Pergamon

Tetrahedron Letters, Vol. 37, No. 10, pp. 1641-1644, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00080-9

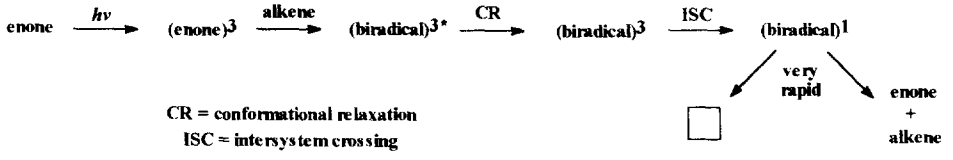
The Regiochemistry of Intramolecular Photochemical [2 + 2] Cycloaddition Reactions: Biradical Conformation Control.

Martina Audley and Niall W.A.Geraghty*

Chemistry Department, University College, Galway, Ireland.

Abstract: A basic MM2 force-field is shown to give minimum energy conformations for radicals which are generally comparable to those obtained previously using a modified force-field. The conformations of biradicals determined by the method are used to assess whether this factor plays a role in determining the regiochemistry of photochemical [2+2] cycloaddition reactions. This concept of biradical conformation control is shown to account for behaviour which is difficult to rationalise using the 'rule of five'.

The seminal contributions of Corey[1] and De Mayo[2] identified an exciplex and a biradical as possible product determining intermediates in the photochemical [2 + 2] cycloaddition reactions of enones. In the intervening period the relative importance of these species has been the subject of much debate, with the most recent experimental data due to Schuster[3] (flash photolysis) and Weedon[4] (hydrogen selenide trapping) suggesting that exciplex formation is not in fact relevant. Although the suggestion, first made by Bauslaugh[5], that the partitioning of biradical intermediates between ring formation and bond cleavage is the product determining step has received experimental support from the work of Weedon, it has also been suggested by Houk[6], on the basis of *ab initio* calculations, that the initial bond formation rates determine the product regioselectivity. The overall picture is even more complicated for intramolecular reactions, for although their course parallels that of the intermolecular, the facility to predict their regiochemical outcome requires the introduction of an additional concept, the empirical "rule of five"[7]. This suggests that the observed product will result from an initial 1,5 ring closure, and is thus compatible with the concept that the regioselectivity is determined in the biradical formation step. The current paper, following Bauslaugh, considers the possibility that the conformation of the intermediate biradicals may play an important role in determining the regioselectivity, a suggestion which is in keeping with the Bauslaugh - Weedon view that the regioselectivity is determined after biradical formation has occurred.



The radical clock and photoacoustic spectroscopy data available for the initially formed triplet biradicals suggest that their lifetime is of the order of 50ns, thus allowing time for conformational relaxation to occur[8]. The lifetimes of the singlet biradicals formed by intersystem crossing are significantly shorter with the result that there will be insufficient time for any further significant change in structure prior to cyclobutane formation or reversion to starting materials. Thus the partition ratio may be a function of triplet biradical structure, with the biradical which is not spatially orientated for bond closure reverting to a mixture of alkene and enone. In general terms it

might be expected that this concept of biradical conformation control would be most obvious in intramolecular [2+2] cycloaddition reactions as a result of the conformationally constrained nature of the biradicals involved which are necessarily cyclic, and possibly bi- or tricyclic. Predicting the regiochemistry of the reaction may thus require a consideration of the minimum energy geometry of all possible biradicals, with a bond forming orientation of the singly occupied orbitals being an indication of involvement in product formation. The use of MM as a method of determining the conformation of biradical intermediates in intramolecular [2+2] reactions was considered as it would constitute a particularly direct method of evaluating the role played by a particular biradical in controlling the regiochemistry of the reaction.

Although specific force constants are available which allow a restricted number of radicals to be considered using MM2[9] and MM3[10], an evaluation of the biradical conformation control concept required the consideration of biradical structures involving a wide range of radical centres. For this reason a MM approach based on the assumption that radicals are isolated alkene carbon atoms, and that biradicals consist of two independent radical centres[11], was adopted. The validity of this way of dealing with radical centres was assessed by comparing the conformations suggested for a range of radicals with those obtained previously[9,10] using specially modified MM2 and MM3 force fields, subsequently referred to as MM2* and MM3***(Table 1, 2)**. It was found that the two approaches gave similar results with only the isobutyl radical being qualitatively different.

Table 1 Radical Conformations

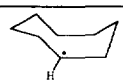
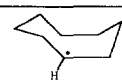
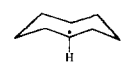
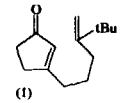
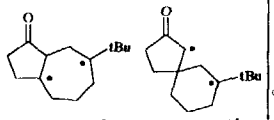
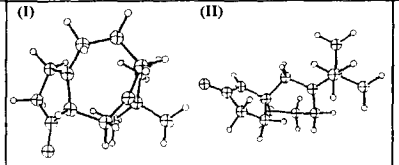
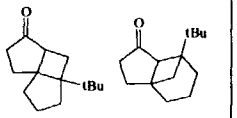
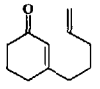
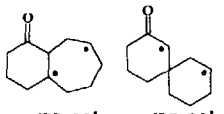
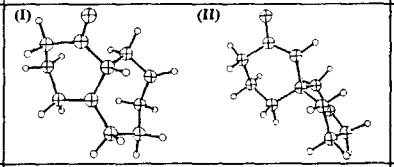
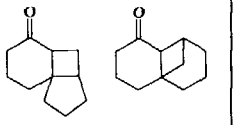
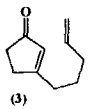
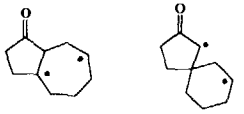
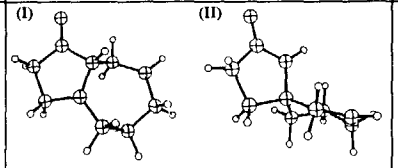
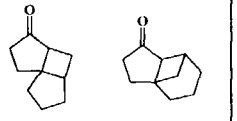
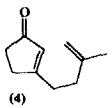
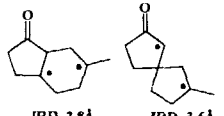
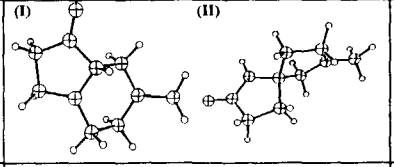
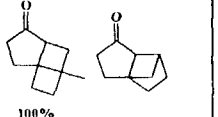
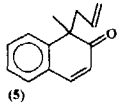
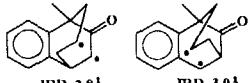
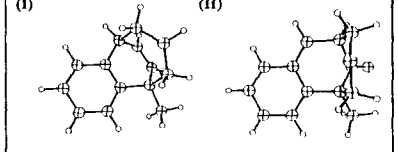
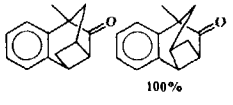
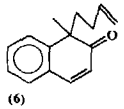
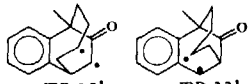
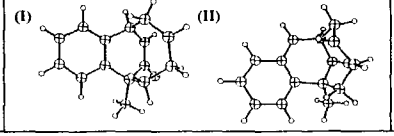
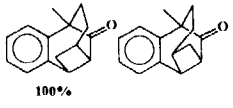
Radical	Minimum Energy Conformation			Comment
	MM3*	MM2*	MM2	
Propyl	C_1(0.17)	C_1(0.06)	C_1(0.01)	C_1 / C_S energy gap in parenthesis
Isobutyl	C_S(0.13)	C_S(0.14)	C_1(0.21)	C_1 / C_S energy gap in parenthesis
Cyclopentyl	half-chair (1.87)	half-chair (2.18)	half-chair (2.40)	half-chair / envelope energy gap in parenthesis
Cyclohexyl	chair (4.11)	chair (3.76)	chair (5.47)	chair / twist-boat (C_2, with radical on C_2 axis) energy gap in parenthesis
Cyclooctyl	-	 other boat-chair forms 1.00-3.00kcalmol^{-1} less stable	 other boat-chair forms 0.02-2.88kcalmol^{-1} less stable	 distorted crown less stable by 1.19 (MM2) and 1.0 (MM2*) kcal mol^{-1}

Table 2 Dihedral Angle ($C_1C_2C_3C_4$)

Radical	MM2	MM2*	MM3*	*ab initio*
1-Butyl	175.4°	179.1°	179°	179.9°
2-Butyl	175.3°	171.1°	166.1°	170.7°

In the case of the biradicals, a suitable conformation for ring closure was considered to be one involving a short inter-radical distance (IRD) and an angular orientation of the singly occupied orbitals which facilitates overlap. An IRD of "approximately 3Å" has been suggested as the upper limit for effective orbital interaction leading to bond closure in the Paterno-Buchi reaction[12], and this value has been adopted here also. The angular relationship between the singly occupied orbitals was evaluated qualitatively, an indicator of the molecular geometry being the angle (IPA) between the planes defined by the sp^2 orbitals of the respective radical centres.

System	Biradicals	MM2 Conformation[13]	Products	Comment
 (1)	 (I) IRD 2.8Å IPA 71.5° (II) IRD 3.8Å IPA 79.4°	 (I) (II)	 100%	The smaller IRD in I facilitates rapid ring closure after spin inversion whereas II requires a conformational change. The regiochemistry can also be interpreted in terms of the Corey postulate / F.O. theory or the "rule of five".
 (2)	 (I) IRD 2.9Å IPA 26.8° (II) IRD 3.8Å IPA 71.1°	 (I) (II)	 100%	A standard application of the concept of biradical conformation control.
 (3)	 (I) IRD 3.2Å IPA 11.4° (II) IRD 3.3Å IPA 89.0°	 (I) (II)	 100%	Although the minimum energy conformations of I and II do not have suitably orientated singly occupied orbitals, a minor conformational change of the seven membered ring in I (chair ⇒ chair) results in significant orbital overlap. The regiochemistry is once again consistent with the Corey postulate / F.O. theory and the "rule of five"
 (4)	 (I) IRD 2.8Å IPA 6.7° (II) IRD 3.6Å IPA 89.0°	 (I) (II)	 100%	This is an example which is consistent with biradical conformation control on the basis of a comparison of the IRD values. Although the result is once again consistent with the Corey postulate / F.O. theory, the "rule of five" suggests that the product should be that derived from biradical II.
 (5)	 (I) IRD 2.8Å IPA 84.3° (II) IRD 3.0Å IPA 83.5°	 (I) (II)	 100%	The effect of changing the length of the methylene chain cannot be rationalised on the basis of the Corey postulate / simple F.O. theory, or the "rule of five": the former would require the regiochemistry to remain unchanged whereas the latter makes incorrect predictions in both cases. Biradical conformation control does not account for the behaviour of (5), but does suggest that the addition of an extra methylene to the chain should result in a particularly facile ring closure from 6(I).
 (6)	 (I) IRD 2.7Å IPA 12.2° (II) IRD 3.2Å IPA 77.5°	 (I) (II)	 100%	

A representative range of systems whose intramolecular cycloaddition reactions had been studied previously was investigated. Biradical intermediates involving non-primary radical centres were not considered; this assumption may need to be revised in more detailed studies for although trapping experiments suggest that such biradicals are not involved when electron-rich alkenes react with enones, they also show that the reactions of methyl acrylate may involve such biradicals.[4] The structures were optimised from two different starting geometries. In many of the cases considered a simple evaluation of the biradicals from the point of view of the IRD is sufficient to provide a rationalisation for the regiochemical course of the reaction: (1)[14] and (2)[15] belong to this category. It should, however, be pointed out that the Corey postulate / F.O., or 'rule of five' approach is equally successful in accounting for the experimental result in these cases. The behaviour of (3)[14] requires an extension of the basic principle as neither of the alternative biradicals involve a favourable arrangement of the singly occupied orbitals. However whereas no low energy conformation of (3)(II) would allow significant orbital interaction, a minor conformational change in (3)(I) would result in such interaction. This result suggests that the energy barrier between a minimum energy, but geometrically unfavourable conformation, and a conformation which facilitates ring closure, may need to be considered in some cases. (4)[16] is an exception to the generally reliable 'rule of five' but is well behaved in terms of biradical conformation control. In some cases, such as (5)[17], the biradical geometries determined by this MM approach do not provide a basis for understanding the regiochemical outcome of a reaction. It is not clear whether this is because of limitations in the MM analysis or because the reaction is controlled by other factors along the reaction pathway. The MM analysis does show that the minimum energy conformation of (6)(I)[18] would allow particularly facile ring closure thus accounting for the regiochemistry in this case.

These results show that a very simple MM approach can produce reasonable minimum energy conformations for biradicals and provide further support for Bauslaugh's suggestion that the conformation of the biradical intermediates plays a role in determining the outcome of [2+2] cycloaddition reactions. It remains to be seen whether a more refined computational approach would increase the number of systems whose behaviour can be interpreted in terms of biradical conformational control, and to what extent the energy barrier between minimum energy, but non-interactive, conformations and those allowing interaction between the singly occupied orbitals, needs to be considered.

Acknowledgement: the financial support provided by the Irish science and technology agency, Forbairt, is gratefully acknowledged.

References

1. Corey, E. J.; Bass, B. D.; LeMahieu R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570-5583.
2. Loutfy, R. O.; de Mayo, P. *J. Am. Chem. Soc.* **1977**, *99*, 3559-3565.
3. Schuster, D. I.; Heibel, G. E.; Brown, P. B.; Turro, N. J.; Kumar, C. V. *J. Am. Chem. Soc.* **1988**, *110*, 8261-8263.
4. Andrew, D.; Hastings, D. J.; Weedon, A. C. *J. Am. Chem. Soc.* **1994**, *116*, 10870-10882.
5. Bauslaugh, P. G. *Synthesis* **1970**, 287-300.
6. Broeker, J. L.; Eksterowicz, J. E.; Belk, A. J.; Houk, K. N. *J. Am. Chem. Soc.* **1995**, *117*, 1847-1848.
7. (a) Srinivasan, R.; Carlough, K. H. *J. Am. Chem. Soc.* **1967**, *89*, 4932-4936. (b) Liu, R. S. H.; Hammond, G. S. *J. Am. Chem. Soc.* **1967**, *89*, 4936-4944. (c) Fischer, E.; Gleiter, R. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 925-927.
8. Schuster, D. I.; Lem, G.; Kaprinidis, N. A. *Chem. Rev.* **93**, *1993*, 3-22.
9. Imam, M. R.; Allinger, N. L. *J. Mol. Struct.* **1985**, *126*, 345-362.
10. Liu, R.; Allinger, N. L. *J. Comput Chem.* **1994**, *15*, 283-299.
11. Samuel, C. J. *J. C. S. Perkin Trans. I* **1989**, 1259-1265.
12. Griesbeck, G. G.; Mauder, H.; Stadmuller, S. *Acc. Chem. Res.*, **1994**, *27*, 70-75.
13. ORTEX (McArdle, P. *J. Appl. Cryst.* **1994**, *27*, 438) representations of minimum energy conformations obtained using MM2 (CHEM-X, Chemical Design Ltd., Oxford, U.K.).
14. Matlin, A. R.; George, C. F.; Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1986**, *108*, 3385 -3394.
15. Cargill, R. L.; Dalton, J. R.; O'Connor, S.; Michels, D. G. *Tetrahedron Lett.* **1978**, 4465-4466.
16. Wolff, S.; Agosta, W. C. *J. Org. Chem.* **1981**, *46*, 4821-4825.
17. Hanly, N. M.; Geraghty, N. W. A. Unpublished results.
18. Monaghan, M. J.; Geraghty, N. W. A. Unpublished results.

(*Received in UK* 1 *November* 1995; *accepted* 12 *January* 1996)