Tetrahedron Letters, Vol.32, No.2, pp 165-168, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

HIGH DIASTEREOSELECTIVITY IN THE CYCLIZATION OF 1,5-BIRADICALS: WHAT CAUSES SUCH SIZEABLE STERIC BARRIERS TO BIRADICAL COUPLING?

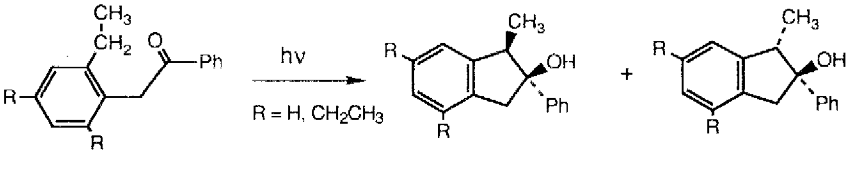
Peter J. Wagner* and Bong Ser Park

Chemistry Department, Michigan State University, East Lansing, Michigan 48824

The high diastereoselectivities observed in the photocyclization of α-(o-ethylphenyl)acetophenones appear to reflect conformational equilibria in the triplet 1,5-biradical intermediates rather than steric barriers created during cyclization. The necessary biradical triplet→singlet intersystem crossing is proposed to occur along the cyclization reaction coordinate since the orthogonality of the two singly-occupied p orbitals does not depress biradical lifetimes .

Variable diastereoselectivity has been observed in the cyclization of many biradicals generated by intramolecular triplet state hydrogen abstraction.[1-3] We wish to report examples of really large diastereoselectivity involving orientation of methyl and phenyl groups at the ends of a 1,5-biradical.

The photocyclization[4] of α-(o-ethylphenyl)acetophenone α**EAP** and of α-(2,4,6-triethylphenyl)acetophenone were followed by NMR in benzene-d_6 and in methanol-d_4 solutions.[5] The two ketones undergo clean conversion to 1-methyl-2-phenyl-2-indanol and to its diethyl derivative, respectively. Z/E ratios of 20:1 and 2:1, respectively, were obtained for the former[6] in the two solvents; 30:1 and 4.3:1 for the latter.[7] The stereochemistries of the methyl and hydrogen cis or trans to the shielding phenyl were obvious from their relative chemical shifts. These diastereoselectivities are even larger than the ~10:1 Z/E ratios found for o-benzyloxy and o-ethoxybenzophenone.[8]

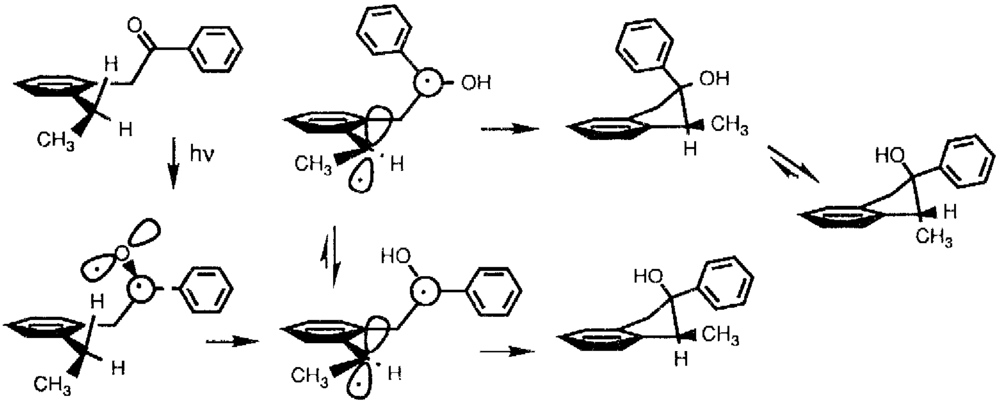


The observed diastereoselectivities in benzene demand 1.8-2.1 kcal/mole energy differentials between the Z and E modes of cyclization. As Lewis' work first showed[9], the nonbonded interactions that cause such selectivity can either pre-exist in the biradicals or be created during cyclization as the methyl and phenyl groups on the biradical ends approach each other. In the latter case, the energy differences between the two isomeric products would have to be even greater than the differential transition state energies for cyclization. The thermodynamic energy difference between the Z and E products is not known, but molecular mechanics calculations[10] suggest that puckering of the five-membered ring reduces the difference to near zero.

Therefore the discrimination between the two modes of cyclization probably reflects pre-existing energy differences that persist during cyclization.

We have tested this idea by performing MMX calculations on the biradical from α**EAP**. After minimization with respect to rotation about all acyclic C-C bonds, the two minimum energy geometries shown in Scheme 1 were calculated to differ in energy by 1.6 kcal/mole. The preference is easily understood in terms of the smaller group on the radical center that was originally the carbonyl carbon pointing in over the benzene ring. When the OH group is solvated by hydrogen bonding, it is comparable in size to the phenyl group, such that the two rotamers are nearly equal in energy and selectivity is lost. Given the 30-50 ns lifetimes of such 1,5-biradicals[11], they have plenty of time to establish such a conformational equilibrium. If the two biradical rotamers indeed differ by 1.6 kcal, most of the observed selectivity simply reflects this conformational equilibrium in the biradical before cyclization, provided that cyclization of both rotamers involves the same motion. This supposition seems reasonable here, since a simple disrotation around the two ortho C-C bonds is all that is required for coupling. Scheme 1 traces molecular geometry from ground state to products, starting with the most likely *reactive* conformation of the ketone.

Scheme 1

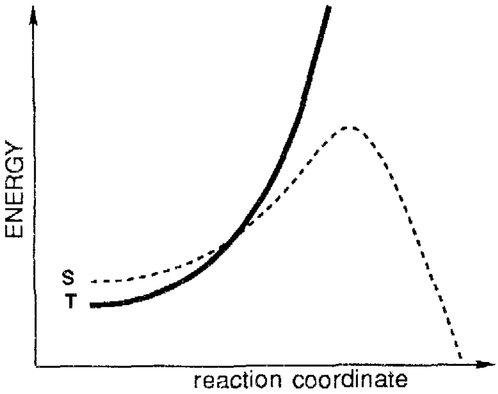


Lewis' early example of large diastereoselectivity in biradical cyclizations being set by pre-existing conformational preferences involved the fact that α-methylbutyrophenone gives only the Z cyclobutanol,[9] whereas valerophenone gives a 3:1 Z/E ratio.[1,12] Our current results provide a quite different example of the same phenomenon; the phenyl and methyl groups' preferred orientations are determined by interactions not with each other, as they are in the α-methylbutyrophenone biradical, but with the rest of the molecule. The phenyl group on one radical center prefers to be twisted away from the central benzene ring and the methyl group on the other radical center prefers to be twisted away from the large ortho substituent. Given the significant barriers to rotation of a benzylic radical center,[13] the *anti*-methyl orientation most likely stays fixed during the biradical's lifetime. It may be generally true that steric effects on the distribution of biradical conformations are larger than those that develop as the biradical cyclizes. We are now analyzing other examples of large diastereoselectivity, such as occurs in the o-alkoxy ketones.[8]

Scaiano[14] has proposed that the product composition from triplet biradicals is determined by variations in intersystem crossing rates of various biradical conformations. These rate differences can be intrinsic, representing different amounts of spin-orbit or hyperfine coupling in different conformers, or due to different populations of conformers with comparable isc rates. One of us recently suggested that large diastereoselectivities during biradical cyclization may arise from significant barriers to cyclization in the singlet biradicals and thus occur *after* isc.[3] These particular 1,5-biradicals do not exemplify such an effect, since the stereoselectivity appears to be set before cyclization. Nonetheless, it is very worthwhile to consider how isc occurs in these biradicals. Scheme 1 indicates that the two singly occupied p orbitals are nearly orthogonal in the biradical's lowest energy conformations. The orbitals fluctuate between parallel and perpendicular orientations as rapidly as C-C bonds can rotate. Adam and Wilson have proposed that the isc rates of various biradicals increase as their singly occupied p orbitals approach orthogonality[15], in agreement with earlier proposals of Salem[16] and of Shaik and Epiotis[17]. Several similar 1,5-biradicals formed from substituted α-(o-tolyl)acetophenones all have relatively long lifetimes of 20-50 ns.[11,18] Since phenyl substitution lengthens hydroxy-biradical lifetimes only slightly,[19] the behavior of these biradicals does not support any strong connection between orthogonality and rapid isc.

If these biradicals just sit around as triplets until isc occurs and then couple on the next appropriate rotation, what actually causes isc? We would like to reiterate the possibility that it may occur during rather than before reaction. The notion of coupled isc and reaction has already been presented[3] in terms of enhanced spin-orbit coupling as the two radical sites approach each other,[20] allowing isc at various points onto the potential surface that describes the reaction coordinate for singlet reaction. Perhaps a better picture is presented in the figure below, which translates biradical cyclization motion into a potential energy surface. The basic idea is that both the singlet and the lower energy triplet surfaces rise in energy as movement along the reaction coordinate develops steric and electronic strain, but the singlet surface is soon stablized by the developing bond, such that the two surfaces cross at points that represent very low observed activation energies. The singlet biradical is then trapped in a conformational well that leads to reaction. One interesting aspect of this proposal is that the parallel solvent effects on hydroxybiradical lifetimes and reaction efficiencies noted for several different biradical systems[3] become entropy differences as various possible near-zero activation energy biradical reaction modes become restricted or suppressed.

Closs has pointed out that "the long lifetime of triplet biradicals must be attributed to the poor energy match of singlet and triplet levels rather than to a lack of mixing interactions."[21] He also has suggested coupled isc and reaction, based on mixing of singlet character into the triplet biradical, with lifetimes and rate constants for reaction reflecting the degree off singlet character in a particular biradical. Our two views of isc coupled with reaction differ more in perspective than in substance and still require more detailed analysis of how isc rates depend on exact structure.



Acknowledgement: This work was supported by NSF Grant NO. CHE88-15052. The NMR used was purchased with funds provided by NSF Grant No. CHE88-00770.

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7. Z-isomer: ($CDCl_3$) δ 1.25 (d, J = 7.2 Hz, $CH_3C\underline{H}$) 1.22, 1.28 (each t, J = 7.5 Hz, $C\underline{H_3}CH_2$) 1.85 (br s, OH) 2.60, 2.67 (each quar, J = 7.5 Hz, $C\underline{H_2}CH_3$) 3.15, 3.36 (AB quar, J = 18.0 Hz, ring CH_2) 4.00 (quar, J = 7.0 Hz, $C\underline{H}CH_3$) 6.92, 6.95 (each s, Et_3Ar-H); (CD_3OD) δ 1.20 (d, $CHC\underline{H_3}$) 3.13, 3.30 (AB quar, ring CH_2) 3.455 (quar, $C\underline{H}CH_3$); E-isomer (CD_3OD) δ 0.70 (d, $CHC\underline{H_3}$) 3.14, 3.58 (AB quar, ring CH_2) 3.335 (quar, $C\underline{H}CH_3$).
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(Received in USA 9 October 1990)