Biradicals

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Orbital-Overlap Control of the Reactivity of a Bicyclic 1-Hydroxy-1,4-Biradical**

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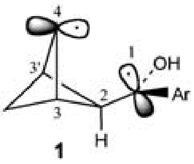
1,4-Biradicals are among the most ubiquitous reactive intermediates in organic chemistry, and are formed or implicated in a variety of reactions including [2+2] photocycloaddition,[1] the Paterno–Büchi reaction (oxetane formation),[2] the Norrish–Yang type II reaction,[3] and the elimination of nitrogen from cyclic azo compounds.[4] Once formed, 1,4-biradicals suffer two main fates: closure to form compounds containing a four-membered ring, and cleavage of the central bond to produce a pair of double-bond-containing fragments.[5] Based on organic intuition backed by semiempirical calculations,[6] and supported by a wide variety of product studies,[1–4] the generally accepted qualitative picture of biradical reactivity is that cleavage is favored when the conformation allows the radical-containing orbitals at positions 1 and 4 to overlap with the sigma bond between positions 2 and 3. Increasing amounts of cyclization are observed as this overlap diminishes, provided that the radical termini are within reasonable bonding distance of one another.

However, quantitative experimental tests of this hypothesis are rare, in part as a result of the difficulty of establishing structure–reactivity relationships for conformationally mobile systems in fluid media. In the case of triplet 1,4-biradicals, the picture is complicated by the likelihood that biradical behavior reflects the geometry in which the singlet biradical is formed by intersystem crossing (isc) from the triplet, which may differ significantly from the geometry of the conformationally equilibrated species.[7] For these reasons, we have elected to work with compounds in the crystalline state, where molecular conformation is fixed and determinable by X-ray crystallography, and where the singlet biradical formed by isc has the same geometry as its triplet precursor. We have shown that 1-hydroxy-1,4-biradicals can be generated conveniently in the solid state by the Norrish–Yang type II reaction, and that because hydrogen-atom transfer occurs with very little movement of the associated heavy atoms, the structure and conformation of the biradicals can be inferred directly from the X-ray crystal structures of their ground-state precursors.[8] Herein, we compare and contrast the behavior of 1-hydroxy-1,4-biradicals of general structures **1** and **2**. These biradicals are interesting because, unlike the majority of biradicals studied previously, they have only one significant degree of conformational freedom, namely, rotation about the C1–C2 bond. Among the questions we wished to answer about these biradicals were: 1) how does the orientation of the p orbital at the C1 position affect the ratio of cyclization to cleavage; and 2) can we correlate the orientation of the p orbital at C1 with preferential cleavage of either the C2–C3 or C2–C3′ bond? As described below, satisfactory answers to these questions were obtained by generating biradicals **1** and **2** in the crystalline state and correlating their behavior in this medium with their conformations as determined by X-ray crystallography.



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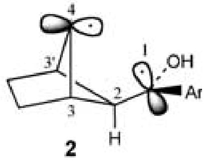

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We are not the first to study biradicals of types **1** and **2**. The solution-phase behavior of biradical **2** (Ar = Ph) was reported in 1972 by Padwa and Eisenberg and shown to consist of 66% cleavage and 30% cyclization.[9] Similarly, Alexander and Uliana showed in 1976 that, in solution, biradical **1** (Ar = Ph) bearing a phenyl substituent at the C2 position undergoes 100% cyclization.[10] In both cases, the biradicals were formed by a Norrish–Yang type II photoreaction of the corresponding ketone. In the present work, we chose to investigate ketones in which the aryl group bears a carboxylic acid substituent in the *para* position, that is, ketones of general structures **3** and **6** (Scheme 1). This choice was based on the following considerations: previous work from our group had shown that when achiral keto acids such as **3a** and **6a** are treated with optically pure amines, the resulting salts (**3b** and **6b**) crystallize with the carboxylate anions in homochiral conformations.[11] In principle, these salts could react when photolyzed in the solid state to produce, after diazomethane workup, the achiral Yang cyclization products **4c**/**7c** along with the chiral Norrish type II cleavage products **5c**/**8c** (Scheme 1). Cleavage of the

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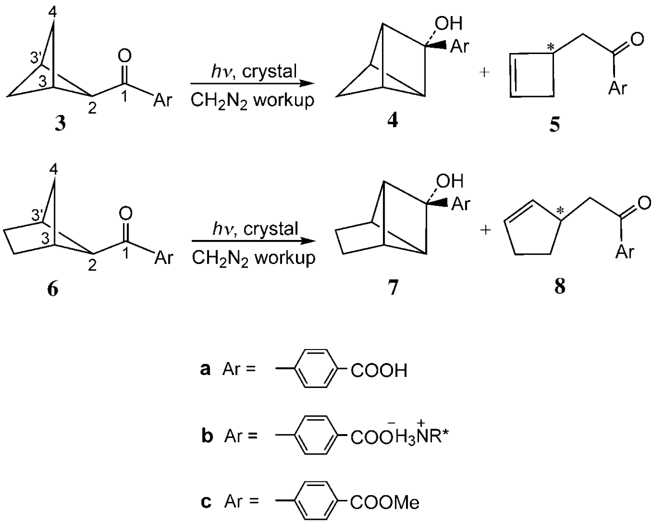

Scheme 1. Ketone reactants and their cyclization/cleavage photoproducts.

C2–C3 bond leads to (*R*)-**5c**/**8c** and cleavage of the C2–C3′ bond leads to (*S*)-**5c**/**8c**. Thus, by determining the absolute configuration of the cleavage product in each case and correlating this information with the absolute conformation of the carboxylate anion obtained by X-ray crystallography, we were able to establish which bond was cleaved and its degree of overlap with the p orbital on C1.

Although a number of different salts were prepared and their solid-state photochemistry investigated, we limit the present discussion to the two salts whose X-ray crystal structures were successfully determined, namely, the (*S*)-(−)-1-phenylethylamine salts of keto acids **3a** and **6a**.[12] Polycrystalline samples of these salts (2–5 mg) were crushed between pyrex microscope slides and the resulting sandwiches taped together, sealed under nitrogen in polyethylene bags, and irradiated (450-W medium-pressure mercury lamp) on both sides at various temperatures for different lengths of time. Even at high conversions, no melting could be detected. After photolysis, the crystals were treated with diazomethane in ether to remove the ionic chiral auxiliaries and form the corresponding methyl esters. The reaction mixtures were then subjected to GC analysis to determine the cyclization-to-cleavage ratios, and to chiral HPLC analysis to measure the enantiomeric excess (*ee*) in which photoproducts **5c** and **8c** were formed. The results are summarized in Table 1.[13]

Table 1: Solid-state photochemistry of (*S*)-(−)-1-phenylethylamine salts of keto acids **3a** and **6a**.

Acid	*T* [°C]	Conversion [%][a]	CY/CL[b]	*ee* [%][c]	α[d]
3a	−20	45	88:10	90	(−)
3a	20	38	87:11	87	(−)
3a	20	72	87:11	70	(−)
6a	−20	85	21:75	98	(−)
6a	20	21	20:79	>98	(−)
6a	20	53	21:77	98	(−)

[a] Determined by GC. [b] Ratio of cyclization (CY) to cleavage (CL). [c] Determined by chiral HPLC. [d] Sign of rotation of major enantiomer at sodium D line.

An independent, enantioselective synthesis of photoproduct **8c** was carried out to determine whether the major enantiomer produced in these photolysis reactions was of *R* or *S* configuration. Optically pure (*S*)-2-cyclopentene-1-acetic acid was prepared by resolution of the racemate with brucine according to the procedure of Mislow and Steinberg.[14] This material was then converted by reduction with lithium aluminum hydride, oxidation with pyridinium chlorochromate (PCC), addition of *p*-carbomethoxyphenylmagnesium iodide, and oxidation with PCC to (*S*)-**8c**, which proved to be dextrorotatory ($[\alpha]_D^{22} = +98.0°$, $c = 0.45$, MeOH). According to the sign of rotation shown in Table 1, this means that compound **8c** formed in the photolysis of the (*S*)-(−)-1-phenylethylamine salt of keto acid **6a** has the *R* absolute configuration. On the basis of the very close structural similarity between photoproducts **8c** and **5c**, we assume that the latter also has the *R*-(−) absolute configuration.

Concomitant with the photochemical and synthetic studies, the X-ray crystal structures of the (*S*)-(−)-1-phenylethylamine salts of keto acids **3a** and **6a** were determined (see Figure 1). A number of important geometric parameters were calculated from the crystal structures, including the γ-hydrogen-atom abstraction geometries as well as the geometric relationships relevant to the cyclization and cleavage of the 1-hydroxy-1,4-biradical intermediates (see Table 2).

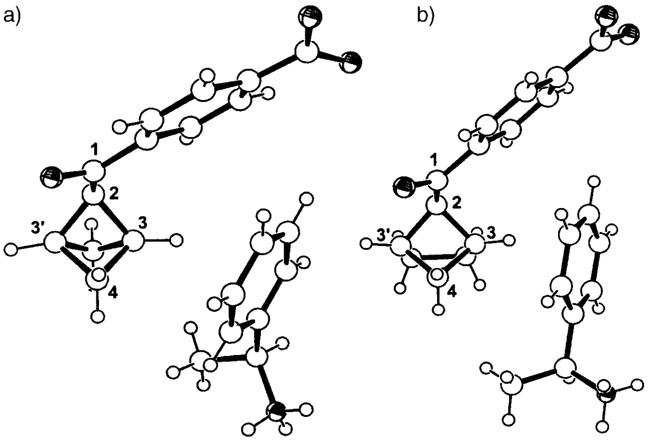

Figure 1. X-ray crystal structures of (*S*)-(−)-1-phenylethylamine salts of keto acids a) **3a** and b) **6a**.

To begin our discussion of the geometric parameters, we note that the value of d_{O-H4}, the distance between the carbonyl oxygen atom and the γ-hydrogen atom on C4, is similar for both salts and well within the guidelines established by us for

Table 2: Geometric data derived from the X-ray crystal structures of the (*S*)-(−)-1-phenylethylamine salts of keto acids **3a** and **6a**.

Acid	d_{O-H4} [Å][a]	d_{C1-C4} [Å][b]	β [°][c]	φ_1 [°][d]	φ_4 [°][e]
3a	2.67	2.81	22	22 (67)	43 (43)
6a	2.62	2.82	32	16 (78)	35 (35)

[a] C=O⋯H4 distance. [b] C1–C4 distance. [c] Angle between p orbital on C1 and the C2–C4 vector. [d] Angle between p orbital on C1 and C2–C3 (C2–C3′). [e] Angle between p orbital on C4 and C2–C3 (C2–C3′).

successful Norrish type II hydrogen abstraction in the crystalline state ($d = 2.7 \pm 0.2$ Å).[15] Similarly, the value of d_{C1-C4}, the distance between atoms C1 and C4 in the biradical produced by hydrogen abstraction, is the same for both salts. As a result, distance factors can be excluded as the source of the cyclization-to-cleavage ratio differences. The parameter β, defined as the angle between the p orbital on C1 and the C2–C4 vector, is ideal for cyclization when $\beta = 0°$, that is, when the p orbitals are pointing directly at one another. The values of β in Table 2 indicate that the **3a**-derived biradical is better arranged for cyclization than the **6a**-derived species.

The parameters φ_1 and φ_4 represent the angles formed between the p orbitals on atoms C1 and C4 and the C2–C3 and C2–C3′ bonds (the values of φ_1 and φ_4 for the C2–C3′ bond are shown in parentheses). The best arrangement for cleavage is expected when φ_1 and $\varphi_4 = 0°$, and the data indicate that cleavage of the C2–C3 bond is favored over cleavage of the C2–C3′ bond for both salts. This finding predicts that cleavage photoproducts **5c** and **8c** should have the *R* absolute configuration, a prediction that agrees with the configurational assignment made by independent synthesis of optically pure (*S*)-(+)-**8c**. It is interesting to speculate that the *ee* for **5c** is lower (70–90%) than that for **8c** (98%), because the difference in φ_1 for the former is less ($67-22=45°$) than that for the latter ($78-16=62°$). Of course, supramolecular factors[16] could contribute to the difference in *ee*, but the fact that the (*S*)-1-phenylethylammonium ion is common to both salts supports the notion that the major determinant of solid-state biradical behavior in these systems is the structure and conformation of the carboxylate anion.

The values of φ_1 and φ_4 also show that the biradical derived from **6a** has a better geometry for cleavage ($\varphi_1 = 16°$, $\varphi_4 = 35°$) than that from **3a** ($\varphi_1 = 22°$, $\varphi_4 = 43°$). Taken together with the earlier conclusion that the biradical from **3a** has a better geometry for cyclization than that from **6a**, the data clearly predict that salts derived from keto acid **3a** should have a higher Norrish–Yang cyclization-to-cleavage ratio than those derived from keto acid **6a**. This prediction is in accordance with the counterintuitive result that Yang photocyclization predominates in the bicyclo[1.1.1]pentane system **3a**, even though the cyclobutanol product in this case is more strained than that formed from the bicyclo[2.1.1]hexane reactant **6a**.

The work reported herein complements our previous research in this area[8] and highlights, in a quantitative fashion, the fact that relatively small differences in geometry can have a profound effect on 1-hydroxy-1,4-biradical behavior. Furthermore, it demonstrates once again the efficacy of the solid-state ionic chiral auxiliary approach to asymmetric synthesis in organic photochemistry.[17]

Experimental Section

Full experimental details on the synthesis of the starting materials, photolysis of the salts in the crystalline state, the diazomethane workup procedure, and the characterization of the photoproducts are available in the Supporting Information. CCDC 265554 and 265555 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[1] D. Andrew, A. C. Weedon, *J. Am. Chem. Soc.* **1995**, *117*, 5647, and references therein.

[2] a) A. G. Griesbeck, H. Mauder, S. Stadtmüller, *Acc. Chem. Res.* **1994**, *27*, 70; b) A. G. Griesbeck, S. Buhr, M. Fiege, H. Schmickler, J. Lex, *J. Org. Chem.* **1998**, *63*, 3847.

[3] a) P. J. Wagner, P. Klán in *CRC Handbook of Organic Photochemistry and Photobiology*, 2nd ed. (Eds.: W. Horspool, F. Lenci), CRC, Boca Raton, **2004**, chap. 52; b) P. J. Wagner in *CRC Handbook of Organic Photochemistry and Photobiology*, 2nd ed. (Eds.: W. Horspool, F. Lenci), CRC, Boca Raton, **2004**, chap. 58.

[4] a) W. Adam, C. Sabin in *CRC Handbook of Organic Photochemistry and Photobiology* (Eds.: W. M. Horspool, P.-S. Song), CRC, Boca Raton, **1995**, p. 937; b) W. Adam, A. V. Trofimov in *CRC Handbook of Organic Photochemistry and Photobiology*, 2nd ed. (Eds.: W. Horspool, F. Lenci), CRC, Boca Raton, **2004**, chap. 93.

[5] In the case of 1-hydroxy-1,4-biradicals generated in the photochemical Norrish–Yang type II reaction, a third possibility is reverse hydrogen transfer to regenerate the ground-state ketone, a quantum yield-lowering process.

[6] a) P. J. Wagner, A. E. Kemppainen, *J. Am. Chem. Soc.* **1968**, *90*, 5896; b) R. Hoffmann, S. Swaminathan, B. G. Odell, R. Gleiter, *J. Am. Chem. Soc.* **1970**, *92*, 7091.

[7] a) J. C. Scaiano, *Tetrahedron* **1982**, *38*, 819; b) A. G. Griesbeck, H. Heckroth, *J. Am. Chem. Soc.* **2002**, *124*, 396; c) A. G. Griesbeck, *Synlett* **2003**, 451.

[8] D. Braga, S. Chen, H. Filson, L. Maini, M. R. Netherton, B. O. Patrick, J. R. Scheffer, C. Scott, W. Xia, *J. Am. Chem. Soc.* **2004**, *126*, 3511.

[9] A. Padwa, W. Eisenberg, *J. Am. Chem. Soc.* **1972**, *94*, 5852.

[10] E. C. Alexander, J. Uliana, *J. Am. Chem. Soc.* **1976**, *98*, 4324.

[11] B. O. Patrick, J. R. Scheffer, C. Scott, *Angew. Chem.* **2003**, *115*, 3905; *Angew. Chem. Int. Ed.* **2003**, *42*, 3775.

[12] See the Supporting Information for a description of the preparation and solid-state photochemistry of the salts whose structures were not determined by X-ray crystallography.

[13] The photoreactions were significantly less selective in solution. The cyclization-to-cleavage ratio resulting from irradiation of keto ester **3c** in acetonitrile was 77:23 and that from **6c** was 30:66; in both cases, the cleavage products were racemic.

[14] K. Mislow, I. V. Steinberg, *J. Am. Chem. Soc.* **1955**, *77*, 3807.

[15] J. R. Scheffer in *Molecular and Supramolecular Photochemistry: Chiral Photochemistry, Vol. 11* (Eds.: V. Ramamurthy, Y. Inoue), Marcel Dekker, New York, **2004**, p. 463.

[16] By supramolecular factors, we refer to the interaction of the reactant with the surrounding crystal lattice during reaction. For a qualitative treatment of this aspect of solid-state photochemistry, see: R. G. Weiss, V. Ramamurthy, G. S. Hammond, *Acc. Chem. Res.* **1993**, *26*, 530; for a quantitative treatment, see: H. E. Zimmerman, E. E. Nesterov, *Acc. Chem. Res.* **2002**, *35*, 77.

[17] For reviews, see: a) J. R. Scheffer, *Can. J. Chem.* **2001**, *79*, 349; b) "Organic Solid State Reactions": J. R. Scheffer, W. Xia, *Top. Curr. Chem.* **2005**, *254*, 233.