Estimation of a Cyclic 1,4-Biradical Lifetime Using the Cyclopropylcarbinyl Rearrangement

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Received June 3, 1982

The chemistry of biradicals is currently a subject of intensive research.[1] These short-lived intermediates can be generated from a number of precursors, the cleanest and most versatile of which are cyclic azo compounds.[2] We report here the thermolysis and photolysis of a bicyclic azoalkane whose resulting biradical contains a "free radical clock".[3]

1-Cyclopropyl-2,3-diazabicyclo[2.2.2]oct-2-ene (CPDBO) was prepared from 1-cyclopropylcyclohexa-1,3-diene by the usual triazolinedione route.[4] After purification by low-temperature recrystallization from pentane followed by sublimation, CPDBO[5] exhibited a melting point (49.5–52.5 °C) and a UV spectrum (λ_{max} 382 nm, ϵ 123) very similar to that of DBO.[6,7]

Decompostion of CPDBO under a variety of conditions produced hydrocarbons **3–6** (Scheme I) whose yields are shown in Table I. Control experiments revealed that the product composition under benzophenone sensitization was invariant with reaction time, indicating that **3–6** are primary products. The formation of **5** is of particular significance and will be discussed further below.

The structures of **3** and **4** rest on their NMR and mass spectra[5] while compounds **5** and **6** were synthesized independently from 4-propylidenecyclohexanone. After separation by preparative GC, the isomers were distinguished conclusively by nuclear Overhauser effects.

The greatly different product distribution between direct and sensitized photolysis of CPDBO (a spin correlation effect)[2] immediately suggests that intersystem crossing in the azoalkane is inefficient. This conclusion would be unjustified in other DBO derivatives because they give nearly the same products under the two decomposition modes.[8]

In the simplest rationalization of the data in Table I, singlet **1** (**1S**) and triplet **1** (**1T**) apportion themselves differently among competing pathways to product, so that only k_2, k_3, and k_4 need be considered in Scheme I. We then calculate the value of ratio $R \equiv k_2/(k_3 + k_4)$ from the product yields as 0.053 for **1S** and 1.56 for **1T**. Since k_2 is associated with a 5.9 kcal mol^{-1} activation barrier,[9] the increased yield of **5** at elevated temperatures is readily understood. These values of R could be used to estimate the lifetime of biradicals **1S** and **1T** from $\tau = 1/(k_2 + k_2/R)$ if a value for k_2 were available. Cyclopropylcarbinyl itself exhibits $k_2 = 2.0 \times 10^8$ s^{-1} [9] at 25 °C but the rearrangement of α,α-dimethylcyclopropylcarbinyl has not been studied. However, the analogous dimethylcyclobutyl radical rearranges 8.9 times slower than cyclobutylcarbinyl.[10] Applying this ratio to cyclopropyl carbinyl provides an estimate of $k_2 = 2.2 \times 10^7$ s^{-1}. If k_2 in Scheme I equals this value regardless of biradical multiplicity,[11] it follows that biradical **1S** should have $\tau_S = 2.3$ ns while **1T** has $\tau_T = 28$ ns.

Scheme I

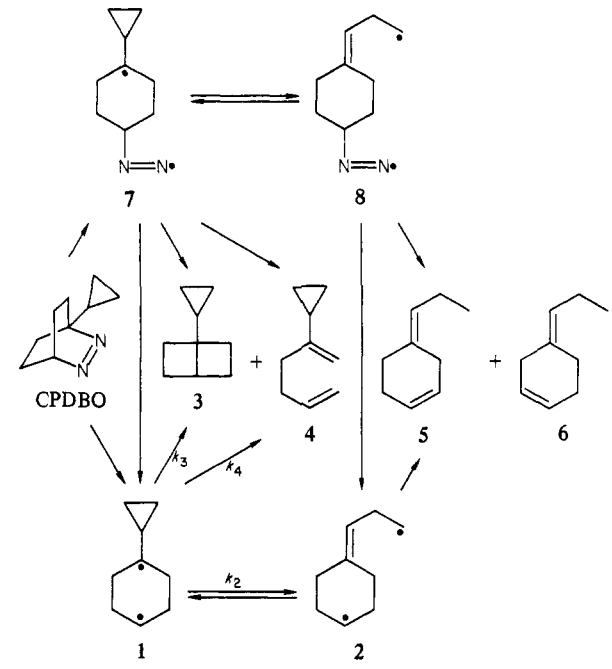

Table I. Product Yields (%) from CPDBO

decomp mode	temp, °C	3	4	5	6
direct $h\nu$, 366 nm[a]	10	31	64	5	<1
	25	30	65	5	<1
	53	27	69	4	<1
sensitized,[b] 313 nm[a]	9.5	45	39	9	7
	25	18	21	53	8
	54	10	11	68	12
thermolysis[c]	230		98	2	

[a] In benzene. [b] Benzophenone or *p*-methoxyacetophenone. [c] In *n*-hexadecane.

This difference in biradical lifetime arises because **1S** undergoes ring closure and opening faster than does **1T**, which must first spin invert.[12] If spin inversion is indeed the rate-determing step,[11] this process has a rate constant ($k_3 + k_4$) of 1.3×10^7 s^{-1}, which is about an order of magnitude faster than in 1,4-biradicals derived from photolysis of aliphatic aldehydes.[13] Although lack of an oxygen atom attached to one radical site may enhance spin inversion, the present estimate of τ_T is only as correct as our assumed mechanism.

In fact this mechanism may be oversimplified, because of the possible intermediacy of diazenyl radicals **7** and **8**[2,7,14] and the reversibility of cyclopropylcarbinyl rearrangement.[9] Furthermore, since a small amount of intersystem crossing might occur in CPDBO, the observed 5% yield of **5** on direct irradiation could arise in part via triplet CPDBO giving **1T**. Consequently, the 2.3-ns estimated lifetime for **1S** must be considered as a maximum. This problem does not arise in thermolysis of CPDBO, which still gives a 2% yield of **2**. The estimated lifetime of **1S** is 0.9 ns, on

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(12) If **3** and **4** arise by spin inversion of **1T**, their ratio should be the same as from **1S**. Since this ratio differs both here and in DBO,[8] not all of the **1T** goes to product via **1S**. Our treatment is still valid because k_3 and k_4 are always considered as a sum.
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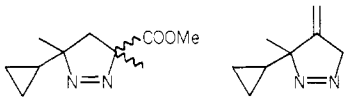
0002-7863/82/1504-6860$01.25/0

the basis of $R = 0.020$. Because thermolysis of **3** at 205 °C yielded exclusively **4**, the absence of **3** in the thermolysis of CPDBO is not surprising. As seen in Scheme I, it is possible that cyclopropylcarbinyl rearrangement occurs not in **1** but in diazenyl radical **7**, meaning that the 0.9-ns estimated singlet lifetime and the 28-ns triplet lifetime apply to **7**.

Whatever the detailed mechanism might be, the present results are unique, for Sanjiki and Ohta[15] were unable to observe cyclopropylcarbinyl rearrangement products from **9** or **10** under any

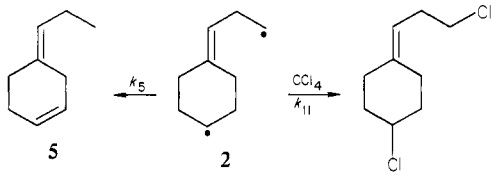


9 10

conditions tried. Thermolysis of two related azoalkanes[16,17] gave only small amounts of such products. On the other hand, cyclopropylcarbinyl rearrangement are common in the photochemistry of ketones[18] where the biradicals live for 30–100 ns.

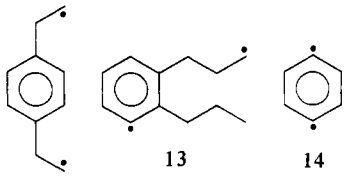
The formation of **5** from biradical **2** is a fascinating reaction because it represents disproportionation over a distance of at least 3 Å. The closest analogy of which we are aware is intramolecular hydrogen transfer over 2.25 Å.[19] Although we entertained the possibility that dienes **5** and **6** formed intermolecularly, this mechanism ought to produce them in more nearly equal amounts, rather than a predominance of **5**. An intermolecular pathway remains appealing in the case of **6** for obvious geometric reasons.

The observation that **2** undergoes such an unfavorable-looking reaction suggested to us that its lifetime might be relatively long. When the benzophenone-sensitized irradiation of CPDBO was carried out in CCl_4, the GC trace revealed about a dozen products, one of which was three times larger than the second most abundant product. Mass spectral analysis showed that it was a dichlorinated hydrocarbon, whose structure (**11**) is strongly supported by



5 2 11

NMR.[20] Although some **5** was formed in Ph_2CO/CCl_4, the absence of **6** in this radical scavenging solvent verifies the above suggestion that **6** is an intermolecular product. Because CCl_4 is not a very efficient radical trapping agent, it seems that **2** is indeed long lived. The trapping rate[21] is $k_{11}[CCl_4] = 1.3 \times 10^3 \times 10.4 = 1.4 \times 10^4\ s^{-1}$. The ratio **11**/**5** was 6.32, which allows us to calculate from the above mechanism that k_5 is $2.2 \times 10^3\ s^{-1}$ and that τ in the absence of a trapping agent is 0.45 ms. It must be emphasized that this very long lifetime is correct only if **11** derives exclusively from **2**; in fact, other possible sources of **11** are under consideration. The closest literature analogies for the trapping of **2** by CCl_4 are the reaction of **12** with dienes,[22] hydrogen donation from 1,4-cyclohexadiene to **13**,[23] and formation of *p*-dichlorobenzene from **14** and CCl_4.[24] Only a few other examples of biradical trapping have appeared.[11,18,25]



12 13 14

In summary, we can rationalize our data if azoalkane CPDBO decomposes to biradical **1** or **7**, which upon cyclopropylcarbinyl rearrangement, ultimately gives **2**. The latter biradical undergoes predominant intramolecular disproportionation over the extraordinarily long distance of 3 Å. Triplet-sensitized photolysis of CPDBO in CCl_4 allows trapping of biradical **2** as the dichloroalkene **11**.

Acknowledgment. We thank the National Science Foundation and the Robert A. Welch Foundation for financial support. Valuable criticism from Professor Peter B. Dervan is gratefully acknowledged.

Registry No. 1, 83615-84-3; **2**, 83615-85-4; **3**, 83615-86-5; **4**, 83615-87-6; **5**, 83615-88-7; **6**, 83632-67-1; **7**, 83615-89-8; **11**, 83615-90-1; CCl_4, 56-23-5.

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(20) **11**: *m/e* (rel abundance) 41 (52.9), 79 (100.0), 107 (55.0), 143 (4.24), 145 (1.36), 192 (1.45), 194 (0.79), 196 (0.22); NMR (90 MHz) δ 1.64–2.72 (m, 10 H), 3.49 (t, 2 H), 4.04–4.36 (m, 1 H), 5.16 (t, 1 H). The 500-MHz ^{1}H NMR spectrum with decoupling experiments also supports the structure of **11**. We thank Professor Peter B. Dervan for carrying out this work at the Southern California Regional NMR facility.
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Design and Synthesis of a Sequence-Specific DNA Cleaving Molecule. (Distamycin–EDTA)iron(II)

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Received August 16, 1982

The sequence-dependent recognition of nucleic acids by proteins and small molecules is important in the regulation of many biological processes. A large class of these molecules are bifunctional in nature, combining a chemically reactive moiety with a DNA binding unit. One such molecule is the naturally occurring antitumor antibiotic bleomycin, which binds to and cleaves DNA sequence specifically in a reaction that depends on Fe(II) and oxygen.[4] Recently we reported the synthesis of a DNA binding–DNA cleaving molecule, methidiumpropyl–EDTA (MPE).[5] This bifunctional molecule has the DNA intercalator, methidium, tethered to a metal chelator, EDTA. MPE·Fe(II) cleaves double helical DNA in the presence of dithiothreitol (DTT) with efficiencies comparable to those of bleomycin·Fe(II)/DTT. Unlike bleomycin·Fe(II), MPE·Fe(II) cleaves DNA non-sequence-specifically,[6] consistent with solution studies demonstrating that the intercalator methidium has no overall base composition specificity.[7]

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