follows: 0.94, 0.38, 62; 4.86, 0.18, 79; 7.81, 0.14, 76; 10.5, 0.11, 77.

(21) Newcomb, M.; Glenn, A. G.; Williams, W. G. *J. Org. Chem.* **1989**, *54*, 2675.

(22) Janzen, E. G.; Haire, D. L. In *Advances in Free Radical Chemistry*; Tanner, D. D., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 1, p 253.

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(24) We thank Professor Ned A. Porter for raising this possibility.

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(26) Heats of formation of azoxyalkanes were determined by Bystrom: Bystrom, K. *J. Chem. Thermodyn.* **1981**, *13*, 139.

(27) Greene, F. D.; Burrington, J. D.; Karkowsky, A. *Organic Free Radicals*; ACS Symposium Series 69; American Chemical Society: Washington, DC, 1978; p 122.

(28) Olsen, H.; Oth, J. F. M. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 983.