CENTENARY LECTURE. The Pursuit of Selectivity in Radical Reactions

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1 Introduction

Moses Gomberg's paper, 'An Instance of Trivalent Carbon: Triphenylmethyl'[1] appeared in 1900 in the December 5th issue of the *Journal of the American Chemical Society*. It was written in the first person in a delightful idiosyncratic style typified by the concluding cautionary note: 'This work will be continued and I wish to reserve the field to myself'. Gomberg need not have been concerned. Although gas phase radical processes received considerable attention during the next three decades, the possibility that some synthetically useful organic reactions in solution might involve free radical intermediates was not seriously considered until W. A. Waters in Durham, D. H. Hey in London, and M. S. Kharasch in Chicago commenced the mechanistic studies that contributed so profoundly to the development of organic free radical chemistry. The English groups concentrated on the homolytic substitution of aromatic systems. This was understandable in the light of Ingold's success in developing mechanistic theory through his scrutiny of electrophilic aromatic substitution, but unfortunate with the wisdom of hindsight, since free-radical reactions are now seen as being particularly useful for the construction of aliphatic and alicyclic systems.

Kharasch, however, worked mainly on the free radical chemistry of relatively simple aliphatic compounds. He was so successful that by the time of his death he had defined and explored virtually all of the elementary mechanistic pathways available to free radicals, namely (i) coupling and its reverse reaction, homolysis (equation 1); (ii) homolytic substitution or S_H2 (equation 2); (iii) addition and its reverse reaction, β-fission (equation 3); and (iv) electron transfer (equation 4).

$$A^{\bullet} + B^{\bullet} \rightleftharpoons A{-}B \quad (1)$$

$$A^{\bullet} + B{-}D \rightleftharpoons A{-}B + D^{\bullet} \quad (2)$$

$$A^{\bullet} + B{=}D \rightleftharpoons A{-}B{-}D^{\bullet} \quad (3)$$

$$A^{\bullet} + e \rightleftharpoons A^{-};\ A^{\bullet} - e \rightleftharpoons A^{+}\ \textit{etc.} \quad (4)$$

Most free radical processes can be rationalized in terms of these elementary steps, or simple variations of them. Since Kharasch's time only one completely new type of radical process, namely pericyclic reactions of radicals[2] and radical-ions,[3] has been added to this list.

However, it is one thing to be able to recognize the types of reaction available to a reactive intermediate. It is another matter to be able to predict which pathway will be followed or, for complex substrates, what will be the regiochemistry and stereochemistry. It was this lack of predictability and selectivity that so delayed the realization of the synthetic potential of free radical chemistry. Long after Kharasch had defined their basic mechanisms, free radical reactions continued to be regarded by most organic chemists as erratic, capricious, and prone to give intractable mixtures; in short, as unsuitable for the efficient preparation of pure compounds.

During the past decade this view has been radically changed.[4] It is now widely recognized that radical reactions, even with highly complex and heavily substituted substrates, can be conducted in a highly selective and efficient manner, and often display advantages over alternative ionic processes. Consequently, free radical methodology has become a major weapon in the armoury of the synthetic organic chemist, of particular value in natural product synthesis.[5]

One might well ask what has brought about this change in attitude. In my view it is the development of our understanding of the factors that influence the various forms of selectivity – chemoselectivity, regioselectivity, and diastereoselectivity. With a knowledge of these factors it is often possible to define reaction conditions and reagents which will ensure that a reaction proceeds at one functional group in preference to another, at one position in preference to another, and with one diastereisomer in preference to another, or to afford one diastereisomer in preference to another.

In this article I shall outline some of the experiments which contribute to the recognition and definition of the factors affecting the selectivity of radical processes. The examples will be drawn mainly from work carried out by my group;[6] further relevant results may be found in papers and reviews by such pioneers in the field as Walling, Julia, Tedder, Rüchardt,and Ingold,[7] and more recently by Curran, Porter, Newcomb, Giese, and others.[5,8,9]

Much of our knowledge about the factors influencing the selectivity of radical reactions comes from kinetic studies. This is understandable since a highly selective reaction is one in which the formation of the desired product is very much more rapid under the experimental conditions used than all other possible reactions. The factors which affect selectivity are therefore those factors which affect the energies of transition complexes and hence the magnitudes of the rate constants.

The importance of thermochemistry was recognized in the earliest studies. The thermochemical approach was expressed in such generalizations as 'radical reactions follow the most exothermic available pathway' or 'radical reactions afford the most stable possible product'. It is based on the assumption that activation enthalpies reflect reaction enthalpy changes, and it leads to the conclusion that the relative rates of related reactions

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Professor Beckwith's research lies in the general area of physical organic chemistry and has been mainly concerned with reactive intermediates. It covers structural, kinetic, and mechanistic investigations involving ESR spectroscopy and laser flash photolysis, the development of theoretical approaches to radical reactivity, the role of radical intermediates in biological processes, and the application of radical reactions to synthesis.

can be estimated from bond dissociation energies. It underlies Benson's approach to the quantitative calculation of kinetic parameters.[10]

The thermochemical approach is especially useful for assessing the relative rates and directions of simple addition and β-fission processes (equation 3). Thus, when A$^{\bullet}$ represents a carbon-centred radical and B=D a carbon–carbon double bond, the addition is exothermic. Such reactions are usually relatively fast, and the relative rate constants often roughly reflect the exothermicities.[11] However, when B=D represents the carbonyl group, the reverse reaction, *i.e.* the β-fission of alkoxy radicals, is favoured on thermochemical grounds. The same is true for homolytic substitution reactions (equation 2). Thus, the order of reactivity of various substrates with $Bu_3Sn^{\bullet}$ radicals, namely RI > RBr > RSeAr > RCl > RSAr > RSMe is roughly in the same order as the exothermicities of the transfer reaction.[12]

However, thermochemistry is not the only factor, nor even the predominant factor, affecting the outcome of many free radical processes. The others are:

Stereoelectronic effects: these reflect the way in which the requirement for overlap of frontier orbitals affects the energy of the transition structure.

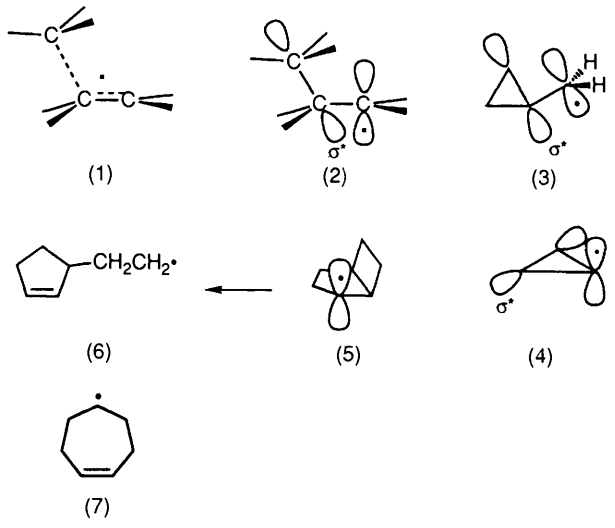
Polar effects: these reflect the way in which the electronegativities of the constituent atoms affect the energy of the transition structure.

Steric effects: these reflect the contribution of non-bonded interactions to the energy of the transition structure.

The outcome of any particular reaction will reflect the subtle interplay of all of these factors. They apply to all of the general elementary radical reactions (equations 1—4) but are best illustrated by reference to addition and β-fission reactions (equation 3) and to homolytic substitution reactions (equation 2); these processes will be the subject of this lecture. Furthermore, I shall give special attention to intramolecular reactions. By comparison with their intermolecular analogues they often reveal more clearly the constraints that arise from the necessity for the intimate transition structure to be accommodated within the overall molecular architecture of the reactant. Furthermore, they are of especial interest because of their utility for the synthesis of complex natural products.[5]

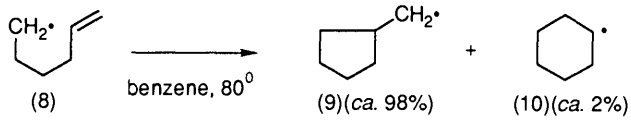
2 Intramolecular Addition and β-Fission Reactions

The relative rates and regiochemistry of intramolecular addition and β-fission processes clearly reveal the limitations of the thermochemical approach to selectivity. The opening of the cyclopropane ring in suitably constituted radicals provides a case in point. β-Fission of the cyclopropyl radical to give the allyl radical, although highly exothermic (*ca.* 96 kJ mol^{-1}),[10] has a rate constant at least six orders of magnitude less than that for the mildly exothermic ring opening of cyclopropylcarbinyl radical ($E_{act} \approx 29$ kJ mol^{-1}, $k \approx 1.3 \times 10^8$ s^{-1} at 25 °C).[13] Many substituted cyclopropylcarbinyl radicals undergo ring-opening even more rapidly. An explanation[6,14,15] for these observations rests on the assumption that the transition structure (1) for β-fission comprises a triangular array of centres arising from interaction of the SOMO orbital with the σ* orbital (or possibly the σ orbital) of the bond undergoing fission as illustrated in (2). This array is readily attained in cycloalkylcarbinyl radicals (3) in which rotation about the exocyclic bond allows coplanarity between the SOMO and σ* orbitals to be reached, but not in the cyclopropyl radical (4) where the orbitals involved are essentially orthogonal. For the same reason, cyclobutylcarbinyl radicals undergo moderately fast ring-opening whereas the cyclobutyl radical does not.[16] In bicyclic systems such stereoelectronic effects underly the direction of ring opening.[15,16] Thus ring opening of (5) exclusively affords (6),[16] the less stable of the two possible products (6) and (7), in clear contravention of the thermochemical guideline. The regioselectivity of the β-

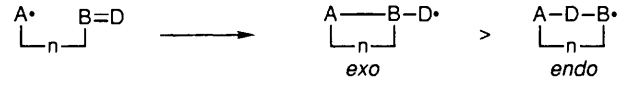


fission of (5) reflects the ability of the SOMO orbital to overlap with the σ* orbital of the cyclobutane bond exocyclic to the cyclopentane ring, whereas there is no such effective interaction possible with the σ* orbital of the bond forming the ring junction.

Stereoelectronic factors also play a dominant role in determining the regiochemistry of many intramolecular addition reactions. The well known regioselective cyclization of hex-5-enyl radical (8) to give the less stable cyclopentylmethyl radical (9) in preference to the more stable cyclohexyl radical (10), provides another clear contravention of predictions based on thermochemical criteria. The suggestion, first made more than twenty years ago, that this reaction is under stereoelectronic control,[14] is now widely accepted.



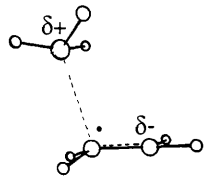
The preference for formation of the smaller possible ring (*exo* cyclization) also applies to a large number of substituted hexenyl radicals and related systems (*e.g.* Scheme 1 where B=D represents C=C, C=O, N=N, C=N, C≡C, C≡N, *etc.*; A$^{\bullet}$ represents C$^{\bullet}$, Si$^{\bullet}$, S$^{\bullet}$, O$^{\bullet}$, N$^{\bullet}$, *etc.*; and *n* represents a chain of 1 to 5 atoms, not all of which are necessarily carbon atoms).



Scheme 1

This behaviour is a reflection of the stereoelectronic demands of the intimate transition structure for homolytic addition which incorporates the three atoms involved in bond breaking and bond making at the corners of an obtuse triangle orthogonal to the nodal plant of the π system. Molecular orbital calculations[17] on the transition structure (11) for addition of an alkyl radical to an olefin show that the bond being formed is very long (*ca.* 2.4 Å) and forms an angle of about 106° with the ethylenic C–C bond. Formation of the transition complex is thought to involve interaction of the SOMO orbital with the vacant π* orbital as shown in (12). Essentially, this requires the radical centre to behave as a nucleophile. The transition structure should therefore be dipolar, and its energy should be sensitive to the polar nature of substituents.

The qualitative rationale for the preferred *exo*-cyclization of hex-5-enyl radical and related species rests on the hypothesis that the strain engendered in accommodating the mandatory



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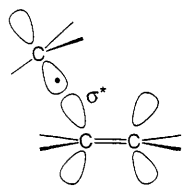
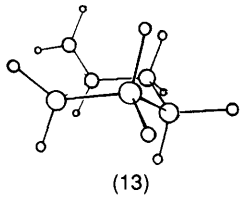


(12)

disposition of reactive centres within the transition structure for 1,6-ring closure outweighs those steric and thermochemical factors expected to favour the formation of the more stable possible product.[6] Theoretical considerations support this view. The geometries and strain energies of the transition structures for *exo*- and *endo*-cyclization of the hex-5-enyl radical can be estimated by a combination of molecular orbital and molecular mechanics calculations. In our approach[18] the dimensions of the intimate transition structure, as determined by the MNDO-UHF method, were incorporated in the transition structures for 1,5- and 1,6-ring closure and the minimum strain energy of each was calculated by the MM2 program. In accord with the hypothesis that the strain engendered in accommodating the required disposition of reactive centres is greater for the *endo*-transition structure than it is for the *exo*, the calculated energy for (14) was found to be *ca.* 11 kJ mol^{-1} greater than for (13). The assumption made in this method that the dimensions of the intimate transition structure are invariant for a variety of cyclization reactions is clearly invalid and must lead to inaccurate outcomes. An alternative method devised by Houk[19] resolves this difficulty. Nevertheless, our method correctly predicts the major isomer formed in more than sixty reactions, and is a useful adjunct to the use of radical cyclizations in synthesis.



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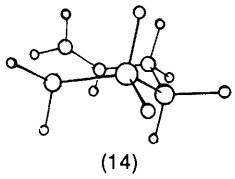
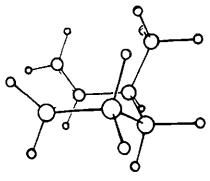


(14)

The calculated transition structure (13) for *exo*-cyclization of hex-5-enyl radical resembles cyclohexane in its chair form. For a typical monosubstituted system (*e.g.* the 4-methylhex-5-enyl radical) there are therefore two possible diastereoisomeric transition structures: one (15) in which the substituent is pseudo-axial, and the other (16) in which it is pseudo-equatorial. The latter is expected to be of lower energy, and this is confirmed by calculation.[18] Hence, cyclization of 4-substituted hexenyl radicals affords preferentially the *trans*-product.[20] The observed preference for *trans*-cyclization of 2-substituted hexenyl systems and for *cis*-cyclization of 1- or 3-substituted systems[20] can be similarly rationalized.[18]



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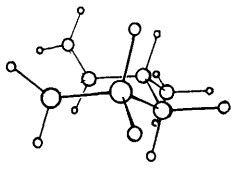
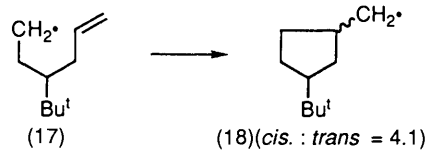
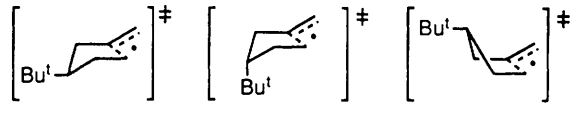


(16)

Although calculations based on pseudo chair transition structures such as (15) correctly predict the stereochemistry of the major cyclization product, they tend to overestimate the degree of selectivity. This led ourselves[21] and Houk [19] to consider the possibility that pseudo boat structures might lie on the pathways to minor isomers. The cyclization of 3-t-butyl-hex-5-enyl radical (17) allows a clear cut distinction to be made. The calculated difference in strain energy between the chair-like transition structure (19) leading to the *cis*-isomer and that (20) leading to the *trans* is 19.5 kJ mol^{-1}. On this basis the diastereoisomeric ratio *cis*:*trans* should be about 200:1. However, the calculated difference between the chair-like structure (19) and the boat-like structure (21) is only 5.1 kJ mol^{-1} and the predicted *cis*:*trans* ratio is 3.5:1. The experimental *cis*:*trans* ratio is 4.1:1.[21] We conclude, therefore, that the minor diastereomer (*trans*) formed from cyclization of 3-t-butylhex-5-enyl radical (17) arises from the boat-like transition structure (21). The same is believed to be true for the cyclization of many other monosubstituted hexenyl systems.[21] The involvement of boat-like transition structures sets an upper limit to the *cis*:*trans* ratio since their energies are relatively insensitive to the size of the substituent. However, since the differences in strain energy appear mainly in the activation energy term of the Arrhenius equation the diastereoselectivity is markedly increased by decrease in temperature. Thus the *trans*:*cis* ratio for cyclization of 4-methylhex-5-enyl radicals is *ca.* 3.7 at 80 °C, but is *ca.* 8.3 at − 40 °C.



(17) (18)(*cis.* : *trans* = 4.1)



(19) (20) (21)

The formation of bicyclic and polycyclic systems by intramolecular homolytic addition to a suitably constituted cycloalkene illustrates another important facet of stereoelectronic effects. Since the intimate transition structure requires the approach of the radical centre orthogonal to the nodal plane of the π system, the reaction can only proceed through that conformation of the ring which places the side chain in a pseudo-axial position (Figure 1). Consequently, such reactions afford exclusively *cis*-fused products; *e.g.* the formation of (23) by ring closure of (22) (R = Me).[22]

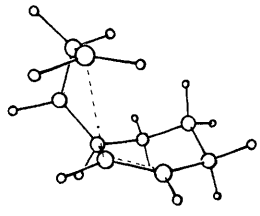
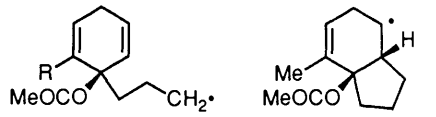


Figure 1 Transition structure for formation of a bicyclic system [ring closure of 4-(cyclohex-2-enyl)butyl radical].

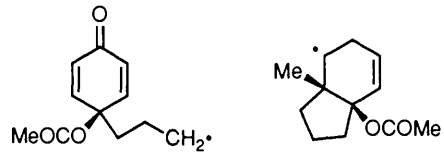
This type of reaction also reveals the importance of polar and steric effects. Thus, the radical (24) containing a carbonyl group undergoes ring-closure some 40 times more rapidly than does (22) (R = H), which does not.[22] This is a manifestation of the polar effect. The electron-accepting carbonyl group facilitates the reaction by stabilizing the dipolar transition state. This is a general phenomenon which has been extensively explored by Giese.[23]

Radicals such as (22) which contain a substituent at one of the possible points of attack undergo reaction mainly at the unsubstituted double bond. This illustrates another important generalization, namely that substituents on a double bond exert a powerful steric retardation on the rate of homolytic attack at the position of substitution.[24] Thus, the rate constant for the ring-closure onto the substituted double bond of (22) (R = Me) to give (25) is about 30 times less than that for addition on the unsubstituted double bond to give (23). In the light of this, and

similar results, it is clear that the observed Markownikoff mode of addition for intermolecular radical attack on unsymmetrical olefins reflects the steric hindrance of approach to the more substituted position rather than, as is often supposed, the greater stability of the more substituted adduct radical. Thus the outcome of such addition reactions depends more on steric than on thermochemical effects.



(22) (23)



(24) (25)

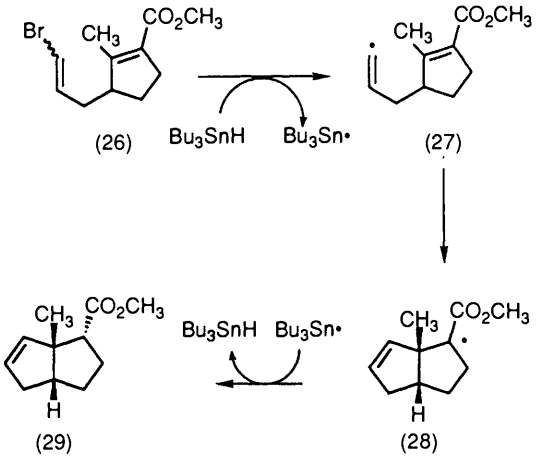
All of the factors affecting selectivity are nicely illustrated by the formation of the bicyclic compound (29) from the precursor (26).[25] The noteworthy features of the mechanism are:

(i) The chemoselective transfer of a bromine atom from (26) to the tin-centred radical to afford (27): an example of the importance of thermochemical factors, since this is a highly exothermic process.

(ii) Cyclization of the radical (27) to give exclusively the smaller possible ring and the *cis*-fused product: manifestations of stereo-electronic effects.

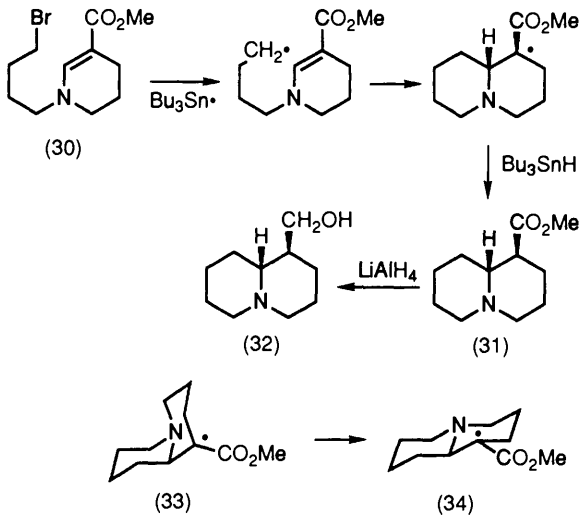
(iii) Highly efficient ring closure, despite steric hindrance by the methyl group, reflecting the polar effect of the electron-withdrawing substituent.

(iv) Diastereoselective hydrogen transfer from stannane to the less sterically encumbered convex face of the radical (28).

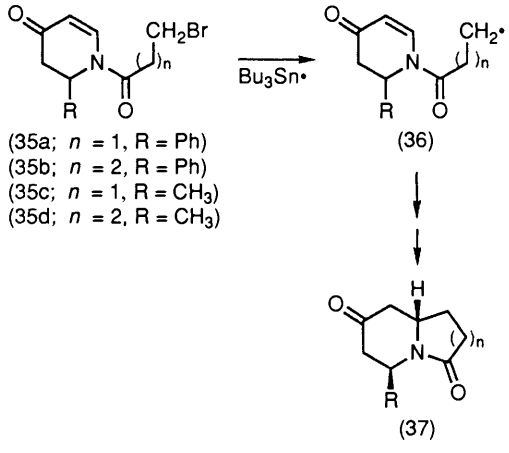


Ring closure to form bicyclic systems also occurs readily in suitably substituted dihydropyridines. Thus, treatment of the bromo compound (30) with tributylstannane in the usual way gives the quinolizidine (31) in high yield.[26] It is noteworthy that in this case the final atom transfer step is opposite in diastereoselectivity to that observed for (28). This is attributed to rapid inversion at the nitrogen centre of the initially formed *cis*-fused radical (33) to give a species (34) with a pseudo-*trans* ring junction. The hydrogen transfer then proceeds from the less sterically hindered pseudo-axial direction to give exclusively the product (31) with an equatorial carbomethoxy group. Reduction of (31) gives (±)-epilupinane (32) in good overall yield.[26]

Cyclizations to give pyrrolizidines or quinolizidines also occur readily by intramolecular homolytic substitution in



appropriately constituted pyridones and dihydropyridones. Substituted radicals of the general type (36) undergo highly diastereoselective cyclization. Thus the compounds (35a—d) when treated with tributylstannane each give high yields (≥ 90%) of the corresponding products (37) formed by intramolecular addition on the face of the dihydropyridone *trans* to the substituent.[27]



This outcome can be understood in the light of models of the transition structures incorporating the reactive centres in the usual triangular array orthogonal to the nodal plane of the π system. Figure 2 depicts the structures for the cyclization of (36d) viewed from above the plane of the heterocyclic ring. When the approach of the radical centre is *anti* to the methyl substituent it assumes a pseudo-axial position in the transition structure (38). However *syn* attack leads to a transition structure (39) in which the methyl is pseudo-equatorial. The strain energy of structure (38) leading to the preferred product, (37d), was found to be almost 12 kJ mol^{-1} less than that of the alternative structure (39). The calculations indicate that in the higher energy

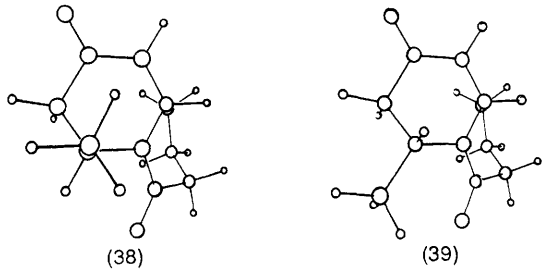
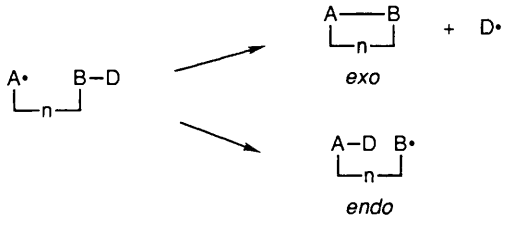


Figure 2 Transition structures for cyclization of the radical (36d).

structure (39) there is a severe non-bonded interaction between the pseudo-equatorial methyl group and the amide oxygen atom. This is not present in (38) where the substituent is pseudo-axial.

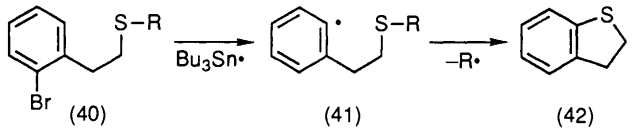
3 Homolytic Substitution

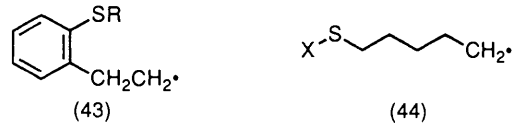
The preceding examples show how stereoelectronic factors strongly influence the outcome of many intramolecular homolytic addition and β-fission reactions. The same applies to intramolecular homolytic substitution (S_H2) reactions. In general terms, there are two modes available for such a reaction affording two different types of product (Scheme 2). When the atom undergoing substitution lies at the remote end of the group (B—D) under attack, the reaction (*endo*-S_H2) affords a rearranged radical; when it lies at the nearer end of B—D, the reaction (*exo*-S_H2) proceeds with ring formation and the expulsion of D·. The outcome in specific cases is expected to depend on the ability of the alternative gross transition structures to accommodate the optimum shape and dimensions of the intimate transition structure.



Scheme 2

Examples of both modes of reaction have been well documented. Hydrogen atom transfer from carbon to oxygen involves an approximately linear transition structure and lengths of about 1.4 Å for C---H and about 1.2 Å for O---H. This can be accommodated in a six-membered cyclic structure but not in smaller rings.[28] It is not surprising, therefore, that the well-known Barton method for remote functionalization usually proceeds mainly, and sometimes exclusively, by 1,5-hydrogen atom transfer.[29] The Barton reaction is an example of an intramolecular homolytic substitution reaction that proceeds in the *endo* mode, and is regioselective because of stereoelectronic factors. Intramolecular homolytic substitution at sulfur, however, appears always to be confined to the *exo* mode. Thus, treatment of sulfides of the general type (40) with tributylstannane in low concentration affords only the cyclized product (42) and the appropriate alkane, RH.[30,31] Clearly, the reaction involves exclusive *exo* homolytic substitution at sulfur in (41) with expulsion of an alkyl radical R· which then undertakes hydrogen atom transfer from the stannane. Stereoelectronic factors must be of prime importance since the more exothermic possible process would involve *endo* substitution to give the rearranged radicals (43).

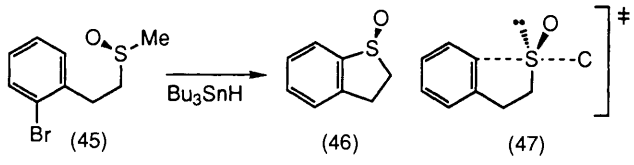




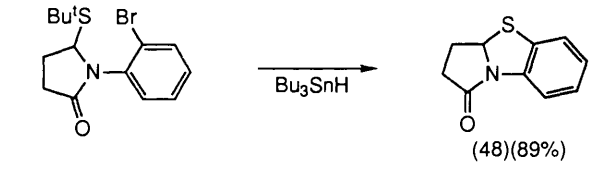
Cyclization of radicals of the general type (41) is relatively fast with rate constants of the order of 10^8 s^{-1} at 80 °C.[30] The values of the relative rate constants reflect the relative stabilities of the radicals expelled, *i.e.* the rates of cyclization of (41) for various groups R are in the order benzyl > t-butyl > methyl. Intramolecular attack by an *alkyl* radical on sulfur in suitably constituted substrates is much slower.[32] Thus, radicals of the general type (44) where X is an alkyl group undergo cyclization with rate constants in the range 10^2—10^4 s^{-1}. The reaction is also slow when the leaving group is acyl or aroyl, but is much faster when it is an alkylthio group. Thus, k_c for 44 (X = PhCO) is about 2×10^4 s^{-1} at 80 °C, while for (44) (X = Bu^{t}S) it is about 2×10^7 s^{-1} at 80 °C.[30]

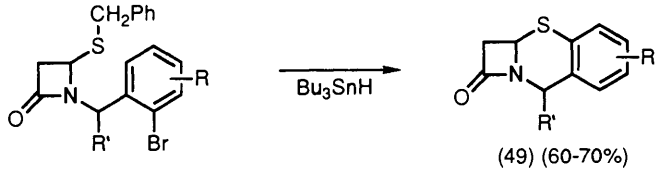
A plausible explanation for these observations is that radical substitution at sulfur proceeds through an approximately linear transition structure and involves concerted bond-formation and bond-fission. Such an arrangement of centres could not be accommodated in the 5- or 6-membered cyclic transition structures involved in *endo* substitution. Molecular orbital calculations recently completed by Schiesser support this hypothesis.[33]

Intramolecular homolytic substitution at the sulfur centre in appropriately constituted sulfoxides also proceeds under stereoelectronic control. Thus, treatment of the optically active sulfoxide (45) with tributylstannane affords only the one enantiomer (46) of the *exo*-cyclization product. Thus this reaction is highly regioselective and also stereospecific since it proceeds with strict inversion of stereochemistry.[31] Presumably it involves an intimate transition structure (47); it represents, therefore, a homolytic analogue of the Walden inversion.



Reactions involving intramolecular homolytic substitution of sulfur are useful for the preparation of a variety of complex heterocyclic systems. Examples include compounds *e.g.* (48) and (49) related to the penems and cephems;[30,34] some of them show interesting biological activity. The formation of such compounds raises the question of whether the biosynthesis of penicillin involves a somewhat similar mechanism. The notion that the thiazolidine ring might be formed by intramolecular alkyl radical attack on sulfur attached to the enzyme through iron, appears to be compatible with all the results obtained from biosynthetic studies.[35]



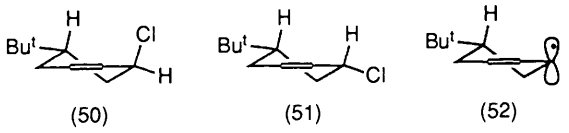


In all of the preceding examples of intramolecular S_H2 reactions, the high regioselectivity, and, in the case of substitution at sulfoxide sulfur, the stereospecificity, is imposed by the necessity for the intimate transition structure to be accommodated within the overall molecular architecture of the radical undergoing reaction. For intermolecular S_H2 processes, this constraint no longer applies and the factors affecting selectivity are more subtle. Sometimes electronic interactions with neighbouring groups or atoms are important. For example, maximum stabilization of the transition structure for an S_H2 process will be attained when the bond being broken or formed can assume

coplanarity with a neighbouring p or π orbital containing one or two electrons [24]

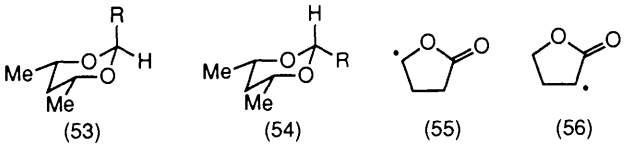
An early example of this type of stereoelectronic effect was detected when *trans*-3-chloro-5-t-butylcyclohexane was found to react with tributyltin radicals 10 times more rapidly than the *cis*-isomer [36] Since the chlorine is pseudo-axial in the *trans*-isomer (50), the transition structure can readily adopt the energetically favoured disposition of centres whereby the bond undergoing fission lies in the same plane as the adjacent π orbital This would only be possible for the *cis*-isomer (51) if it were to adopt the alternative highly energetic conformation with the bulky t-butyl group in a pseudo-axial position

Similarly, chlorination of 4-t-butylcyclohexene with t-butyl hypochlorite affords mainly the *trans*-isomer (5) [36] The intermediate allylic radical (52) undergoes preferential pseudo-axial bond formation, even though the product, being less stable than its isomer, is disfavoured on thermochemical grounds



(50) (51) (52)

An early example of the effect of adjacent lone pairs on the diastereoselectivity of radical reactions was provided by an examination of the relative rates of reaction of some conformationally locked dioxanes with t-butoxyl radical It was observed that the compound (53) (R = Me) in which the hydrogen at C-2 is equatorial reacts about 12 times more slowly than its more stable isomer (54) (R = Me) containing an axial hydrogen atom [37] This contravention of the thermochemical rule is consistent with the view that substitution at the axial hydrogen atom proceeds *via* a transition structure in which the bond undergoing fission can interact efficiently with the adjacent oxygen lone pairs [37] Further confirmation that the reaction is relatively unaffected by thermochemical factors was obtained when the reactivity of the methoxy compounds was examined Because of the anomeric effect, the isomer (53) (R = OMe) with an axial methoxy substituent is the more stable Nevertheless, the preference for cleavage of the axial C–H bond in (54) (R = OMe) over that in *cis*-isomer (53) (R = OMe) was almost the same as that observed for the methyl-substituted compounds



(53) (54) (55) (56)

Stereoelectronic factors should also favour axial attack on radicals derived from other cyclic ethers Examples of reactions of radicals derived from carbohydrates which display the predicted diastereoselectivity have recently been reported [38]

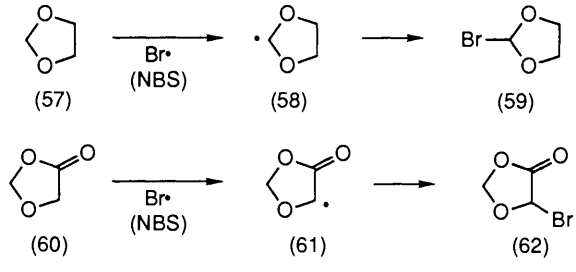
The regiochemistry of intermolecular radical substitution is often determined by thermochemical factors For example, halogenations with t-butyl hypochlorite or *N*-bromosuccinimide usually proceed through highly regioselective hydrogen-atom abstraction at allylic or benzylic positions because of the resonance stabilization of the resulting radicals However, recent experiments by Roberts[39] have shown that in some hydrogen atom transfer reactions polar effects can play a crucial role A good example[39 40] is provided by an ESR examination of hydrogen atom abstraction from butyrolactone When t-butoxyl radicals act as the hydrogen acceptor the reaction is confined to the position adjacent to the ether oxygen to afford the radical (55) Since the t-butoxyl radicals are strongly electrophilic the transition structures for hydrogen atom abstraction are dipolar The transition structure, on the pathway to (55), is stabilized by the electron donating character of the oxygen atom of the substrate However, hydrogen atom abstraction by the aminoboryl radical $Et_3N{-}BH_2^{\bullet}$ proceeds exclusively at the position adjacent to carbonyl Since the boryl radical is nucleophilic,[39] the dipolar transition structure for hydrogen atom transfer on the pathway to (56) is stabilized by the electron accepting carbonyl group

4 Captodative Radicals and Related Species

It has been suggested from time to time[41 42] that carbon-centred radicals, *e g* D–Ċ–X=Y, flanked by an electron accepting substituent X=Y (*e g* C=O, C≡N) and an electron donating atom D (*e g* O, N, S) are more stable than would be expected from the sum of the stabilizing effects of the two substituents In such 'captodative' radicals[41] the presence of both types of substituents allows contributing structures to be drawn which indicate that conjugation extends from one end of the system to the other In other words, the two substituents act synergistically to bestow enhanced stabilization on the radical

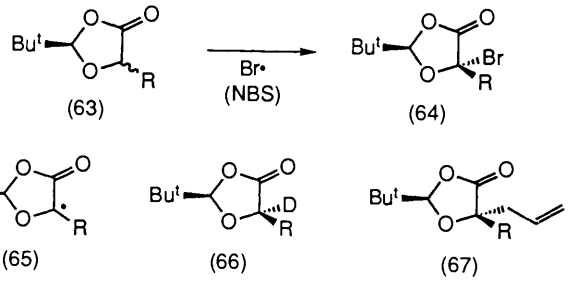
The concept of captodative stabilization has been criticized, and recent experimental work[43] seems to indicate that synergistic stabilization is, at best, relatively unimportant, a conclusion also reached in a comprehensive review [42] Nevertheless, it is clear that radicals with captodative substituents exhibit the restriction of rotation expected from systems with extended delocalization [44] Since radicals derived from such biologically significant compounds as α-hydroxy acids and α-amino acids are formally captodative, it is important to ascertain whether species of this type show any special selectivity arising either from their thermodynamic stabilization or the extended delocalization of the unpaired electron

In order to avoid possible ambiguities in the interpretation of results of experiments with acylic radicals arising from the effect of non-bonded interactions on their conformations, we chose to work with cyclic compounds Bromination of the dioxolane (57) with *N*-bromosuccinimide under bromine atom chain conditions gave only the product (59) (> 90%), whereas similar bromination of the dioxolanone (60) occurred exclusively at the position adjacent to the carbonyl group to give (62) (> 92%) [45] Clearly hydrogen atom transfer to Br$^{\bullet}$, an electrophilic radical, affords only (58) from (57), and (61) from (60) This regioselectivity is unexpected in view of the preference for attack on butyrolactone by the electrophilic t-butoxyl radical at the position adjacent to the ether oxygen to give (55) Although it is tempting to propose that the selectivity of the bromination reaction reflects captodative stabilization of the radical (61) it is more likely that it represents the outcome of the subtle interplay of polar and thermochemical effects



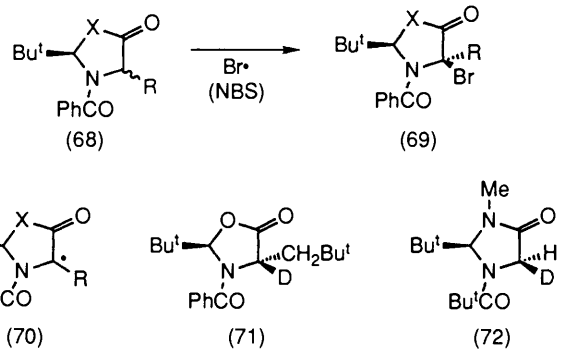
(57) (58) (59) (60) (61) (62)

What is significant, however, is that the reaction with the substituted dioxolanone (63) (R = H) affords exclusively and in excellent yield (96%) the *trans*-brominated product (64) (R = H) [45] Similarly, bromination of disubstituted substrates of the general type (63) (R = alkyl) always occurs *anti* to the t-butyl substituent This propensity of radicals of the general type (65) to undergo stereoselective bond formation *anti* to the t-butyl substituent applies also to other radical reactions Thus, treatment of the bromo compound (64) (R = Me) with tributyltin deuteride affords (66) as the major diastereoisomer (> 90%), while the reaction of (64) (R = Me) with allyltributyltin gives a mixture of isomers (7 1) in which (67) is the major component [45] Surprisingly, the diastereoselectivity of the latter reaction is



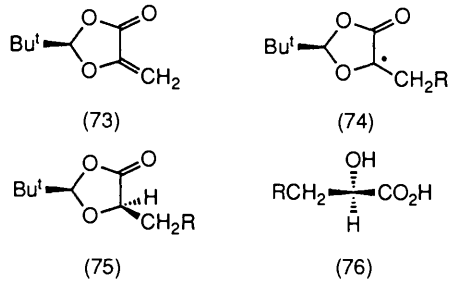
greater than that (*trans*:*cis* = 1.9) for the allylation of (64) (R = H) to give (67) (R = H).

Oxazolidinones and imidazolidinones of the general type (68) (R = H or Me; X = O or NMe) also undergo bromination exclusively at the 'captodative' position.[45] The determination of the stereochemistry of the bromination products is difficult but the bulk of the evidence suggests that they have the general structure (69) (R = H or Me; X = O or NMe). The situation for other radical reactions of oxazolidinones and imidazolidinones is more clearcut as some of the products have been examined by *X*-ray crystallography.[46] It appears that reactions involving the intermediacy of radicals (70) (X = O or NMe) exhibit diastereoselectivity opposite to that for the dioxolanones to afford products (69) arising from bond formation *syn* to the t-butyl group. Although compounds of the general type (70) (X = O or NMe, R = H; R′ = Ph) show relatively little diastereoselectivity in their reactions with tributylstannane, the selectivity is enhanced markedly when the size of the substituent R or of R′ in the acyl group is increased.[45] The corresponding imidazolidinones behave similarly but usually with higher diastereoselectivity. The tendency for radicals of the general type (70) (X = O or NMe) to undergo diastereoselective bond formation *syn* to the t-butyl group is exemplified by the highly diastereoselective formation of (71) and (72) by treatment of the appropriate precursors with tributyltin deuteride.[45]



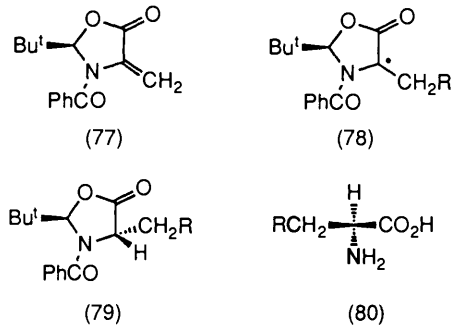
As yet, a satisfactory explanation for the highly selective behaviour of radicals of the general types (65) and (70) (X = O or NMe) has eluded us. In the case of radicals [*e.g.* (65)] derived from dioxolanones the preference for bond formation *anti* to the bulky t-butyl group may reflect steric hindrance to the *syn* face of the molecule. The fact that allylation of (64) (R = H) and (64) (R = Me) with allyltributylstannane occurs anti to the t-butyl group in both cases but that the diastereoselectivity is *greater* when R is methyl suggests that the reaction cannot be under thermochemical control. For reactions of radicals of the general type (70) (X = O or NMe) the factors underlying diastereoselectivity are even more obscure; attempts to probe possible stereoelectronic effects by application of the usual molecular mechanics calculations have failed because of the lack of appropriate parameters.

Radical reactions of appropriately constituted dioxolanones, oxazolidinones, and imidazolidinones are very useful for the enantioselective synthesis of α-hydroxy acids and α-amino acids. From the readily available enantiomers of lactic acid or malic acid it is a relatively straightforward matter to prepare either the (2*R*)-methylene compound (73) or its (2*S*)-enantiomer.[45] Treatment of (73) either with tributylstannane and an alkyl iodide or bromide, or with an alkylmercuric halide and a borohydride reducing agent, affords the enantiomerically pure (2*R*, 5*R*) product (75) with high diastereoselectivity. The optically active hydroxy acid (76) can then be readily obtained by hydrolysis of (75). The (*S*)-enantiomer of (76) can be similarly prepared from the (2*S*)-enantiomer of (73).[45]



The stannane and alkylmercuric halide procedures involve essentially the same mechanism. An alkyl radical generated by reaction of RX with $Bu_3Sn^•$, or by α-fission of RHg•, adds regioselectively to (73) to give the radical adduct (74) which then undergoes highly diastereoselective hydrogen atom transfer either from the stannane, or from the alkylmercuric hydride (RHgH) generated by borohydride reduction of the alkylmercuric halide.

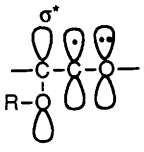
In similar vein, the optically active (2*S*)-oxazolidinone (77), which can be readily prepared from (*R*)-alanine, undergoes addition of an alkyl radical to afford the radical (78). In this case hydrogen atom transfer occurs *syn* to the t-butyl group with high diastereoselectivity to give the (2*S*, 5*S*)-oxazolidinone (79) from which the (*S*)-α-amino acid (80) can be obtained in good yield.[45] The preparation by this method of naturally occurring α-amino acids allows the stereochemistry of intermediates in the reaction sequence to be securely assigned.[45]



Although it has not yet been possible to define the role of stereoelectronic effects in the reactions of such formally 'captodative' radicals as (74) and (78), there is good evidence that they are important in defining the stereochemical behaviour of some related species. Carbon centred radicals [*e.g.* (83)] flanked by an oxygen atom and a C—O single bond can be formally regarded as captodative, since the former acts as the electron donor and the σ* orbital of the latter acts as the electron acceptor. Evidence for a stabilizing interaction between the SOMO orbital, the σ* orbital, and the filled oxygen orbital as indicated in structure (81) (the 'homoanomeric effect'[47]) comes from ESR studies[44,48] which show that radicals containing this type of system have high barriers to rotation about the C—O and C—CO bonds, and assume a relatively stable conformation in which the C—O bond is co-planar with the SOMO orbital.[44]

This has a dramatic effect on the diastereoselectivity of the reactions of suitably constituted radicals. Thus, the ESR spectrum of the 2-butanoyloxycyclohexyl radical shows that it preferentially assumes the conformation (82) in which the ester

group is pseudo-equatorial [48,49] Atom transfer to (82) from tributyltin deuteride occurs selectively from the axial direction to afford mainly the *cis*-isomer of (84) (X = CH_2) [49] However, when the radical contains an oxygen atom α to the radical centre, it takes up the conformation (83) in which the ester group is axial The reaction with tributyltin deuteride then occurs on the less encumbered face of (83) *anti* to the acyloxy group to afford mainly the *trans*-isomer of (84) (X = O) [49]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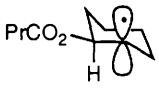
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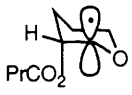
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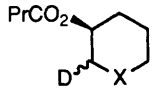
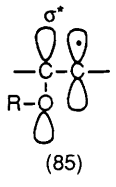

(84)

The evidence that radicals of the general type (81) are stabilized by interaction of the SOMO with both the adjacent lone pair and the adjacent σ^* orbital raises the question of whether a C–O σ^* orbital alone will stabilize an adjacent carbon radical centre Earlier observations that xanthates and similar species derived from β-alkoxy alcohols give good yields of deoxygenated products on treatment with tributylstannane under Barton conditions, whereas substrates lacking the oxygen substituent do not, prompted the suggestion that β-alkoxyalkyl radicals are stabilized by the so-called 'β-oxygen effect' [50] A stabilizing interaction between the SOMO and σ^* orbitals would require their co-planarity as indicated in (85) However, ESR measurements on β-alkoxyalkyl radicals indicate that the preferred conformation has the C–O bond nearly orthogonal to the SOMO orbital [51] Furthermore, when a mixture of a xanthate (86) (X = CH_2) with its analogue containing a β-oxygen atom (86) (X = O) is treated with tributylstannane, the two deoxygenated products (87) (X = CH_2) and (87) (X = O) are formed in approximately equal yields [51] These and similar experiments involving the competitive formation of radicals both inter- and intra-molecularly suggest that the presence of a β-oxygen substituent has little effect on the ease of formation and, by implication, on the stability of a carbon-centred radical The results previously adduced in support of the 'β-oxygen effect' must, therefore, have some other explanation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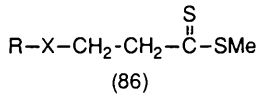
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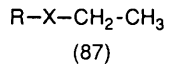
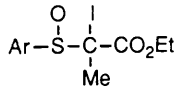

(87)

Finally, I turn to another example of a highly diastereoselective homolytic reaction, the outcome of which appears to reflect the conformational preference of the intermediate radical Treatment of the iodosulfoxide (88) with tributylstannane gave mainly one diastereoisomer (90) of the product (d e > 94%) [52] The reaction with allyltributylstannane was even more selective and afforded only one detectable diastereisomer (d e > 98%) of the product (91) The reactions of (88) with hex-1-ene and with hexa-1,5-diene were equally diastereoselective The relative stereochemistry of (91) was determined by *X*-ray crystallography, while assignments of stereochemistry for other products were based on the comparison of NMR spectra These results are all consistent with the view that the intermediate radical (89) has a relatively stable conformation (92), the preference for which results from the dielectric repulsion between the oxygens of the carbonyl and sulfoxide groups Bond formation, either by hydrogen atom transfer or by addition to a carbon–carbon double bond, is confined to the less encumbered face of (92)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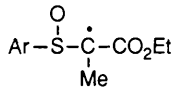
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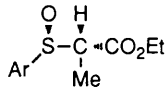
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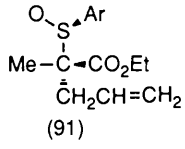
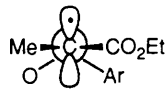

(91)


(92)

Unfortunately, the hypothesis of restricted rotation in (92) lacks experimental support since we have, as yet, been unable to conduct successful ESR experiments However, the corresponding radical containing an arylthio group in place of the arylsulfinyl clearly exhibits a large barrier to rotation in the ESR,[44] presumably because of interaction of the sulfur lone pair with the adjacent SOMO and π^* orbitals Recently Porter, Curran, and Giese have described a number of highly diastereoselective radical reactions, the selectivity of which appears to depend upon the relative stability of the preferred conformations of radical intermediates [8]

5 Conclusion

In this article I have tried to give an overview, albeit one based mainly on our own work, of experiments that have contributed to our understanding of the factors affecting the selectivity of radical reactions, an understanding that has underpinned the dramatic developments during the past decade in the application of radical methodology to organic synthesis The picture is far from complete Although it is clear that stereoelectronic effects play a dominant role in determining the outcome of many simple homolytic intramolecular and substitution reactions, the selectivity exhibited by intermolecular radical reactions with complex substrates is often less easily rationalized Undoubtedly, in some cases thermochemical, polar, stereoelectronic, and steric effects all play a part The further investigation of the factors affecting the structure, stability, and reactivity of radicals, and the selectivity of their reactions remains an important and fascinating field of research deserving the attention of spectroscopists, kineticists, and synthetic organic chemists I have no doubt that their endeavours will be well rewarded

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