Conformational Control of Product Ratios from Triplet 1,5-Biradicals

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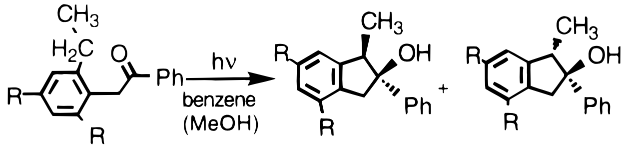
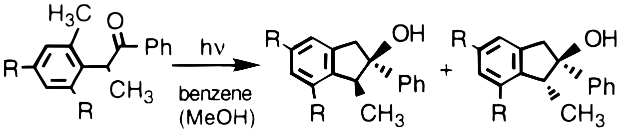
Product distributions from 1,5-biradicals formed *via* δ-hydrogen abstraction by triplet phenyl ketones are very sensitive to structural changes.[1] We have analyzed[2] the high diastereoselectivity observed in the photocyclization of **1** and **2** in terms of conformational preferences that pre-exist in the biradicals[3,4] and entropic factors related to isc during product formation.[2] This selectivity involves molecule-induced conformational preferences imposed on groups at each end of the biradical, which suffer no nonbonded interactions with each other until bond formation occurs. Compounds **3** and **4** reveal another source of high selectivity based on pre-existing conformational preferences between methyl and phenyl groups that are vicinal to each other throughout the reaction.[5] We report here examples of how steric congestion, temperature, and viscosity can combine to produce huge variations in product ratios when both molecule-wide and vicinal conformational preferences coexist in biradicals.

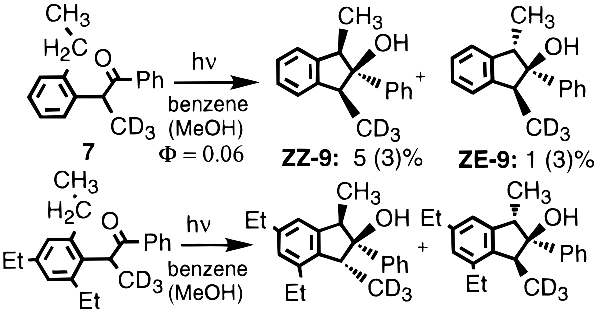


1 : R = H 95 % (67 %) 5 % (33 %)
2 : R = CH_2CH_3 97 % (81 %) 3 % (19 %)



3 : R = H **Z-5** 14 % (12 %) **E-5** 0.9 % (3 %)
4 : R = CH_3 Z-6 90 % **E-6** 10 %

We have re-examined **3** and **4** and expanded our studies to the α-(*o*-ethylphenyl)propiophenones **7** and **8**. Like **3**, **7** undergoes competitive cyclization and radical cleavage, the latter increasing at higher temperatures.[6] In benzene, **7** provides an indanol ratio favoring **ZZ-9** over **ZE-9**, as might be predicted from the behavior of **1** and **3**. As in **1**, this selectivity is lost in methanol. In sharp contrast to the behavior of **7** and to what might have been inferred from the behavior of **2** and **4**, **8** does not form an indanol with both methyls trans to the phenyl; instead, it forms both possible indanols with one methyl cis to the phenyl and one trans. Moreover, it shows high selectivity in methanol but very little in benzene, the exact opposite of **1** and **2**.



7 **ZZ-9:** 5 (3)% **ZE-9:** 1 (3)%
8 **EZ-10:** 36(6)% **ZE-10:** 44(74)%

Since differentiation of the two indanol methyls by NMR analysis was ambiguous for both **10**'s and impossible for **ZE-9**, we have studied **7** and **8** with their α-methyls deuterated. These provided unambiguous stereochemical assignments based on the large differences in chemical shifts between methyls cis or trans to a vicinal phenyl. It is now clear that the α-methyl remains trans to phenyl in both indanols from **7** but ends up cis to the phenyl in the minor indanol from **8**. Its tendency to avoid the vicinal phenyl perturbs biradical geometry sufficiently to drastically alter the cyclization stereoselectivity of the ethyl-derived methyl.

Diastereoselectivity varies widely with temperature, as listed in Table 1. The *Z*/*E* ratios from **3** and **4** increase much more with decreasing temperature than do those from **1** and **2**. Whereas lower temperatures favor formation of (*Z*)-indanol from **1** and **2**, the *ZE*-diastereomers, with the ethyl-derived methyl *cis* to the phenyl, are favored at lower temperatures for **7** and **8**. With increasing temperature, **7** and **8** both furnish increasing yields of an indanol with the ethyl-derived methyl *trans* to the phenyl. Ketone **7** forms **ZZ-9** but no **EZ-9**. In contrast, **8** forms no **ZZ-10** but mainly **EZ-10** above 90°.

Figure 1 portrays the temperature dependence of product ratios in the form of Arrhenius plots (**8** is plotted both ways). Product yields were measured by both NMR and GC analysis. For ketones **1**−**3** and **8** there is a linear relationship over the 180° temperature range. For **7** the plot is linear below 25° but curves down above 25°; for **4** the plot plateaus below −20°. Activation parameter differences are listed in Table 1, with those for **1** included for comparison and those for **4** and **7** taken from just the linear portions of the plots.

For each ketone the two stereoisomeric indanols presumably arise from different conformations of the 1,5-biradical intermediate. Temperature-dependent product ratios in solution may reflect three possible kinetic scenarios: (1) equilibrium between two or more freely interconverting conformers; (2) competition between cyclization of the initial biradical geometry and irreversible bond rotation to another conformer; or (3) ground-state conformational control. Superimposed on these effects, there can be inherent differences in the cyclization rates of different conformers,[2] the temperature dependence of which is unknown. These sterically congested ketones demonstrate all three boundary conditions. The highest solution selectivity occurs at the lowest temperature and is magnified in the crystal, in which ground-state structure controls product geometry.

The small temperature effects on ketones **1** and **2** reflect relatively small enthalpy differences between biradical conformers with different inherent cyclization

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[1] Wagner, P. J. *Acc. Chem. Res.* **1989**, *22*, 83.

[2] Wagner, P. J.; Zand, A.; Park, B.-S. *J. Am. Chem. Soc.* **1996**, *118*, 12856.

[3] Wagner, P. J.; Subrahmanyam, D.; Park, B.-S. *J. Am. Chem. Soc.* **1991**, *113*, 709.

[4] 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.

[5] Wagner, P. J.; Zhou, B.; Hasegawa, T.; Ward, D. L. *J. Am. Chem. Soc.* **1991**, *113*, 9640.

[6] All yields shown in the schemes are absolute. For **9** and **10** we specify the geometric relationship of the originally α-methyl-d_3 relative to the indanol OH first, that of the ethyl-derived methyl second.

[7] Scheffer, J. R. *Org. Photochem.* **1987**, *8*, 249. Ramamurthy, V.; Venkatesan, K. *Chem. Rev.* **1987**, *87*, 433.

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Table 1. Medium and Temperature Effects on Cyclization Stereoselectivity

		products				
conditions		**Z/E-5** from **1**[a]	**Z/E-5** from **3**	**Z/E-6** from **4**	**ZZ/ZE-9** from **7**	**ZE/EZ-10** from **8**
toluene	110 °C	11.5	10	4.5	10	0.67
toluene	−72 °C	26	43	23	0.11	6
crystal	24 °C	>50	>50	>50	0.3[b]	>50
A_Z/A_E		4.6	2.1	0.21[c]	10^4 [c]	0.05[d]
$\Delta\Delta H^{\ddagger}(E-Z)$		0.70	1.20	2.38[c]	4.7[c]	1.89[d]

[a] Reference 2. [b] On silica; irradiation melted the crystal. [c] Linear part. [d] $Z = ZE$, $E = EZ$.

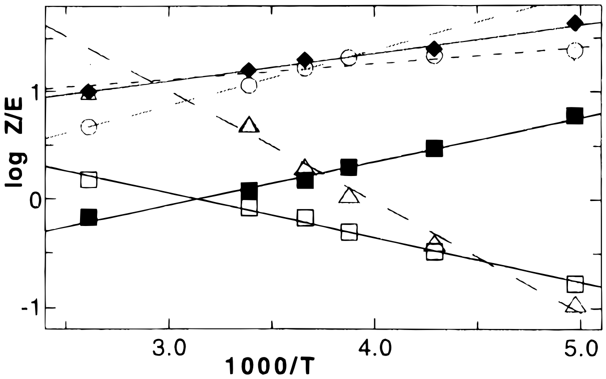
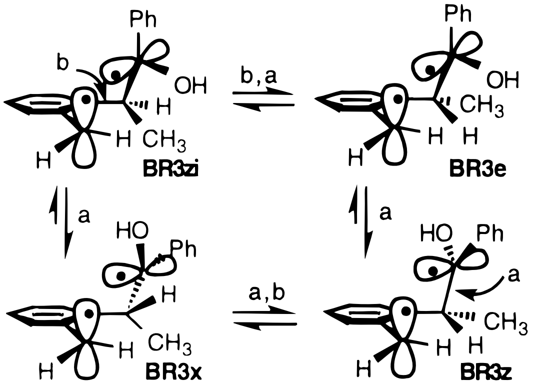


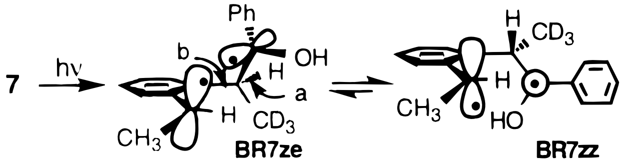
Figure 1. Temperature dependence of product ratios: **Z-5/E-5** (- - -) from **1**, ◆ from **3**; ● **Z-6/E-6**; △ **ZZ-9/ZE-9**; □ **EZ-10/ZE-10**; ■ **ZE-10/EZ-10**.

efficiencies.[2] Since α-arylpropiophenones have conformational preferences different from those of α-arylacetophenones, with very low populations of conformers with the α-aryl eclipsing the carbonyl,[5] the perturbations of biradical behavior caused by the α-methyl group in **7** and **8** probably reflect barriers to bond rotation.[5] We have performed semiempirical calculations on the ground-state ketones and their biradicals to correlate their observed behavior with conformational energies and geometries.

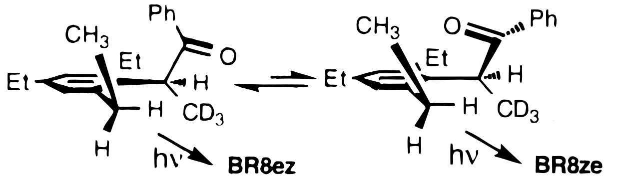
Four low-energy conformers are calculated for the biradical from **3**, with **BR3iz** being formed initially. It and **BR3e** lie 1.2 kcal/mol above both **BR3z** and **BR3x**, which has its two ends too far apart to cyclize. If the two indanols arise only from **BR3z** and **BR3e**, the measured $\Delta\Delta H^{\ddagger}$ value matches the calculated higher enthalpy of **BR3e** and the *A* ratio reflects the different orbital orientations in the two conformers. The puzzle in this analysis is **BR3x**; if it undergoes isc, what *Z*/*E* ratio would subsequent bond rotations provide? Either it forms mainly **BR3z** or it does not undergo isc. A similar scheme holds for **4** at higher temperatures; the added *o*-methyl adds extra nonbonded interactions and raises $\Delta\Delta H^{\ddagger}$ relative to **3**. The plateau beahvior of the *Z*/*E* ratio at low temperatures probably reflects ground-state control while biradical bond rotations are slow.



The low-temperature behavior of **7** apparently reflects bond rotation barely competing with cyclization, equilibration being attained only at temperatures too high for us to measure. A linear plot of the low-temperature points indicates an A_Z/A_E value that would seem to be impossibly high for inherent differences in biradical cyclization efficiencies but consistent with bond rotation having a much higher $\Delta S^{\ddagger}$ than does T → S isc. The ∼4.7 kcal $\Delta\Delta H^{\ddagger}$ must then represent the barrier to conversion of **BR7ze** to **BR7zz**, minus any activation energy for cyclization of **BR7ze**.



Calculations suggest that the minimum energy ketone conformation would form the biradical geometry leading to **ZE-9**, in which the OH group is pointed away from the central benzene ring, just the opposite of the initial geometry for the biradical from **1**.[2] However, the **BR7ze** geometry is but a local minimum; the lower energy global minimum **BR7zz** presumably is favored by OH−benzene hydrogen bonding,[2] which cannot stabilize the equivalent conformation of the ground-state ketone. This geometry is formed by 180° rotation about bonds a and b, which keeps the α-methyl and the phenyl in pseudoequatorial positions. Our calculations suggest a 5 kcal/mol barrier for rotation of **BR7ze** to **BR7zz**, close to the measured $\Delta\Delta H^{\ddagger}$. Under equilibrium conditions, **BR7zz** leads to the major product **ZZ-9**. The large effect of methanol on stereoselectivity in this and probably all of these 1,5-biradicals presumably represents destabilization of this conformer by OH hydrogen bonding to solvent.



Similar calculations on **8** indicate two ground-state conformers that differ in energy by 2 kcal/mol and that lead to pro-*EZ* and pro-*ZE* biradicals of comparable energy. Therefore, the linearity of **8**'s temperature dependence and the 1.9 kcal $\Delta\Delta H^{\ddagger}$ do not represent biradical equilibration. Instead, the product ratio from **8** is subject to ground-state control; the large difference in *A* values indicates inefficient cyclization by **BRze** relative to **BRez** together with any entropy difference between triplet ketone conformers.

These studies provide an intriguing first glimpse at the kinetic parameters that control triplet biradical cyclization; a fuller view is being pursued.

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Supporting Information Available: Description of synthetic and photochemical procedures plus synthesis and spectroscopic identification of **7**−**10** (11 pages).

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