Entropy *vs* Enthalpy Control of 1,5-Biradical Cyclization in the Photochemistry of α-(*o*-Alkylphenyl)acetophenones

Peter J. Wagner,* Ali Zand, and Bong-Ser Park

Chemistry Department, Michigan State University
East Lansing, Michigan 48824

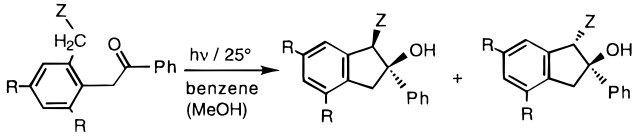
Received August 1, 1996

Over the past decade our group has explored δ-hydrogen abstraction in various phenyl ketones in order to assess how structural factors influence the formation and reactions of triplet 1,5-biradicals.[1] We have noted the importance of benzylic conjugation in inducing regio-[2,3] and stereoselectivity[4,5] and have stressed the need to distinguish between pre-existing conformational preferences and nonbonded interactions that are created only during actual cyclization as factors determining product ratios.[5a] During the same period the idea that triplet → singlet intersystem crossing (isc) determines biradical lifetimes has become widely accepted,[6] although product ratios typically are explained in terms of biradical geometries and product energies, despite the possibility that varying rates of isc for different biradical geometries could in fact dominate product ratios.[7,8] We have attempted to resolve this inconsistency by suggesting that isc occurs dynamically during cyclization rather than statically beforehand.[1,5] We report here temperature and medium effects on the stereoselectivity of 1,5-biradical cyclization that, together with semiempirical computations of biradical structure, reveal geometric effects on apparent entropies of cyclization that may represent the first experimental evidence for geometry-dependent biradical isc rates.

Scheme 1 compares the indanol yields obtained from the ambient temperature photocyclization of α-(*o*-benzylphenyl)-acetophenone (**5**) to those from the previously reported α-(*o*-ethylphenyl)acetophenones **1** and **3**.[5] *Z*/*E* ratios for **1** and **3** are large in benzene but, as usually observed in such cyclizations,[9] smaller in methanol. In stark contrast, **5** shows negligible selectivity.

Table 1 lists product ratios in solution as a function of temperature for these ketones[10] plus results for crystals. The corresponding Arrhenius plots are shown in Figure 1, with the activation parameter differences listed in Table 1. These results add to our earlier findings in two important ways: (1) changing the hydrogen donor from an ethyl to a benzyl group eliminates the stereoselectivity; (2) nonenthalpic factors appear to be as important as enthalpy differences at determining diastereoselectivity. Our original interpretation of the room temperature product ratios for **1** and **3** invoked cyclization from two biradical conformational minima, one *pre-Z* and one *pre-E*, that differed in energy by 1.7−2.0 kcal/mol.[5a] The measured ΔE_a values

Scheme 1



1: R = H Z = CH_3 Φ = 0.75 **Z-2** : 94 % (67 %) **E-2** : 6 % (33 %)
3: R = Et Z = CH_3 Φ = 0.52 **Z-4** : 96 % (81 %) **E-4** : 4 % (19 %)
5: R = H Z = Ph Φ = 0.40 **Z-6** : 54 % (50 %) **E-6** : 46 % (50 %)

Table 1. Medium and Temperature Effects on Cyclization Stereoselectivity

conditions	Z/E-**2**	Z/E-**4**	Z/E-**6**
toluene, 110°	11.5/1	16/1	1.5/1
benzene, 24° [a]	14.6/1 (0.75)	21/1 (0.52)	1.2/1 (0.40)
toluene, 0°	16.5/1	24/1	1.0/1
toluene, −72°	26/1	31/1	0.7/1
methanol, 24°	2/1	4/1	1/1
crystal, 24°	100/0	100/0	1/1
$E_E - E_Z$, kcal/m	0.69	0.55	−0.66
A_Z/A_E	4.6	8	3.5

[a] Product quantum yields in parentheses.

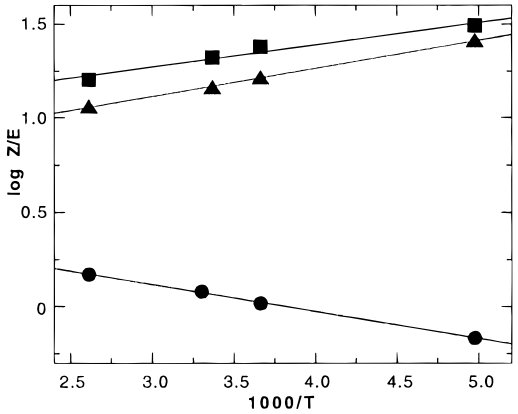


Figure 1. *Z*/*E* indanol ratios for ■ **3**, ▲ **1**, and ● **5**.

for **1** and **3** indicate that enthalpy differences between biradical conformers may be much smaller than we originally surmised, with much of the *Z*/*E* preference contained in the *A* factor for cyclization. Therefore, we have reexamined the geometric aspects of all the steps in this reaction.

Equation 1 describes product ratios when conformational equilibrium is established among various biradical geometries before cyclization.[11,12] The subscripts z and e refer to biradical

$$Z/E = \chi_{BRz}k^{z}_{cycl}/\chi_{BRe}k^{e}_{cycl} + \chi_{BRx}k^{z'}_{cycl}/k^{e'}_{cycl} \qquad (1)$$

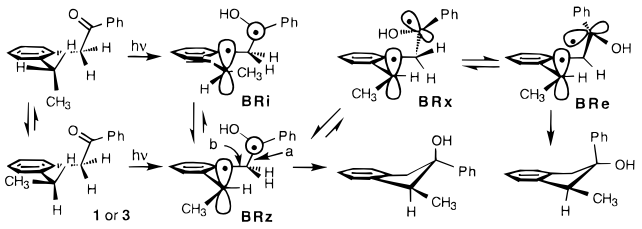
conformers that can cyclize with minimal bond rotations to Z or E indanol; x refers to any other conformer that must rotate into a *pre-Z* or *pre-E* geometry before cyclizing. The χ values ($\Sigma\chi_i = 1$) describe the Boltzman distribution of conformers. The *k* values contain only relative efficiencies of isc (as an entropy term) if isc occurs independently and if subsequent biradical cyclization is faster than any conformational interconversion.[7] If singlet biradicals interconvert before cyclizing or if isc occurs during cyclization, then *k* values also contain differences in activation enthalpies for cyclization of different conformers.

Scheme 2 depicts for **1** and **3** the likely topology for biradical formation and reaction. The geometric requirements for

(1) Wagner, P. J. *Acc. Chem. Res.* **1989**, *22*, 83.
(2) Wagner, P. J.; Meador, M. A.; Scaiano, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 7988.
(3) Wagner, P. J.; Giri, B. P.; Pabon, R.; Singh, S. B. *J. Am. Chem. Soc.* **1987**, *109*, 8104.
(4) Wagner, P. J.; Subrahmanyam, D.; Park, B.-S. *J. Am. Chem. Soc.* **1991**, *113*, 709.
(5) Wagner, P. J.; Park, B.-S. *Tetrahedron Lett.* **1991**, *32*, 165. Wagner, P. J.; Meador, M. A.; Zhou, B.; Park, B.-S. *J. Am. Chem. Soc.* **1991**, *113*, 9630.
(6) (a) Scaiano, J. C. *Acc. Chem. Res.* **1982**, *15*, 252. (b) Caldwell, R. A. *Pure Appl. Chem.* **1984**, *56*, 1167. (c) Doubleday, C., Jr.; Turro, N. J.; Wang, J.-F. *Acc. Chem. Res.* **1989**, *22*, 199.
(7) Scaiano, J. C. *Tetrahedron* **1982**, *38*, 819.
(8) Griesbeck, A. G.; Stadtmuller, S. *J. Am. Chem. Soc.* **1991**, *113*, 6923.
(9) Wagner, P. J. *J. Am. Chem. Soc.* **1967**, *89*, 5898. Wagner, P. J.; Kelso, P. A.; Kemppainen, A. E.; McGrath, J. M.; Schott, H. N.; Zepp, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 7506. Wagner, P. J.; Chiu, C. *J. Am. Chem. Soc.* **1979**, *101*, 7134. Wagner, P. J. *Acc. Chem. Res.* **1989**, *22*, 83.
(10) GC analysis of product ratios has provided slightly lower values than originally estimated[5] from NMR integration alone.
(11) Wagner, P. J. *Acc. Chem. Res.* **1983**, *16*, 461.
(12) Equation 1 is a modified form of the Curtin−Hammett principle in that it includes conformers that cannot react directly but which must be considered if static isc is the rate-determining step for biradical decay.

S0002-7863(96)02683-2 CCC: $12.00

Scheme 2

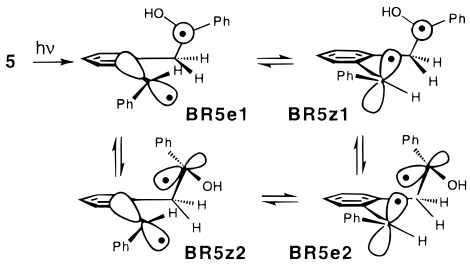


hydrogen transfer[5b] limit the α-hydroxy radical site to a single initial orientation, with the OH facing the central benzene ring. Both models and calculations indicate that **BRz** would be the major initial conformer; any **BRi** also formed would have only a ∼4 kcal/mol barrier to cross in order to form the more stable **BRz**. Thus, we estimate that the δ-methyl group is anti to the other radical center in >99% of the reacting 1,5-biradicals. The fact that both **1** and **3** yield only *Z* indanols in the crystal confirms that **BRz** is the predominant initial biradical geometry and that rotations around the α-hydroxy radical site, which presumably are forbidden in the crystal, are necessary for formation of *E* indanols. This conclusion would demand that the stereoselectivity for **1** and **3** depends on geometric variations at the α-hydroxy radical site, as Scheme 2 shows. The large solvent effects on **1** and **3** strongly support such a conclusion, as originally suggested.[5] Moreover, as we discuss below, the contrasting behavior of **5** further solidifies these conclusions.

Calculations on the conformational distribution around the α-hydroxy radical site of the biradical indicate only two other minima within 5 kcal/mol of **BRz**, the global minimum: **BRx** has the same energy as **BRz** but cannot cyclize directly; **BRe** lies only 0.4 kcal/mol above **BRz**.[13,14] Comparable results are calculated for **3**. The calculated energy of **BRz** varies by 1.5 kcal/mol depending on whether the OH hydrogen points toward or away from the central benzene ring. The former, favored geometry represents hydrogen bonding by the OH to the benzene ring, a well-established phenomenon[15,16] *that apparently controls selectivity in these reactions*. Solvation of the OH group lowers χ_{BRz} by reducing this stabilization of **BRz**.

These findings and the spin-orbit calculations on biradicals[17] of Michl provide an explanation for the activation parameters. Given the 1 kcal/mole activation energy for biradical decay,[5b] part of the measured ΔE_a could be generated during cyclization. Nonetheless, the similar values for ΔE_a and the calculated enthalpy difference between **BRz** and **BRe** do suggest that the product ratios reflect equilibrium biradical conformational populations, as predicted by eq 1. The A factor ratio indicates a lower entropy of cyclization for **BRe**, which is twisted around bonds a and b such that the two singly occupied p orbitals are almost orthogonal but not pointed at each other, as they are in **BRz**. The nonoverlapping orbital orientations in **BRe** and the twist of the α-hydroxy radical site would decrease both through space and through bond spin-orbit coupling.[17] This effect would produce less singlet−triplet mixing and thus less efficient isc in **BRe** than in **BRz** if isc is static, occurring at conformational minima before cyclization, or if isc is dynamic, occurring concurrently with the bond rotation that swings the two p orbitals toward each other. In this regard, the behavior of **BRx**, which represents some 42% of the triplet biradical population, is very important. Does it undergo static isc to form a singlet biradical that must undergo rotation around bond b in order to cyclize? If so, nearly half the product ratio could be determined by the relative rates for rotation of **BRx** to **BRz** or **BRe**. As far as our calculations can determine, there is a 0.7 kcal/mol difference in the two rotational barriers, which indicates at most a 3:1 preference for formation of singlet **BRz**. Assuming the same static isc rate for **BRe** and **BRx**, which have similar bond angles, a 10-fold greater rate of isc for **BRz** is required to fit the measurements to the calculations. That large of a difference seems unlikely; we are currently analyzing the behavior of several more such biradicals.

The lack of stereoselectivity for **5** is consistent with our earlier findings that phenyl substitution substantially lowers rotational barriers at a benzyl radical site in a biradical, since both benzene rings do not have to conjugate with the half-occupied p orbital.[18] As shown below, biradical geometries with the phenyl tilted both up and down are of comparable energy but have significantly different orbital orientations, which could explain the A_Z/A_E ratio, as for **1**. Why E_a is higher for the *Z* isomer is not immediately apparent. The situation when both radical sites are conformationally mobile is obviously complicated and requires additional computational study.



Acknowledgment. This work was supported by NSF grants CHE91-20931 and CHE94-08308. The NMR spectrometers used were partially funded by NSF grant CHE88-00770 and NIH grant RR047550. A.Z. is grateful for a Harold Hart Fellowship; B-S.P. is grateful for a BASF fellowship.

JA962683H

(13) Minimization of the lowest energy conformations found by an AM1 double-dihedral drive search.

(14) We thank Dr. Pablo Wessig of Humboldt Universitat in Berlin for sharing with us his similar calculations.

(15) (a) Oki, M.; Iwamura, H. *Tetrahedron* **1968**, *24*, 1905 and references therein. (b) Biali, S. E.; Rappoport, Z. *J. Am. Chem. Soc.* **1984**, *106*, 5641 and references therein.

(16) Wagner, P. J.; Park, B.-S.; Sobczak, M.; Frey, J.; Rappoport, Z. *J. Am. Chem. Soc.* **1995**, *117*, 7619.

(17) Michl, J. *J. Am. Chem. Soc.* **1996**, *118*, 3568.

(18) Wagner, P. J.; Meador, M. A.; Scaiano, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 7988. Wagner, P. J.; Giri, B. P.; Pabon, R.; Singh, S. B. *J. Am. Chem. Soc.* **1987**, *109*, 8104.