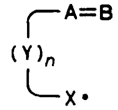
Some Guidelines for Radical Reactions

By Athelstan L J Beckwith,* Christopher J Easton, and Algirdas K Serelis
(*Organic Chemistry Department, University of Adelaide, Adelaide, South Australia* 5000)

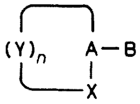
Summary Some generalisations of predictive utility are presented concerning the influence of steric and stereo-electronic effects on radical reactions

Recent work in this laboratory and elsewhere[1] has demonstrated that thermochemical criteria, although widely employed for the prediction or rationalisation of the results of free-radical processes, are sometimes misleading because of the influence of steric, polar, or stereo-electronic factors We believe it may be generally useful, therefore, to adumbrate guidelines which, when used in conjunction with the thermochemical approach, provide a predictive basis for some aspects of free-radical chemistry

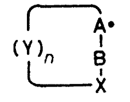
(i) *Intramolecular addition under kinetic control in lower alkenyl and alkynyl radicals and related species occurs preferentially in the* exo-*mode* This guideline suggests that *exo*-ring closure (**1**) → (**2**) is kinetically favoured over the *endo*-process (**1**) → (**3**) for radicals of type (**1**) where Y represents a chain of atoms ($n \leqslant 5$) It is exemplified by ring closure of butenyl,[2] hexenyl, heptenyl, and octenyl radicals,[3] of various substituted alkenyl radicals,[4–8] of alkynyl radicals,[9] of alkenylaryl radicals,[10] and of O-[11–14] and N-centred[15,16] radicals Although definitive experimental evidence is not available it possibly applies to S-,[17] P-,[18] and Si-centred[19] radicals It appears also to apply to ring closure on to C≡N,[20] C=O,[21] and aromatic nuclei [1,22] It does not apply to systems under thermodynamic control,[23] nor in some instances to radicals bearing a substituent at the ω-1 position, *e g* the 5-methylhex-5-enyl radical [see (ii)].



(1)



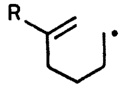
(2)



(3)

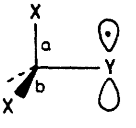
Exo-ring closure of radicals of type (**1**) is kinetically favoured because the strain generated by the accommodation of the triangular disposition of centres required for homolytic addition[24] within the system leading to *endo*-cyclization outweighs the thermochemical and other factors disfavouring the formation of the thermodynamically less stable product [25]

(ii) *Substituents on an olefinic bond disfavour homolytic addition at the substituted position* The 5-substituted hex-5-enyl radicals (**4**) and (**5**) undergo mainly six-membered ring formation because the rate of 1,5-cyclization is greatly retarded by the presence of the substituent [4,8] Similar retardations have been noted in intermolecular additions [26,27] The effect, which is probably mainly steric in origin,[27] accounts more satisfactorily than do thermodynamic criteria for the rates and regioselectivity of homolytic inter- and intra-molecular addition to substituted olefins except when the substituent exerts a strong stabilizing effect (*e g* R = Ph) [5]

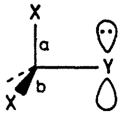


(**4**) $R=Me$
(**5**) $R=Pr^i$

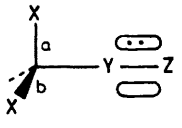
(iii) *Homolytic cleavage is favoured when the bond concerned lies close to the plane of an adjacent semi-occupied orbital or of an adjacent filled non-bonding or* π-*orbital* This guideline indicates that in each of the systems (**6**), (**7**), and (**8**) fission of bond (a) will occur more rapidly than fission of bond (b) Since *exo*-radicals of type (**2**) can readily acquire the required overlap whereas *endo*-radicals (**3**) cannot,[25] the former undergo β-fission much more readily than do the latter Thus cyclopropylmethyl and cyclobutylmethyl radicals undergo rapid ring-opening, but cyclopropyl and cyclobutyl radicals do not [1,28,29] In rigid systems the direction of ring opening conforms to this guideline [29,30] and other manifestations include the preferred *exo*-fission of the cyclic ether radical (**9**),[31] the selective loss of pseudoaxial hydrogen atoms in disproportionation of substituted 4-t-butylcyclohexyl radicals[32] and in hydrogen atom abstraction from cyclic ethers,[33] and the greater rate of homolysis of the axial perester (**10**) as compared with its equatorial isomer.[34] We have now found, as predicted by this guideline that t-butoxyl radicals generated by copper catalysed decomposition of t-butyl perbenzoate react with the comformationally locked olefin (**11**) containing two axial allylic hydrogen atoms twice as rapidly as with the olefin (**12**) containing only one axial hydrogen. Similarly, the *trans*-compound (**13**) which contains two axial chlorine substituents[35] reacts with tributyltin radicals twice as rapidly as does its *cis*-isomer.



(6)

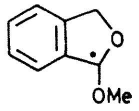


(7)

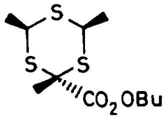


(8)

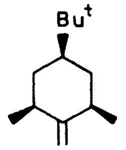
(iv) 1,5-*Ring closures of substituted hex*-5-*enyl and related radicals are stereoselective: 1- or 3-substituted systems afford mainly* cis-*disubstituted products, whereas 2- or 4-substituted systems give mainly* trans-*products.* The preferential formation of the *cis*-product from 1-substituted hexenyl radicals has been ascribed to the effects of orbital symmetry.[6] The guideline may fail when the substituent at C-1 is bulky.[36] The stereoselectivity of ring closure of 2-3-, or 4-substituted hexenyl radicals reflects the conformational preference of the transition state[37] and therefore is likely to be more pronounced for systems containing bulky substituents. Substituted 3-butenylperoxyl radicals undergo stereospecific or highly stereoselective ring closure in accord with this guideline.[14,38]



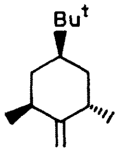
(9)



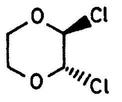
(10)



(11)



(12)



(13)

(*Received*, 31*st December* 1979; *Com.* 1341.)

---

[1] For a review containing much pertinent material see J. W. Wilt in 'Free Radicals,' ed. J. K. Kochi, Wiley-Interscience, New York, 1973, vol. I, p. 333.

[2] A. Effio, D. Griller, K. U. Ingold, A. L. J. Beckwith, and A. Serelis, *J. Am. Chem. Soc.*, 1980, **102**, in the press.

[3] A. L. J. Beckwith and G. Moad, *J. Chem. Soc., Chem. Commun.*, 1974, 472.

[4] A. L. J. Beckwith, I. A. Blair, and G. Phillipou, *Tetrahedron Lett.*, 1974, 2251.

[5] T. W. Smith and G. B. Butler, *J. Org. Chem.*, 1978, **43**, 6.

[6] A. L. J. Beckwith, I. Blair, and G. Phillipou, *J. Am. Chem. Soc.*, 1974, **96**, 1613.

[7] A. L. J. Beckwith and G. Moad, *J. Chem. Soc., Perkin Trans.* 2, 1975, 1726.

[8] M. Julia, C. Descoins, M. Baillarge, B. Jacquet, D. Uguen, and F. A. Groeger, *Tetrahedron*, 1975, **31**, 1737, and references cited.

[9] S. A. Dodson and R. D. Stepanovic, *J. Chem. Soc., Perkin Trans.* 1, 1975, 410; T. Oknuki, M. Yoshida, and O. Simamura, *Chem. Lett.*, 1972, 797, 999; W. M. Moore, A. Salajegheh, and D. G. Peters, *J. Am. Chem. Soc.*, 1975, **97**, 4954; A. L. J. Beckwith and T. Lawrence, unpublished results.

[10] A. L. J. Beckwith and W. B. Gara, *J. Chem. Soc., Perkin Trans.* 2, 1975, 795.

[11] R. D. Rieke and N. A. Moore, *J. Org. Chem.*, 1972, **37**, 413.

[12] For a review see J.-M. Surzur and M. P. Bertrand, *Bull. Soc. Chim., Fr.*, 1973, 8161.

[13] N. A. Porter, M. O. Funk, D. Gilmore, R. Isaac, and J. Nixon, *J. Am. Chem. Soc.*, 1976, **98**, 6000.

[14] A. L. J. Beckwith and R. S. Wagner, *J. Am. Chem. Soc.*, 1979, **101**, 7099.

[15] For reviews see P. Mackiewicz and R. Furstoss, *Tetrahedron*, 1978, **34**, 3241; Y. L. Chow, W. C. Danen, S. F. Nelson, and D. H. Rosenblatt, *Chem. Rev.*, 1978, **78**, 243.

[16] J.-M. Surzur, L. Stella, and P. Tordo, *Bull. Soc. Chim. Fr.*, 1975, 1425, 1429; M. E. Keuhne and D. A. Horne, *J. Org. Chem.*, 1975, **40**, 1278; R. A. Perry, S. C. Chen, B. C. Menon, K. Hanaya, and Y. L. Chow, *Can. J. Chem.*, 1976, **54**, 2385.

[17] J.-M. Surzur, M.-P. Crozet, and C. Dupuy, *Tetrahedron Lett.*, 1971, 2025.

[18] A. G. Davies, M. J. Parrott, and B. P. Roberts, *J. Chem. Soc., Perkin Trans.* 2, 1976, 1066.

[19] H. Sakurai in 'Free Radicals,' ed. J. K. Kochi, Wiley-Interscience, New York, 1973, vol. II, p. 793.

[20] B. P. Roberts and J. N. Winter, *J. Chem. Soc., Perkin Trans.* 2, 1979, 1353; D. Griller, P. Schmid, and K. U. Ingold, *Can. J. Chem.*, 1979, **57**, 831.

[21] F. Flies, R. Lalande, and B. Maillard, *Tetrahedron Lett.*, 1976, 439.

[22] J. C. Chottard and M. Julia, *Tetrahedron*, 1972, **28**, 5615; J. W. Wilt, W. K. Chwang, C. F. Dockus, and N. M. Tomiuk, *J. Am. Chem. Soc.*, 1978, **100**, 5534.

[23] M. Julia, *Pure Appl. Chem.*, 1967, **15**, 167; *Acc. Chem. Res.*, 1971, **4**, 386.

[24] M. J. S. Dewar and S. Olivella, *J. Am. Chem. Soc.*, 1978, **100**, 5290.

[25] A. L. J. Beckwith, 'Essays in Free-Radical Chemistry,' Special Publication No. 24, The Chemical Society, London, 1970, p. 239.

[26] B. Giese and J. Meixner, *Tetrahedron Lett.*, 1977, 2779.

[27] J. M. Tedder and J. C. Walton, *Adv. Phys. Org. Chem.*, 1978, **16**, 86.

[28] B. Maillard, D. Forrest, and K. U. Ingold, *J. Am. Chem. Soc.*, 1976, **98**, 7024.

[29] A. L. J. Beckwith and G. Moad, *J. Chem. Soc., Perkin Trans.* 2, in the press.

[30] A. L. J. Beckwith and G. Phillipou, *Aust. J. Chem.*, 1976, **29**, 123.

[31] C. M. Rynard, C. Thankachan, and T. T. Tidwell, *J. Am. Chem. Soc.*, 1979, **101**, 1196.

[32] A. L. J. Beckwith and C. Easton, *J. Am. Chem. Soc.*, 1978, **100**, 2913.

[33] K. Hayday and R. D. McKelvey, *J. Org. Chem.*, 1976, **41**, 2222.

[34] K. Arai, H. Iwamura, and O. Michinori, *Chem. Lett.*, 1975, 1181.

[35] C. Y. Chen and R. J. W. Le Fèvre, *J. Chem. Soc.* (*B*), 1966, 544; C. Altona and E. Havinga, *Tetrahedron*, 1966, **22**, 2275.

[36] M. A. M. Bradney, A. D. Forbes, and J. Wood, *J. Chem. Soc., Perkin Trans.* 2, 1973, 1655.

[37] A. L. J. Beckwith, T. Lawrence, and A. K. Serelis, *J. Chem. Soc., Chem. Commun.*, 1980, 484 (following communication).

[38] A. L. J. Beckwith and R. D. Wagner, *J. Chem. Soc., Chem. Commun.*, 1980, 485 (accompanying communication).