Chemistry of β-(Acyloxy)alkyl and β-(Phosphatoxy)alkyl Radicals and Related Species: Radical and Radical Ionic Migrations and Fragmentations of Carbon–Oxygen Bonds

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I. Introduction

The predominant role of carboxylate esters in preparative free radical chemistry has been as a substituent on alkenes, activating them toward attack by nucleophilic radicals,[1] or on radicals themselves, modulating their reactivity. α-Halogeno esters are convenient precursors of ester-substituted radicals[2] and are widely employed in synthetic procedures, particularly in those involving cyclization reactions, where they are especially useful for the formation of eight-membered lactones.[3,4] This chemistry is nicely complemented by the manganese triacetate oxidative cyclizations of malonate esters.[5−7] Electrophilic radicals cannot be used to generate enolyl ester substituted radicals, however, as they preferentially abstract hydrogen atoms α to ethereal ester oxygens, giving α-carboxylalkyl radicals. This regioselectivity can be reversed when amine−borane catalysts are employed.[8] In all of this chemistry, the function of the ester group is one of interaction with alkenes (activation) or with adjacent radicals (stabilization): neither cleavage nor formation of C−O bonds nor direct radical attack on the carbonyl group is implicated. As a result, the predominant view has been that the ester function itself is essentially inert to attack by carbon-centered radicals and is thus fully compatible with the application of radical reactions in synthesis. Even a cursory reading of the recent literature on free radical reactions reveals that this is an oversimplification.

The intramolecular addition of alkyl radicals to the carbonyl carbon of ketones, with subsequent alkoxy radical fragmentation, was suggested as long ago as 1961.[9] Despite this, the process attracted little attention until 1984, when it was employed in the expansion of a cyclohexadienone ring to a tropone.[10] This intramolecular radical chemistry of ketones has subsequently been much studied and employed in synthesis.[11,12] The vitamin B_{12}-promoted methylmalonyl Co-A to succinyl Co-A rearrangement has long been considered to provide a possible example of an enzyme-mediated cyclization of an alkyl radical to the carbonyl carbon of an acyl sulfide, with subsequent fragmentation. However, recent work suggests that this might not be the case.[13−15] It is only relatively recently that comparable intramolecular additions of alkyl radicals to acylgermanes[16−19] and acyl selenides, sulfides,[20] and sulfones[21,22] have been described. These reactions result in the expulsion of germyl, selenyl, thiyl, or sulfonyl radicals, respectively. Acyl-

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Athelstan L. J. Beckwith was born in Perth, Western Australia (1930), and received his B.Sc. (1952) from the University of Western Australia and his Ph.D. from Oxford University in 1956 (with Professor W. A. Waters). After a short time as a Research Officer with the CSIRO in Melbourne he joined the University of Adelaide (1958) where he later became Professor and Head of Department. In 1981 he moved to his present position in the Research School of Chemistry, Australian National University. He has been a visiting fellow in Great Britain working at various times with Professors Sir Derek Barton, J. E. Baldwin, R. O. C. Norman, and Sir Ewart Jones and in Germany as a Senior von Humboldt Awardee with Professor Chr. Rüchardt in Freiburg. Other awards received include a Carnegie Fellowship, the Rennie Medal, the H. G. Smith Memorial Medal, the Organic Chemistry Medal of the Royal Australian Chemical Institute, and the Centenary Medal of the Royal Society of Chemistry. He has been a Syntex Lecturer (USA and Canada), a Rayson Huang Lecturer (Hong Kong), a Monsanto Lecturer (Berkeley), a Kharasch Lecturer (Chicago), a Cyanamid Lecturer (Columbus), a Bert Halpern Memorial Lecturer (Wollongong), and a Frontiers of Chemistry Lecturer (Texas A&M). He is a Fellow of the Royal Society, of the Australian Academy of Science (Vice President 1985–6), and of the Royal Australian Chemical Institute (National President, 1983–4). His primary research interests are in the properties, reactions, and synthetic utility of organic free radicals and other reactive intermediates.

David Crich was born in Chesterfield, England (1959), and graduated B.Sc. in Chemistry and French from the University of Surrey in 1981. He obtained his doctorate (Docteur ès Sciences) from the Université de Paris XI in 1984 under the direction of D. H. R. Barton and stayed in France, at the Institut de Chimie des Substances Naturelles in Gif sur Yvette, for a year's postdoctoral study with Professors D. H. R. Barton and P. Potier. He spent five years at University College London as a Lecturer in the Chemistry Department before moving, as Associate Professor in 1990, to the University of Illinois at Chicago where he is now Full Professor. He is a recipient of the Franco-British prize of the French Academy of Sciences and the Corday-Morgan and Tate and Lyle medals of the Royal Society of Chemistry and has been a Fellow of the A. P. Sloan Foundation and a University Scholar of the University of Illinois at Chicago. His main interests are in the chemistry of free radicals, asymmetric synthesis, and carbohydrate chemistry.

silanes are similarly subject to intramolecular attack at the carbonyl carbon by alkyl radicals, but in this case a radical Brook rearrangement of the ensuing

Peter Duggan spent his early years in Yongala, a small town in the midnorth of South Australia. He obtained his Bachelor of Science Honours degree from Flinders University of South Australia, Adelaide, in 1985, and his Ph.D. from Australian National University in 1990, working with Professor Athel Beckwith. He then undertook postdoctoral studies with Professor Ronald Breslow at Columbia University and Dr. Chris Abell at Cambridge University. In 1994, he took up a lectureship at James Cook University of North Queensland, Townsville. In December 1996, Peter moved to Monash University. His current research interests include the mechanism based inhibition of enzymes, particularly those employing radical intermediates, and the molecular recognition of sugars by aryl boron acids.

Qingwei Yao was born in northern Shanxi, Peoples Republic of China, in 1963 and received his college education at Shanxi Medical College (1979–1983). After a two-year teaching appointment at Shanxi Medical College, he joined Professor Chizhong Xia's group at Shanxi University and received his M.S. degree in organic chemistry in 1988. He was then appointed to the faculty of the Chemistry Department at Shanxi University, where he received the University Young Faculty Teaching Award (1990). He came to the United States in 1991 and received his Ph.D. in 1996 with Professor David Crich at the University of Illinois at Chicago, where he was twice recipient of the Deans Scholar Awards (1994–1995 and 1995–1996). His graduate work with Professor Crich centered on designing free radical reactions, particularly those with potential synthetic utility and with implications in biological processes. He came to New York in November 1996 and joined Professor W. Clark Still's group at Columbia University for his postdoctoral studies. He is currently working in the field of combinatorial chemistry. His reseach interests focus on novel synthetic and mechanistic organic chemistry and combinatorial chemistry as a tool in solving chemical and biological problems.

α-silylalkoxy radical results.[23−25] In contrast, the recently described intermolecular acylation of alkyl radicals by acyl selenides and sulfides is very inefficient.[26] On treatment with tributylstannane and a radical initiator, acyl selenides[27,28] provide convenient sources of acyl radicals,[29] as do certain classes of acyl sulfide.[30−32] Alternatively, acyl tellurides[33] and acylcobalt(III)[34] derivatives can provide acyl radicals on white light photolysis.

It is well appreciated[35−37] that in the case of thiocarbonyl derivatives, sulfur is readily and reversibly[38,39] attacked by stannyl, thiyl, and certain silyl[40] radicals. Indeed, this process forms the basis for the Barton deoxygenation and decarboxylation reactions.[41,42] More recent work has shown that phosphinyl,[43] alkyl,[32] and aryl[44,45] radicals may also attack the sulfur atom of thiocarbonyl compounds.

Much less widely held is an appreciation of reactions that involve the homolytic cleavage and formation of carbon−oxygen bonds in ester and related functional groups. This review analyses a wide range of examples of such processes and attempts to demonstrate that this chemistry not only constitutes a fascinating puzzle for aficionados of radical mechanisms but also is of considerable importance in biological spheres and richly deserves the attention of synthetic chemists.

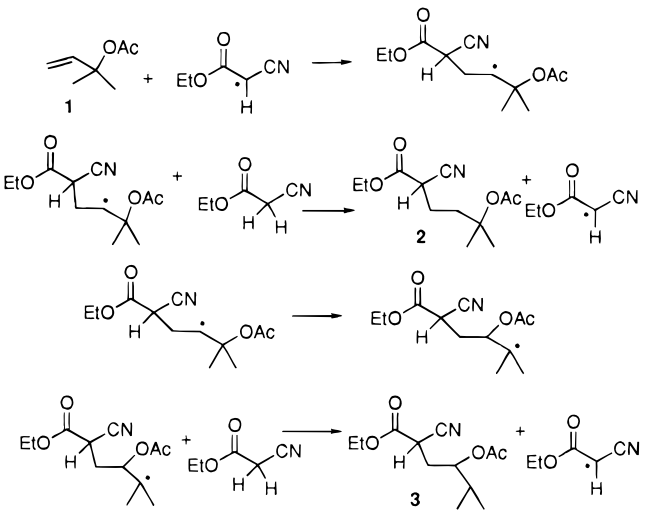
II. Rearrangements

A. β-(Acyloxy)alkyl Rearrangement

1. Esters

The first examples of the β-(acyloxy)alkyl rearrangement were discovered serendipitously by Suzur and Teissier in 1967.[46,47] In the course of an investigation into the dibenzoyl peroxide initiated addition of ethyl cyanoacetate to isoprenyl acetate they observed, together with the anticipated addition product (**2**), a substance (**3**) arising from addition followed by 1,2-migration of the ester function (Scheme 1, Table 1, entry 1).

Scheme 1

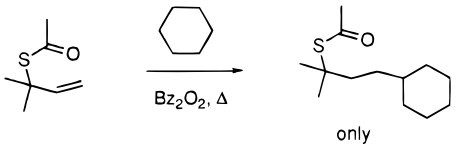


Similar reactions were observed for the addition of ethyl acetoacetate and of cyclohexane to isoprenyl acetate (Table 1, entries 2 and 3). It was noted that the ratio of the simple addition to rearranged product

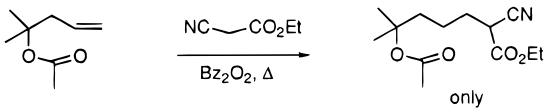
Table 1. β-(Acyloxy)alkyl Radical Rearrangement

entry	substrate	reagent	solvent	temp	products (%, yield)	ref
1	**1**	$NCCH_2CO_2Et$	$NCCH_2CO_2Et$	115	**2** + **3** (24%, 7:3)	46, 47
2	**1**	$CH_2(CO_2Et)_2$	$CH_2(CO_2Et)_2$	115	**4** + **5** (45%, 6:94)	46, 47
3	**1**	C_6H_{12}	C_6H_{12}	80	**6** + **7** (53%, 5:95)	46, 47
4	**8**	$NCCH_2CO_2Et$	$NCCH_2CO_2Et$	115	**9** + **10** (19%, 100:0)	46, 47
5	**11**	$NCCH_2CO_2Et$	$NCCH_2CO_2Et$	115	**12** + **13** (66%, 100:0)	46, 47
6	**11**	C_6H_{12}	C_6H_{12}	80	**14** + **15** (69%, 96:4)	46, 47
7	**16**	$NCCH_2CO_2Et$	$NCCH_2CO_2Et$	115	**17** + **18** (21%, 55:45)	46, 47
8	**19**	none	PhCl	75	**20** + **21** (1.25:1)	48
9	**34**	Bu_3SnH	benzene	80	**37** (63)	55, 56
10	**35**	Bu_3SnH	benzene	80	**37** (59)	55, 56, 57
11	**38**	Bu_3SnH	benzene	80	**39** (57)	55, 57
12	**40**	Bu_3SnH	benzene	80	**41** (63)	55, 57
13	**48**	Bu_3SnH	benzene	80	**50** (92)	60
14	**51**	Bu_3SnH	benzene	80	**52** (92)	60
15	**53**	Bu_3SnH	benzene	80	**54** (71)	60
16	**55**	Bu_3SnH	benzene	80	**56** (70)	60
17	**57**	Bu_3SnH	benzene	80	**58** (81)	60
18	**59**	Bu_3SnH	benzene	80	**60** (65)	60
19	**61**	Bu_3SnH	benzene	80	**62** (75)	60
20	**63**	Bu_3SnH	benzene	80	**64** (72)	60
21	**65**	Bu_3SnH	benzene	80	**66** (50)	60
22	**48**	TTMSS	benzene	80	**50** (71)	64
23	**53**	TTMSS	benzene	80	**54** (70)	64
24	**67**	cyclohexane + 6% lauroyl peroxide	cyclohexane	80	**50** (90)	65
25	**68**	cyclohexane + 6% lauroyl peroxide	cyclohexane	80	**58** (96)	65
26	**48**	Bu_3SnH + 10% PhSeSePh	benzene	80	**49** + **50** (100%, >95:5)	66
27	**69**	Bu_3SnH	benzene	120	**70** + **71** (99%, 1:1.4)	62
28	**72**	Bu_3SnH	MeC_6H_{11}	101	**70** + **71** (0.05:1)	62
29	**81**	Bu_3SnH	benzene	80	**83** + **84** (68%, 10:1.3)	67
30	**81**	Bu_3SnH	benzene	80	**82** + **83** + **84** (97%, 12:6:1)	68
31	**81**	TTMSS	benzene	80	**83** + **84** (86%, 40:1)	68
32	**87**	Bu_3SnH	benzene	80	**88** (56) + **89** (12)	67
33	**90**	Bu_3SnH	benzene	80	**91** (43) + **92** (12) + **89** (10)	67
34	**93**	Bu_3SnH	benzene	80	**94** (60) + **95** (21)	67
35	**48**	$allylSnBu_3$	benzene	80	**96**	69, 70
36	**87**	$allylSnBu_3$	benzene	80	**97** (52) + **89** (11)	67
37	**87**	$allylSnBu_3$	benzene	rt	**97** (66) + **98** (6)	67
38	**99**	$allylSnBu_3$	benzene	80	**100** (46) + **101** (5) + **102** (37)	67
39	**99**	$allylSnBu_3$	benzene	rt	**100** (74) + **101** (5) + **102** (0)	67
40	**103**	Bu_3SnH	benzene	80	**104** + **105** (100%, 4:1)	71
41	**106**	Bu_3SnH	toluene	110	**107** (70) + **108** (<10)	72

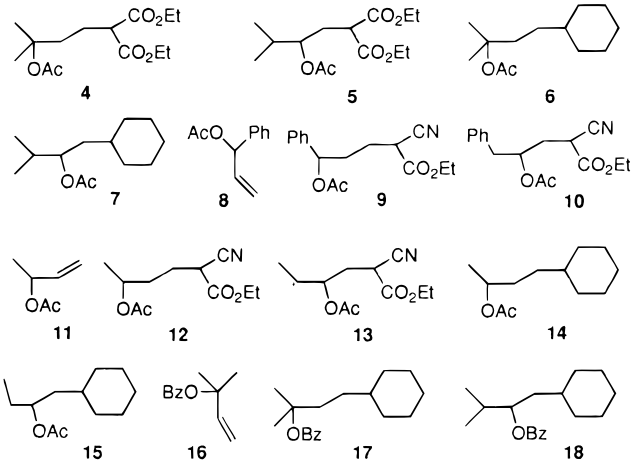
Scheme 2



Scheme 3



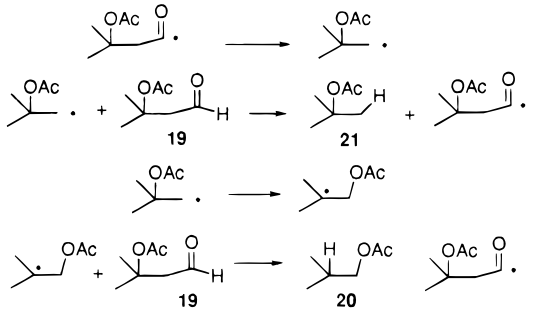
was related to the C−H bond strength of the reagent: cyclohexane, with its stronger C−H bond, gave the highest proportions of rearranged products. No rearrangement product was observed when ethyl cyanoacetate was added to 3-phenyl-3-allyl acetate (**8**) (Table 1, entry 4), an observation which the authors ascribed to the facile dimerization of benzylic radicals rather than to the failure of the migration reaction. Addition of ethyl cyanoacetate to butenyl acetate (**11**) resulted only in the formation of the direct addition product (**12**), whereas with cyclohexane, traces of the rearranged product (**15**) were identified (Table 1, entries 5 and 6). The migration of benzoate esters was also observed by these workers (Table 1, entry 7).



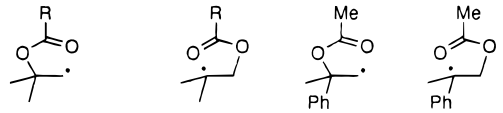
Further exploration of the scope of the reaction led Surzur and Teissier to conclude that thioacetate esters do not undergo the migration (Scheme 2). The probable formation of dimethylallylcyclohexane, by facile elimination of $CH_3COS^{\bullet}$ from the initial adduct radical (section I.A.3), was not investigated. It was also shown that the rearrangement does not occur in γ-(acyloxy)alkyl radicals (Scheme 3).

In 1969, independent of the work of Surzur and Teissier, Tanner and Law reported their observations of the β-(acyloxy)alkyl rearrangement.[48] These workers studied the benzoyl peroxide initiated decarbonylation of 3-acetoxy-3-methylbutyraldehyde (**19**) at 75 °C in benzene and chlorobenzene. They observed two radical-mediated products: namely **21**, due to simple decarbonylation, and **20**, a result of decarbonylation followed by acyloxy migration (Table 1, entry 8, Scheme 4). As anticipated from the proposed chain mechanism (Scheme 4), the use of higher concentrations of aldehyde led to lower proportions of the rearranged product in the reaction mixture.

Scheme 4



Both Surzur and Tanner reflected on the mechanism of the acyloxy migration in their early publications. Several possibilities were advanced, including the intermediacy of dioxolanyl radicals, either as intermediates or transition states in a formal 2,3-shift, and a formal 1,2-shift. From the outset, radical-type fragmentations to alkenes and carboxyl radicals, followed by recombination, were thought unlikely owing to the ease of decarboxylation of acyloxy radicals. The lack of production of isobutylene in Tanner's experiments supported this conclusion. The unprecedented nature of these acyloxy migrations and their continued lack of intermolecular equivalents piqued the curiosity not only of the discoverers but also of other groups involved in mechanistic studies of free radical reactions. The Beckwith laboratory was one of the first to take up the challenge, and in 1971 their initial ESR investigations into the mechanism of the rearrangement were published.[49] The possibility of dioxolanyl radicals as intermediates was specifically addressed by this work (section IV.C.2). These studies were soon followed up[50] by the determination of rate constants for some typical migrations in benzene solutions (Table 2, entries 1−3) using the tin hydride clock reaction[51,52] and by ^{18}O labeling studies (section IV.C.3). Subsequent work by the Ingold group, using the kinetic ESR method, caused the rate constants to be revised downward by approximately an order of magnitude (Table 2, entries 5−10).[53,54] The fact that these reactions are rather slow in comparison to typical radical reactions probably contributed to the prevailing philosophy that ester functions are fully compatible with preparative radical chain reactions and led to the widespread neglect of this, in retrospect, rather common reaction. As will become clear, these initial examples very much represent the lower end of the spectrum of rate constants for radical ester migrations.

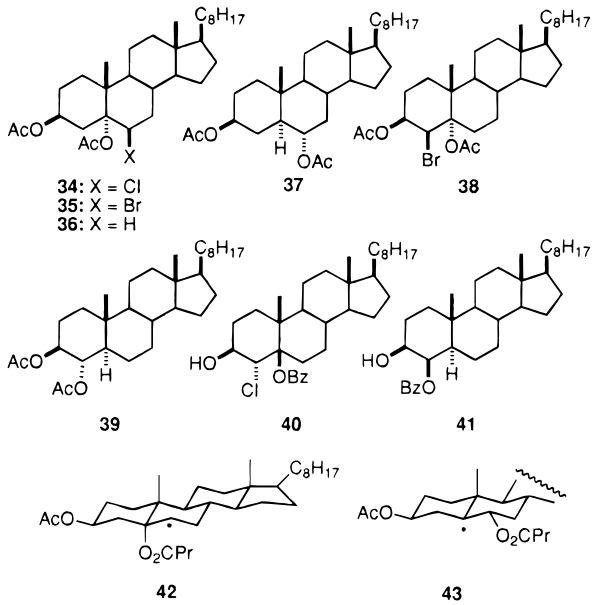


An early report[55] by Julia (Sylvestre) and Lorne in the Comptes Rendus describing highly stereoselective migrations along steroid frameworks unfortunately appears to have gone largely unnoticed until followed up by a full paper 15 years later.[56,57] In this

Table 2. Kinetics of the β-(Acyloxy)alkyl Rearrangement

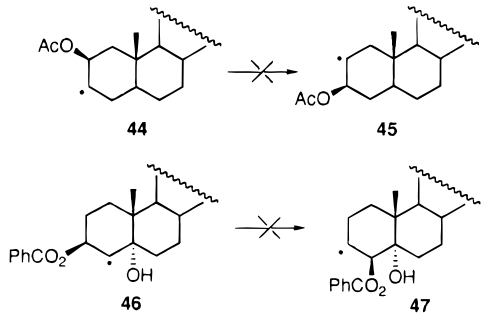
entry	rearrangement	solvent	temp, °C	k, s^{-1}	log A	E_A, kcal/mol	ref
1	**22** → **27**	C_6H_6	75	6.2×10^3			50
2	**23** → **28**	C_6H_6	75	3.6×10^3			50
3	**24** → **29**	C_6H_6	70	3.9×10^3			50
4	**32** → **33**	C_6H_6	70	4.1×10^4			50
5	**22** → **27**	hydrocarbon	75	5.1×10^2	13.2	16.8	53
6	**24** → **29**	hydrocarbon	75	2.5×10^2	13.2	17.3	53
7	**25** → **30**	hydrocarbon	75	1.2×10^2	13.2	17.8	53
8	**22** → **27**	Me_3CPh	75	4.5×10^2	13.9	17.9	54
9	**22** → **27**	H_2O	75	2.1×10^2	12.3	12.7	54
10	**26** → **31**	Freon 113	75	7.0×10^4	11.0	9.8	54
11	**42** → **43**	C_6H_6	75	1.9×10^6	14.8	13.6	58
12	**73** → **74**	C_6H_6	75	5.4×10^3	11.8	12.8	61
13	**75** → **76**	C_6H_6	75	4.0×10^2	8.1	8.7	61
14	**77** → **78**	C_6H_6	80	1.2×10^4	12.7	13.9	58
15	**85** → **86**	C_6H_6	80	7.0×10^4			68
16	**438** → **442**	C_6H_6	75	6.2×10^4	11.7	11.0	164
17	**438** → **442**	C_6H_{12}	75	3.7×10^4			164
18	**438** → **442**	DME	75	5.8×10^4			164
19	**438** → **442**	DMF	75	8.4×10^4			164
20	**438** → **442**	EtOH	75	1.3×10^5			164
21	**438** → **442**	MeOH	75	1.6×10^5			164
22	**439** → **443**	C_6H_6	75	1.7×10^5			164
23	**440** → **444**	C_6H_6	75	1.6×10^4			164
24	**441** → **445**	C_6H_6	75	2.5×10^6			164

work, the authors noted a number of ester migrations provoked by the treatment of steroidal, vicinal acetoxy bromides or chlorides with tributyltin hydride in benzene at reflux (Table 1, entries 9−12). These reactions were completely stereoselective, with the ester migration occurring in a suprafacial manner along one face of the steroid nucleus. This suggests that the reaction is intramolecular or, at worse, involves a very tight cage pair. In retrospect, the relatively high yields observed in these reactions, conducted without the use of syringe pump techniques, should have hinted at rate constants in excess of those measured initially for acyclic substrates (Table 2, entries 1−10). Indeed, subsequent work by Beckwith and Duggan showed that the rearrangement of radical **42** to **43** proceeds with a rate constant of 1.9×10^6 s^{-1} (Table 2, entry 11).[58] Another



important aspect of Julia's work was the demonstration that, in the absence of significant driving force, the radical ester migration does not occur readily.

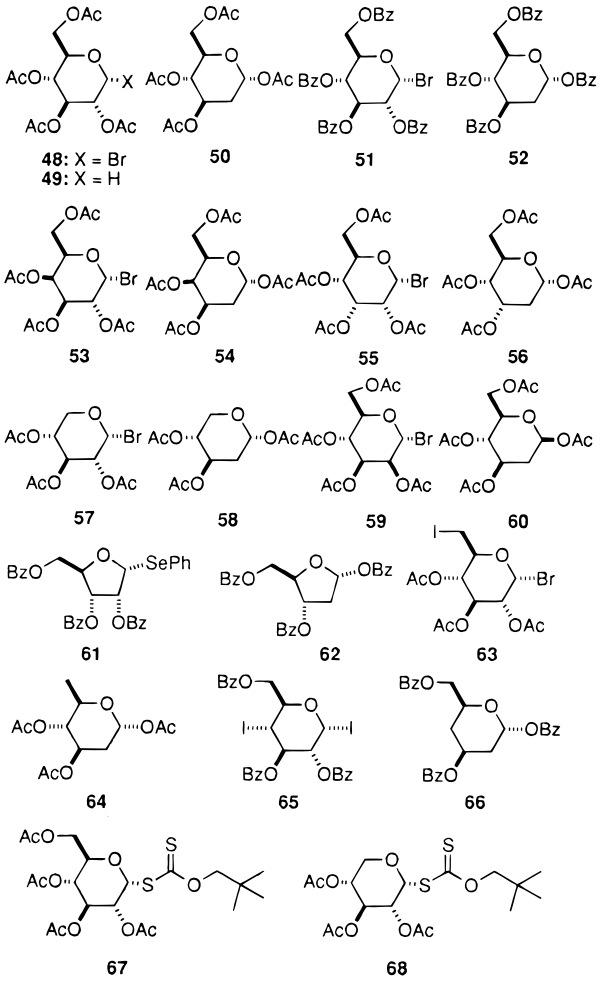
Scheme 5



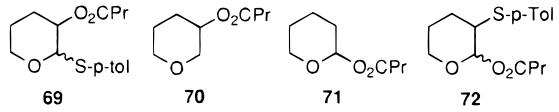
Julia described two cases where the starting radical and anticipated product radical were essentially equivalent in energy. In those cases, no rearrangement was observed (Scheme 5).

The true preparative value of the acyloxy migration was realized by the Giese group, who treated acetobromoglucose **48** with tributyltin hydride and AIBN under dilute conditions and obtained a 92% yield of the 2-deoxyglucose derivative **50** (Table 1, entry 13).[59,60] The surprising feature of this reaction is the fact that it proceeds toward the less electronically stabilized radical. Giese has suggested that the anomeric stabilization attained by placing the ester at the 1-position likely outweighs the loss of stabilization of the actual radical center.[61,62] As is evident from entries 14−18 (Table 1), the migration is applicable to a full spectrum of acetobromopyranoses and also (Table 1, entry 19) occurs in the furanose system. As in the steroidal examples, these carbohydrate based migrations are completely stereoselective, and as such 2-deoxy-α- and β-acetates maybe be obtained from gluco and manno precursors, respectively (Table 1, entries 13 and 18). As illustrated by entries 20 and 21 (Table 1) dideoxy sugars may be obtained in one pot by incorporation of a second halogen substituent into the substrate. Given the ready availability of acetobromopyranoses, this radical rearrangement currently constitutes the most practical access to the 2-deoxypyranoses and, accordingly, an *Organic Syntheses* protocol has been pre-

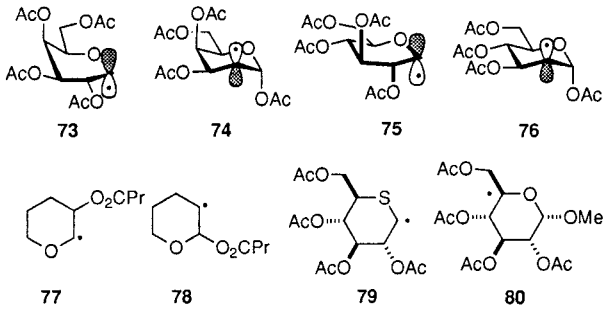
sented.[63] It has also been demonstrated that the slow addition of tributyltin hydride, necessary to avoid the formation of direct reduction products, may be circumvented by the use of the alternative reductant tris(trimethylsilyl)silane (Table 1, entries 22 and 23).[64] This trades the definite advantage of avoiding the formation of organotin byproducts against the use of the considerably more expensive silane reagent. A further alternative to the use of tin hydride has been advanced by Zard.[65] In this chemistry *S*-glycosyl xanthates (e.g., **67** and **68**) are used as radical precursors in refluxing cyclohexane with 5 mol % of dilauroyl peroxide as initiator (Table 1, entries 24 and 25). The cyclohexane serves as hydrogen atom donor to the rearranged radical and the chain is propagated by addition of the cyclohexyl radical to the thiocarbonyl sulfur of the xanthate precursor. Returning to the tin hydride-mediated rearrangements, the superior hydrogen donating capacity of benzeneselenol can be employed to completely suppress the acyloxy migration, if the reaction is conducted in the presence of a catalytic quantity of diphenyl diselenide (Table 1, entry 26).[66]



Beckwith and Duggan studied the closely analogous tetrahydropyranyl system **69** and found, in accordance with the work of Giese and collaborators, that migration occurs toward the anomeric radical (Table 1, entry 27).[62] At the same time the isomeric substrate **72** was subjected to the standard conditions and the formation of approximately 5% of the migration product **70** was observed (Table 1, entry 28), confirming, for the first time, that the acyloxy migration can be reversible, provided that a sufficiently low concentration of reductant is employed.

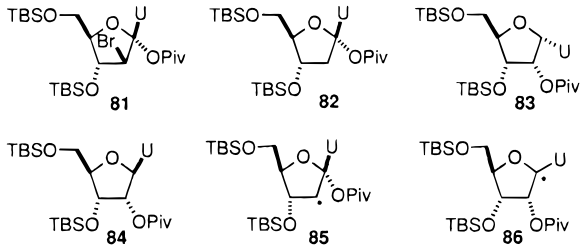


Giese and Sustmann, using the kinetic ESR technique, and Beckwith and Duggan, employing the tin hydride clock reaction, have determined Arrhenius parameters for migrations to anomeric radicals (Table 2, entries 12−14).[61,62] Considerable variation in the *A* value and the activation energy was observed for these reactions which translates into a spread of rate constants, at a given temperature, over almost two orders of magnitude. To some extent this variation reflects the different ground-state conformations of the initial radicals and the distortion they must undergo to satisfy the stereoelectronic requirements of the migration. Thus,[61] above −30 °C the tetraacetyl-1-glucopyranosyl radical (**75**) has been found by ESR to exist in a boat conformation in which the C2-acetoxy group is periplanar with the anomeric radical and so preorganized for the migration reaction. On the other hand, the tetraacetyl galactopyranosyl radical (**73**) is in a half-chair conformation between −15 and +70 °C, which implies that it has to undergo considerable reorganization to a higher energy conformer before rearrangement can occur. Also in the context of their ESR investigation, Giese and Sustmann generated and observed radicals **79** and **80** but found no evidence for acyloxy migration.[61] These two failed shifts draw attention to the considerable susceptibility of the rearrangement to fairly subtle changes in radical stability and/or conformation.

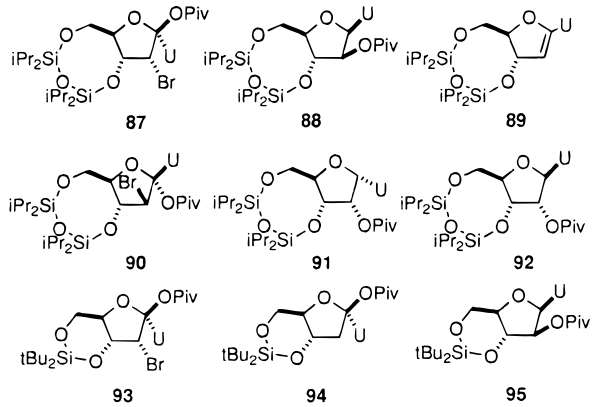


The groups of both Tanaka[67] and, shortly thereafter, Chatgilialoglu[68] have investigated the migration of the pivaloxy group in the uracil derivative **81**. With tributyltin hydride as the overall reductant, Tanaka reports a ratio of 10:1.3 (~7.5:1) in favor of the α-nucleoside, indicative of preferential quenching of the anomeric radical from the less hindered face (Table 1, entry 29). Chatgilialoglu reports a comparable ratio of 6:1 for **83**:**84** but also notes the formation of the simple reduction product **82** (Table 1, entry 30). Clearly, for a given reductant, the ratio of reduction to migration for the initial radical is a function of concentration, whereas the anomeric ratio should be constant. When tributyltin hydride was replaced by tris(trimethylsilyl)silane (Table 1, entry 31) no direct reduction was observed and the anomeric ratio was improved to 40:1, consistent with the

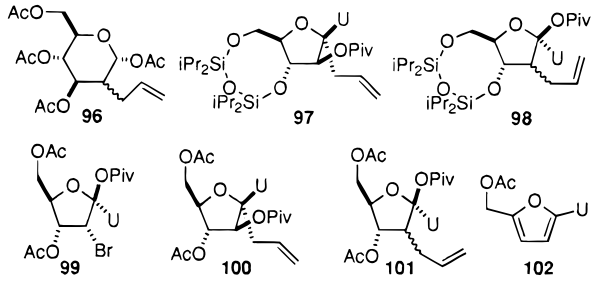
poorer hydrogen-donating capability of TTMSS and its greater steric bulk. The rate constant for the migration of the pivaloxy group in the radical (**85**) derived from **81** was estimated to be 7.0×10^4 s^{-1} by the Chatgilialoglu group (Table 2, entry 15).[68] The contrast between the rearrangement of **81** to **83** and **84** and that of the various carbohydrate derivatives (Table 1, entries 13−28) is of some interest. In the pyranose and furanose series an acyloxy group migrates to an anomeric radical, whereas in the nucleosides the acyloxy group migrates away from the anomeric site to a C2′ radical. As suggested by Chatgilialoglu,[68] the additional stabilization afforded the anomeric radical in the nucleoside series by the additional heteroatomic substituent most likely lies at the root of this change in selectivity.



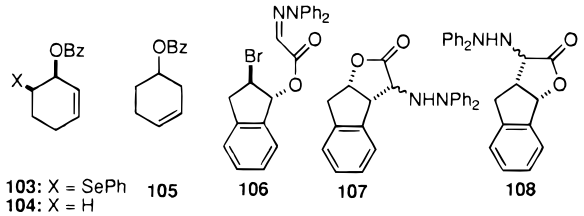
The Tanaka group extended their study to the two isomeric uracil derivatives **87** and **90** and found both to undergo highly stereoselective suprafacial migration of the pivaloxy group (Table 1, entries 32 and 33). In view of the ribo- and arabino configurations of the rearranged radicals, it is not surprising that somewhat different selectivities were observed for the final stannane quenching reaction. Most interestingly from the mechanistic standpoint (section III.A), was the isolation of the glycal derivative **89** from both of these reactions. Application of the standard conditions to the 3′,5′-di-*tert*-butylsilylene derivative **93**, in contrast to the above examples, resulted in a much lower yield of rearranged product **95** (Table 1, entry 34). This observation was rationalized, reasonably, in terms of the greater rigidity of the nucleoside ring and the preference of the initial radical for a conformation not conducive to migration.



The first example of an acyloxy migration coupled to a carbon−carbon bond forming reaction was described by Giese.[69,70] Here, acetobromoglucose (**48**) was allowed to react with allyltributylstannane in benzene at reflux leading to an undefined gluco/manno mixture of 2-*C*-allyl derivatives (**96**): no yield was given (Table 1, entry 35). Further examples of the acyloxy migration coupled to C−C bond forming reactions were subsequently presented by Tanaka and co-workers.[67] Thus, treatment of **87** and **99** with allyltributylstannane, either in benzene at reflux or under photochemical initiation at room temperature, resulted in acyloxy migration followed by allylation (Table 1, entries 36−39). Interestingly, in both series higher yields were obtained when the reactions were conducted photochemically at room temperature.



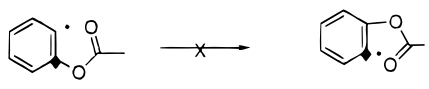
Another example of the acyloxy rearrangement is provided by the reaction of **103** with tributyltin hydride in refluxing benzene, leading to the formation, after migration, of an allylic radical and eventually the two products **104** and **105** (Table 1, entry 40).[71] A final, successful example of the acyloxy shift is taken from recent work of Clive.[72] In this example (Table 1, entry 41) the acyloxy shift of a glyoxalate derivate competes effectively with a 5-exo-trig ring closure onto a hydrazone.



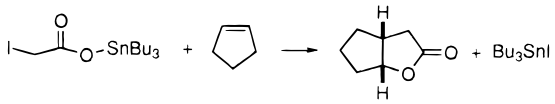
By means of an isotopic labeling experiment Evanochko and Shevlin arrived at the conclusion that *o*-(acyloxy)aryl radicals do not undergo acyloxy shifts (Scheme 6).[73] A related observation was subsequently reported by Shahidi and Tidwell.[74] The consensus was that the *o*-(acyloxy)aryl radical is unable to achieve suitable overlap to allow the ester shift to occur.

Thirty years after the original discovery, there are still no intermolecular counterparts of the acyloxy migration and all known examples involve migration of the acyloxy group to a vicinal radical. As noted above, initial attempts by Surzur and Teissier to locate examples of a 1,3 or higher analogue were unsuccessful. Nor were such processes ever seen in the various carbohydrate series extensively studied by Giese where, if they exist, they might reasonably have been observed as competing rearrangements. Kraus and Langrebe, in 1984, described a useful method for the formation of γ-lactones by the addition of α-iodostannylcarboxylates to alkenes and postulated a mechanism involving intramolecular homolytic attack at the carbonyl or carboxyl oxygen

Scheme 6



Scheme 7



(Scheme 7).[75,76] However, subsequent work, in collaboration with Maillard, pointed toward a more traditional mechanism involving an iodine transfer chain reaction (Kharasch reaction) for addition to the alkene, followed by lactonization through stannyl carboxylate displacement of iodide.[77] Thus, a radical acyloxy shift to all but vicinal carbons remains an elusive process.

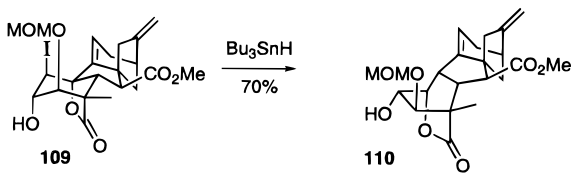
2. Lactones

The radical mediated rearrangement of lactones constitutes a very interesting subclasss of the β-(acyloxy)alkyl shift. Surprisingly, given the widespread use of halolactonization/reductive dehalogenation protocols[78] and their organoselenium counterparts[79] in organic synthesis, the first example of such a reaction was only described in 1995 by the Mander group (Scheme 8).[80] In this example, treatment of the iodo-γ-lactone **109** with tributyltin hydride and AIBN in benzene at reflux provoked a reductive expansion to the δ-lactone **110**, which was isolated in 72% yield. The fact that neither high dilution nor slow syringe pump addition of the stannane was used suggests that this particular rearrangement is relatively rapid.

Such radical lactone rearrangements may take the form of ring expansions or contractions. It is readily appreciated that the position of any equilibrium (Scheme 9) entered into by a cyclic β-(acyloxy)alkyl radical will be a function, *inter alia*, of the propensity of the various substituents to stabilize radicals and/or C−O bonds and of the strain differential between the two ring systems. Evidently, the rearrangement of **109** to **110** is favored from both of these perspectives.

Steric strain (anglular, torsional, and transannular) is very much a feature of the chemistry of medium sized lactones and rings in general, as is the switch from the higher (*E*) to lower energy (*Z*) ester conformation which occurs on going from seven- to eight- to nine-membered lactones.[81−85] It seems reasonable, therefore, that, other things being equal, the relative rates of rearrangement of a series of homologous lactones will vary significantly with ring size. This, and the further possibility that the study of lactone rearrangements might shed more light on the mechanism of the β-(acyloxy)alkyl radical rearrangement, induced the Beckwith and Crich groups to prepare the series of lactones **111**−**119** and to study their reactions with tributyltin hydride under a set of standard conditions.[86] As is seen from Table 3, the rate of rearrangement is very much a function of ring size. The five-membered lactone **111** does not undergo contraction at all (entry 1), as might be expected from the considerable increase in strain this would engender, but the seven-membered lactone **113** does so at such a rate that the simple reduction product **122** is not observed (entry 3). The various other ring sizes provide a relatively narrow range of product ratios with no obvious pattern. The considerable difference in relative rates of contraction of **112** and **113** (Table 3, entries 2 and 3), both of which neccessarily have the *E*-ester conformation and comparable strain, hints that other factors beside steric strain, most likely stereoelectronic effects, need to be taken into account in these lactone ring contraction and expansions.

Scheme 8



Scheme 9

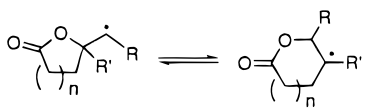
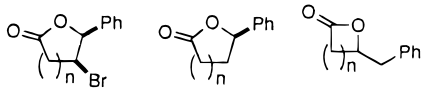


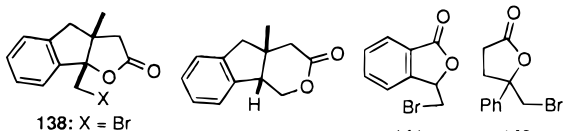
Table 3. Lactone Contractions

entry	substrate	ring size	product ratio
1	**111**	5 → 4	**120/129** = 100/0
2	**112**	6 → 5	**121/130** = 1/2.4
3	**113**	7 → 6	**122/131** = 0/100
4	**114**	8 → 7	**123/132** = 1/1.2
5	**115**	9 → 8	**124/133** = 1.3/1
6	**116**	10 → 9	**125/134** = 2.0/1
7	**117**	11 → 10	**126/135** = 1/1
8	**118**	14 → 13	**127/136** = 1.2/1
9	**119**	16 → 15	**128/137** = 1.2/1



n = 1	**111**	**120**	**129**
n = 2	**112**	**121**	**130**
n = 3	**113**	**122**	**131**
n = 4	**114**	**123**	**132**
n = 5	**115**	**124**	**133**
n = 6	**116**	**125**	**134**
n = 7	**117**	**126**	**135**
n = 10	**118**	**127**	**136**
n = 12	**119**	**128**	**137**

Further examples of lactone expansion were also sought by the Beckwith and Crich groups resulting in the observation that **138** provided a ratio of 5.1:1 of reduced to rearranged products (**139**:**140**) on treatment with tributyltin hydride and AIBN in benzene at reflux.[86] However, when the same reaction was conducted in *tert*-butyl alcohol the ratio of **139**:**140** improved to 1.1:1, reminiscent of the early solvent effects noted for the β-(acyloxy)alkyl rearrangement (section II.A.1, Table 2) and strongly suggestive of polar character at the transition state. At the same time, it was noted that neither **141** nor **142** underwent ring expansion on treatment with tributyltin hydride. This again points to the importance of stereoelectronic effects in these rearrangements.



3. Thiocarbonyl Esters

The simple replacement of the carbonyl oxygen in carboxylate esters by thiocarbonyl sulfur, as in thio-

Scheme 10

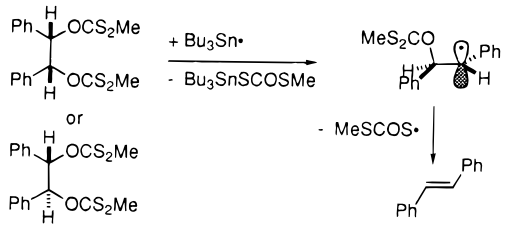
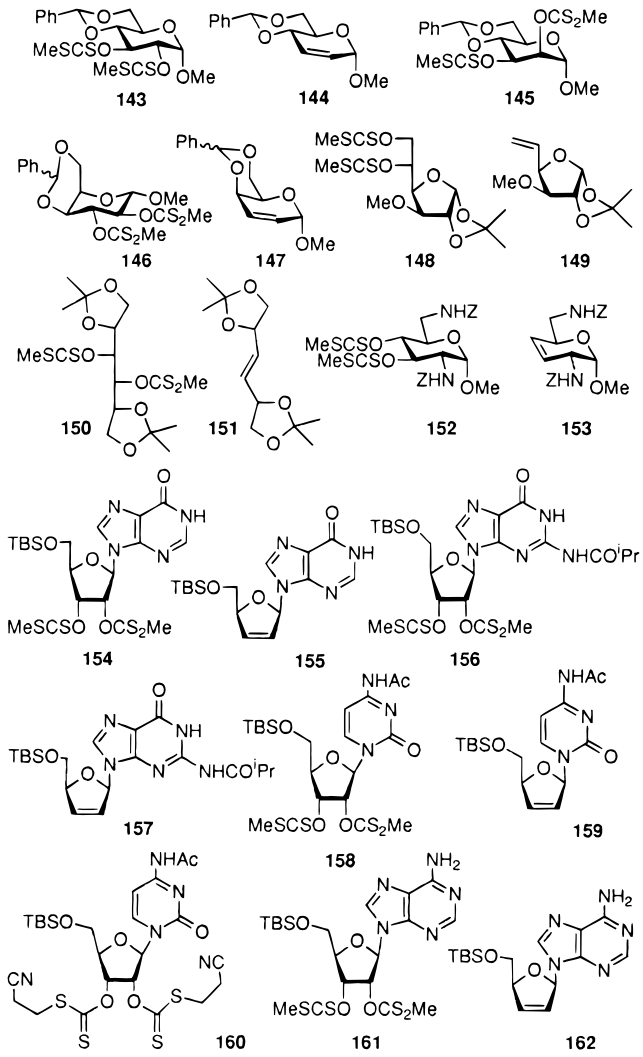


Table 4. Eliminations of Thiocarbonyl Esters

entry	substrate	reagent	product	% yield	ref
1	**143**	Bu_3SnH	**144**	60	87
2	**145**	Bu_3SnH	**144**	79	87
3	**146**	Bu_3SnH	**147**	49	87
4	**148**	Bu_3SnH	**149**	62	87
5	**150**	Bu_3SnH	**151**	65	87
6	**152**	Bu_3SnH	**153**	80	88
7	**154**	Bu_3SnH	**155**	93	89
8	**156**	Bu_3SnH	**157**	50	89
9	**158**	Bu_3SnH	**159**	59	89
10	**160**	Bu_3SnH	**159**	65	89
11	**161**	Et_3SiH, Bz_2O_2	**162**	100	45
12	**150**	Et_3SiH, Bz_2O_2	**151**	82	45

carbonyl esters and xanthates, leads to a considerably expanded repertoire of radical rearrangements. This increase in diversity is very largely a function of the much weaker C═S bond and the greater stability afforded to any radicals (OC•—SX) arising from addition to the thiocarbonyl sulfur. As noted in the introduction, the most important preparative reactions in this class involve intermolecular addition of a thiophilic radical to the thiocarbonyl sulfur such as occurs in the Barton deoxygenation reaction. The general area of free radical chemistry of thiocarbonyl esters has been reviewed by one of us.[35] Here, we only briefly survey fragmentations and rearrangements so as to mark the contrast with simple carbonyl ester substituted radicals and the β-(acyloxy)alkyl rearrangement.

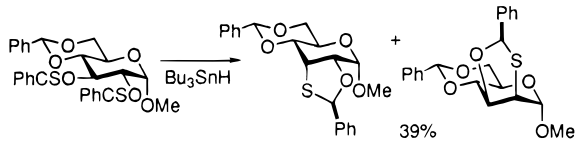
β-(Thiocarbonyloxy)alkyl radicals have been found to undergo rapid elimination to form alkenes. Coupled with the Barton deoxygenation sequence, this reaction has been developed into a method for the formation of alkenes from vicinal diols. Early work showed that, when treated with tributyltin hydride, the dixanthates of both meso- and (±)-dihydrobenzoin gave *E*-stilbene (Scheme 10), leading to the conclusion that the reaction proceeds via a common intermediate radical, which eliminates MeSC(═O)S• to yield the alkene.[87] The contrast between this elimination reaction and the myriad of examples of β-(acyloxy)alkyl radicals which do not undergo elimination (section II.A.1) is remarkable and results from the enhanced stability of the thiocarboxyl type radical over and above that of carboxyl radicals. Further examples from the carbohydrate,[87] aminoglycoside,[88] and nucleoside fields[89] are given in Table 4. Entry 10 is noteworthy for the unusual use of the *S*-cyanoethyl xanthate and entries 11 and 12 for the replacement of the more common tributylstannane by the triethylsilane/benzoyl peroxide couple. This later combination is thought to act, at least in part, through silyl radical-induced decomposition of the benzoyl peroxide and subsequent addition of the phenyl radical to the thiocarbonyl sulfur of a xanthate ester. The isolation of *S*-methyl-*S*′-phenyl dithiocarbonate lends weight to this hypothesis.[45] At the present time no data exist pertaining to the rate of elimination of the xanthate radical common to each of these olefin-forming reactions.



Despite the success of the above radical elimination reactions, not all β-(thionoalkoxy)alkyl radicals undergo rapid elimination. In their original publication on the deoxygenation reaction, Barton and McCombie noted the formation of two isomeric 1,3-oxathiolanes on treatment of a bis(thiobenzoyl) derivative of a carbohydrate based vicinal diol (Scheme 11). This chemistry was ascribed to the cyclization of an alkyl radical onto thiocarbonyl sulfur giving a 1,3-oxathiolan-2-yl radical (Scheme 12).[41]

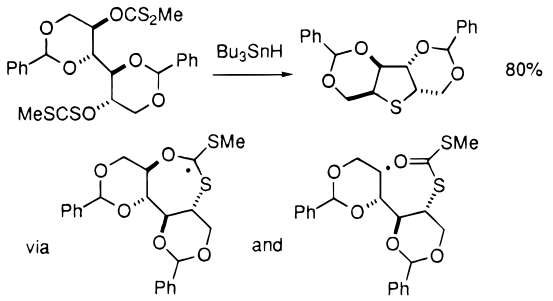
In contrast to γ and higher (acyloxy)alkyl radicals, which do not rearrange or cyclize, γ- and δ-(thiocarbonyloxy)alkyl radicals can also undergo ring closure

Scheme 11

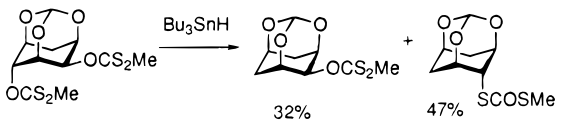


Scheme 12

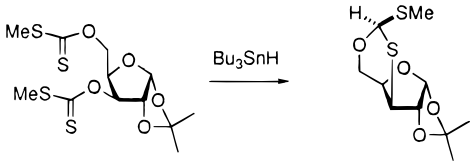
Scheme 13



Scheme 14



Scheme 15

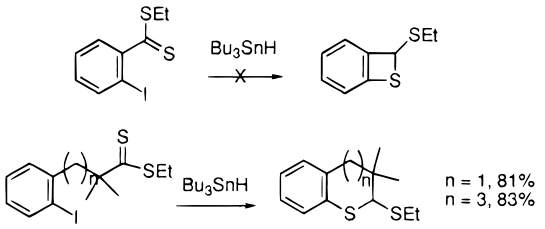


reactions. Such a process was advanced by Rao to rationalize the formation of a tetrahydrothiophene on treatment of a mannitol derived 1,4-dixanthate (Scheme 13).[90] Thus, deoxygenation of one of the two xanthates leads to a δ-(thiocarbonyloxy)alkyl radical which closes onto the second xanthate giving a seven-membered heterocyclic radical. This in turn fragments to a second, rearranged alkyl radical. This migration is obviously driven by the thiocarbonyl to carbonyl transposition at the root of the standard Barton deoxygenation reaction. Finally, homolytic substitution at sulfur results in the formation of the tetrahydothiophene derivative.

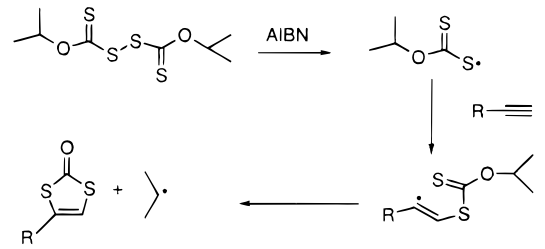
A related shift of a γ-(thiocarbonyloxy)alkyl radical was subsequently reported by Beckwith and co-workers in the context of their study of the β-oxygen effect.[39] In this study a trioxaadamantane derived dixanthate was treated with tributyltin hydride resulting in the isolation of two monodeoxy compounds, one with the thiocarbonyl to carbonyl inversion (Scheme 14). The first is readily explained by the standard deoxygenation of the xanthate antiperiplanar to the skeletal oxygens. The second requires deoxygenation of the synclinal xanthate followed by the 3,3-xanthate shift. Similar 1,3-shifts have been postulated for other related γ-(thiocarbonyloxy)alkyl radicals.[91,92] An interrupted version of such a 3,3-shift has also been described (Scheme 15), which clearly indicates that this type of shift is stepwise and that the intermediate radical can be trapped if a sufficient concentration of tin hydride is employed.[93]

In pursuit of his notion of the endocyclic restriction test as a probe for transition state geometry, Beak has studied the cyclization of aryl radicals, generated from aryl iodides with tributyltin hydride, onto dithioesters (Scheme 16).[94] It was found that four-membered ring formation did not occur, but that 6-, 8-, and 15-membered congenors were prepared efficiently. The suggestion was advanced that the

Scheme 16



Scheme 17



cyclization involves the attack of the SOMO of the aryl radical on the thiocarbonyl HOMO orbital and that sufficient overlap was not possible in the case of the lowest homologue.

This study is complimented by the work of Gareau in which diisopropyl xanthogen disulfide was treated with a radical initiator in the presence of an alkyne, leading to the formation of a 1,3-dithiol-2-one.[95] According to the mechanism outlined in Scheme 17, this interesting reaction involves the cyclization of vinyl radical onto thiocarbonyl sulfur with expulsion of an isopropyl radical. This cyclization is to be contrasted with the reluctance of *o*-(acyloxy)aryl radicals to undergo cyclization or migration (Scheme 6).

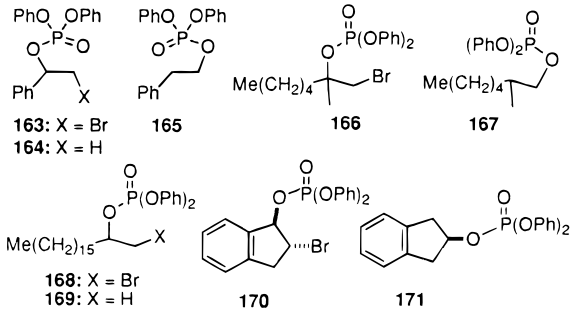
B. β-(Phosphatoxy)alkyl Rearrangement

The β-(phosphatoxy)alkyl radical migration was first described, independently, by Crich and Yao[96] and the Giese group[97] in 1993. In the first example it was demonstrated, by use of the tin hydride method, that the formation of secondary benzylic radicals from primary radicals was a sufficient driving force for this novel migration (Table 5, entry 1).

Table 5. β-(Phosphatoxy)alkyl Rearrangement

entry	substrate	temp (°C)	products (% yield)	ref
1	**163**	80	**164** (20), **165** (80)	71
2	**166**	80	**167** (75)	71
3	**168**	80	**169** (100)	71
4	**170**	80	**171** (100)	71
5	**172**	80	**173** (100), **174** (0)	71
6	**175**	80	**176** (18), **177** (82)	71
7	**178**	80	**179** (69)	71
8	**180**	80	**181** (79)	71
9	**182**	80	**183** (27), **182** (73)	71
10	**185**	20	**186** (100)	97
11	**187**	20	**188** (100)	99
12	**189**	20	**190** (100)	99
13	**191**	20	**192** (50), **193** (50)	99
14	**194**	20	**195** (100)	97
15	**218**	80	**219** (95), **220** (5)	71
16	**221**	80	**222** (60), **223** (40)	71
17	**224**	80	**225** (71), **226** (20.3), **227** (8.7)	71
18	**228**	80	**229** (77), **226** (6.0), **227** (17.0)	71
19	**230**	80	**231** (58), **232** (42)	71
20	**233**	80	**231** (25), **232** (75)	71
21	**234**	80	**235:236** = 2:1	71

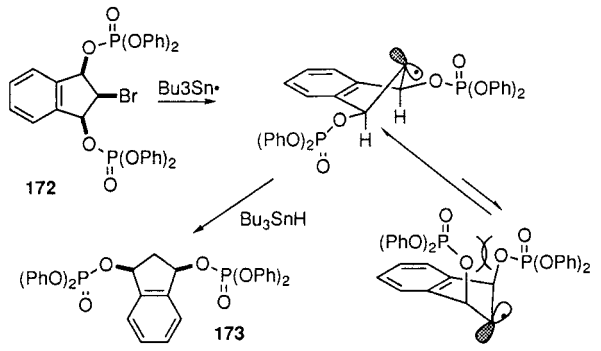
That **165** was indeed the result of a shift of the phosphatoxy group and not the result of neophyl rearrangement was demonstrated with the help of a deuterium labeling experiment. The formation of a tertiary radical from a primary one (Table 5, entry 2) is also a sufficient driving force, but apparently that of a secondary from a primary radical is not (Table 5, entry 3). This pattern of reactivity parallels that seen in the acyloxy series (cf. Table 1, entries 1 and 5). When the indene-based bromophosphate **170** was treated with tributyltin hydride under the same conditions as its acyclic counterpart **163**, only **171** was formed (Table 5, entry 4) suggesting this particular rearrangement to be somewhat more rapid than that of **163**.

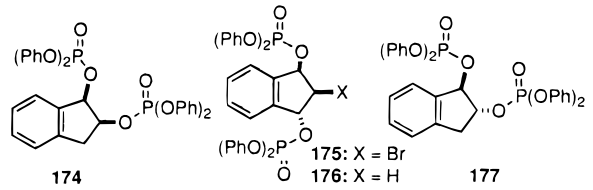


In stark contrast, subsequent work revealed that the reduction product **173** was formed to the exclusion of the rearrangement product **174** when the related diphosphate **172** was treated with tributyltin hydride in benzene at reflux (Table 5, entry 5).[71] This dichotomy may be rationalized in terms of the stereoelectronic requirements of the migration reaction. Thus, it is readily appreciated that, as for the acyloxy shift, the scissile C−O must be periplanar with the initial radical and also, in order to benefit from benzylic stabilization at the transition state, be perpendicular with the plane of the aromatic ring. It is clear (Scheme 18) that, for the radical derived from **172**, such a conformation would suffer from significant dipolar and steric interactions which effectively prevent the rearrangement. In agreement with this rationale, the diastereoisomer **175** rearranges cleanly on treatment with tributyltin hydride (Table 5, entry 6). It is also noteworthy in this last example that, as for the acyloxy shift, migration occurs suprafacially along one face of the indanyl system.

The first examples of highly stereoselective ester migrations in a fully acyclic, conformationally mobile system involved the diastereomers **178** and **180**

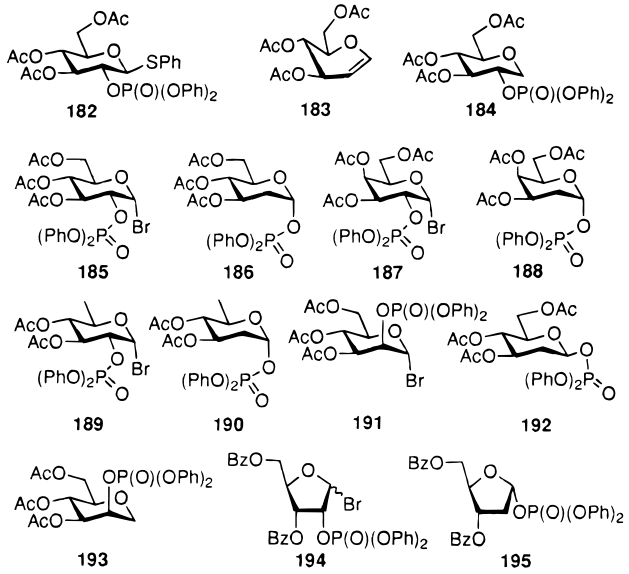
Scheme 18





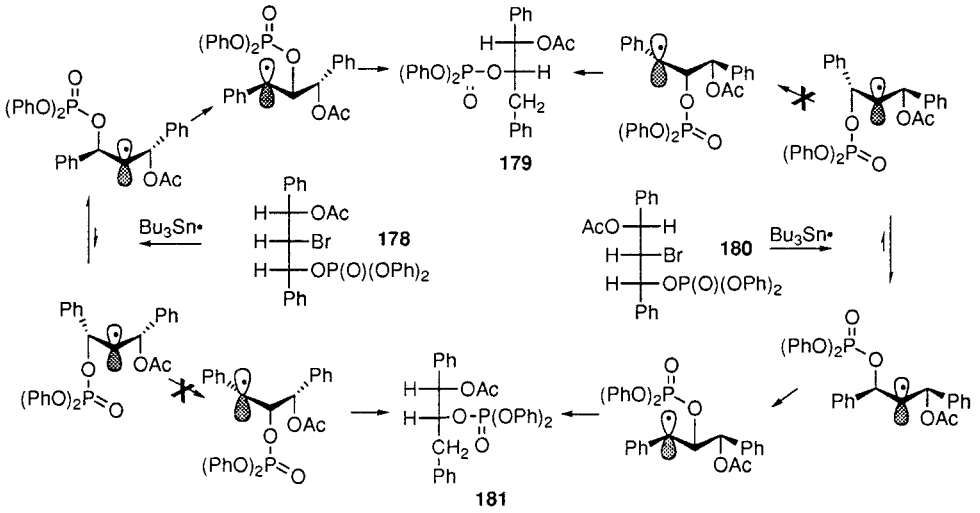
which underwent complete stereoselective rearrangement to give **179** and **181**, respectively, on treatment with tributyltin hydride in benzene at 80 °C (Table 5, entries 7 and 8). No stereochemical leakage could be detected by ^{1}H-NMR spectroscopy in either case. Scheme 19, in which each radical migrates suprafacially along one face of the diphenylpropane system from a conformation which minimizes steric and dipolar interactions, was advanced to rationalize these observations.[71]

In the carbohydrate domain, Crich and Yao examined the reaction of **182** with tributyltin hydride but could only isolate the glucal **183** and the recovered substrate (Table 5, entry 9).[71,96] Control experiments demonstrated the stability of the absent reduction product **184**. The formation of **183** was therefore attributed to the instability of the anticipated product **186** under the conditions of the reaction: a reasonable assumption in view of the chemistry of 2-deoxyglycosyl phosphates.[98] In contemporaneous work the Giese group, using the more reactive glycosyl radical precursor **185** and conducting the reaction under photochemical conditions at room temperature, was able to demonstrate by NMR spectroscopy that **186** was indeed the product of the reaction and that it underwent decomposition to **183** on prolonged standing or on warming to 80 °C (Table 5, entry 10).[97] Further examples include galactose, 6-deoxyglucose, and mannose derivatives **187**, **189**, and **191**, respectively as well as the ribofuranose **194** (Table 5, entries 11−14).[97,99] In each case, yields were high and the migration follows the now familiar pattern of suprafacial migration along the carbohydrate framework. The driving force for these carbohydrate based migrations is again thought to be the formation of the anomeric C−O bond.

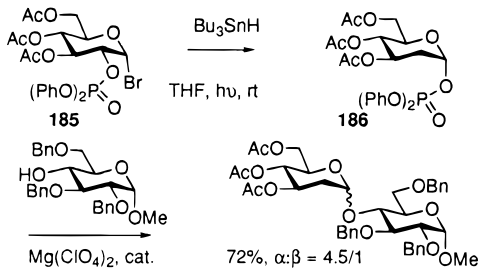


As with the acyloxy shift, the preparative potential of the phosphatoxy migration in carbohydrates was

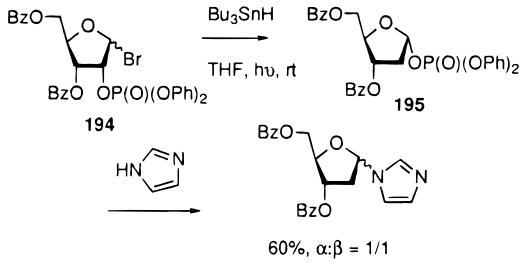
Scheme 19



Scheme 20

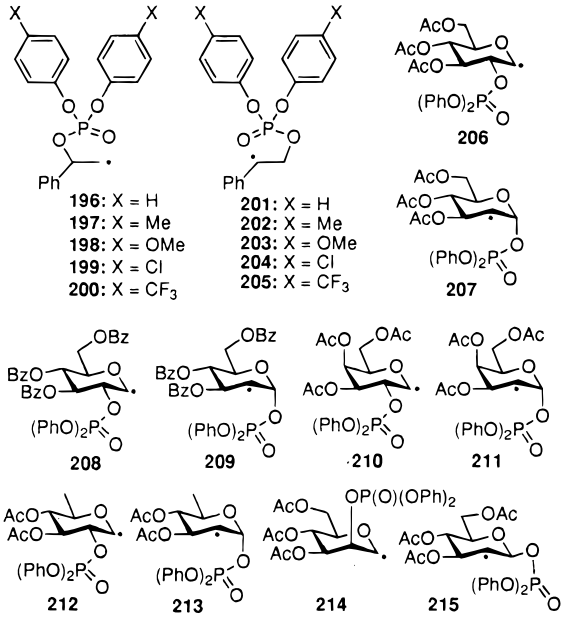


Scheme 21



recognized and exploited by the Giese laboratory. Thus, although the various 2-deoxyglycosyl phosphates were too unstable to be isolated, on activation with magnesium perchlorate, they could be coupled *in situ* in THF solution to various glycosyl acceptors as typified in Scheme 20.[97,99] Nucleosides could be formed from **195** and appropriate bases even in the absence of promoter (Scheme 21).[97]

In contrast to the acyloxy shift, relatively little kinetic data have been collected for examples of the phosphatoxy migration. Crich and Jiao, using a variant[100] on the Newcomb benzeneselenol clock reaction,[101,102] determined the Arrhenius parameters for the rearrangement of radical **196** in benzene to be $\log(k) = 10.2-7.0/2.3RT$ leading to a rate constant at 80 °C of 8.0×10^5 s^{-1} (Table 6, entry 1).[103] This rate constant is several orders of magnitude greater than those recorded for comparable acyloxy migrations in benzene (Table 2). In the same study, rate constants were determined for the migration of a series of para-substituted diphenylphosphatoxy groups (Table 6, entries 3−6): the results having mechanistic significance (section IV.C.4). Using a tin hydride clock reaction, Giese and Koch determined the rate constant for the rearrangements **206**, **208**, **210**, **212**, and **214** (Table 6, 7−11).[97,99] Again, the rate constants are orders of magnitude greater than those for directly comparable carbohydrate based acyloxy shifts (Table 2). However, there is not the distinct spread observed in the acyloxy series and the rate constants for rearrangement of the 2-glucosyl and galactosyl diphenylphosphates **206** and **210**, respectively, differ by less than a factor of 2 (Table 6, entries 7 and 9). Curiously, the 6-deoxy-2-glucosyl diphenylphosphate **212** underwent rearrangement more than 10 times more rapidly (Table 6, entry 10) than the corresponding 6-substituted series. As with the acyloxy shift, the radical having the mannose stereochemistry and leading to the 2-deoxy-β-glycosyl phosphate had a somewhat lower rate constant (Table 6, entry 11).

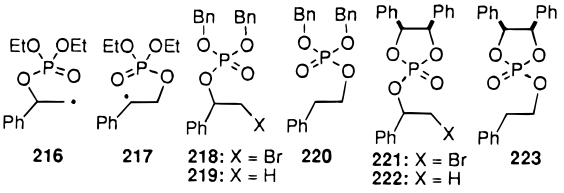


Crich and Jiao also determined the rate constant for the rearrangement of the (diethyl phoshatoxy)-alkyl radical **216** and found it to be almost two orders of magnitude lower than that of the corresponding diphenyl-substituted system **196** (Table 6, entries 1 and 12).[103] In this respect, it is not surprising that only low yields of the rearrangement product **220** are obtained on treatment of the dibenzyl phosphate **218**

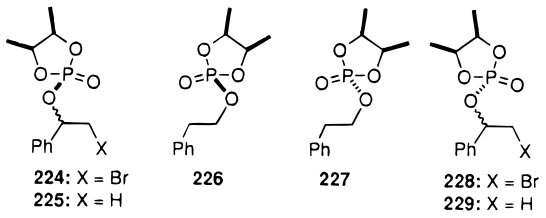
Table 6. Kinetics of the β-(Phosphatoxy)alkyl Rearrangement

entry	rearrangement	temp, °C	k, s^{-1}	ref
1	**196** → **201**	80	8.0×10^5	103
2	**196** → **201**	27	1.2×10^5	103
3	**197** → **202**	80	4.1×10^5	103
4	**198** → **203**	80	5.3×10^5	103
5	**199** → **204**	80	3.2×10^6	103
6	**200** → **205**	80	1.2×10^7	103
7	**206** → **207**	27	8.0×10^6	97
8	**208** → **209**	27	4.58×10^6	99
9	**210** → **211**	27	4.6×10^6	99
10	**212** → **213**	27	2.0×10^8	99
11	**214** → **215**	27	1.0×10^5	99
12	**216** → **217**	80	1.2×10^4	103

with tributyltin hydride in benzene at reflux (Table 5, entry 15). Interestingly though, the directly analogous cyclic phosphate **221** gave a rather higher yield of migration product **223** under the same conditions (Table 5, entry 16), perhaps suggesting that the migration is accelerated by the presence of the five-membered cyclic ester.



The tetrahedral nature of the phosphate ester group provides the opportunity to probe the ester migration with chiral substrates. Toward this end Crich and Yao prepared and chromatographically separated the diastereomeric cyclic phosphate esters **224** and **228**. Each was then subjected to reaction

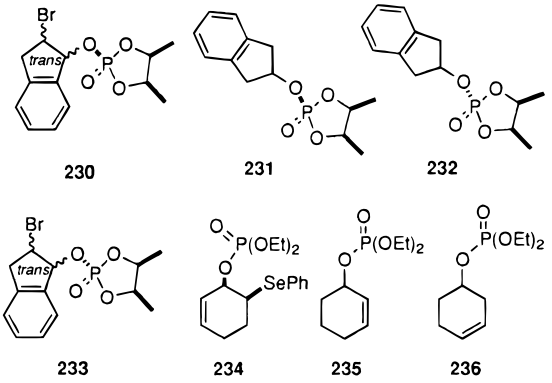


with tributyltin hydride and the reaction mixtures scrutinized for evidence of retention or inversion of configuration at phosphorus in the migrations products (Table 5, entries 17 and 18).[71,104] A parallel experiment was also conducted with a second, indane derived, pair of diastereomers (Table 5, entries 19 and 20). In each of the four cases studied, an excess of retention over inversion of configuration at phosphorus was noted in the migration products, hinting at the existence of multiple mechanistic pathways for radical ester shifts (section IV.C.3).

Finally with the aid of probe **234**, it was demonstrated that the formation of allylic radicals also provides a sufficient driving force for the β-(phosphatoxy)alkyl radical migration (Table 5, entry 21).[71,105]

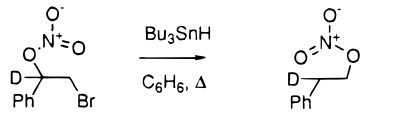
C. β-(Nitroxy)alkyl and β-(Sulfonatoxy)alkyl Rearrangements

The evident ease of the β-(phosphatoxy)alkyl, and certain cases of the β-(acyloxy)alkyl, migrations led

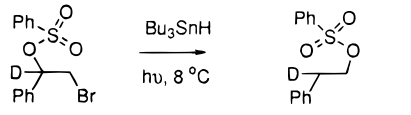


Crich and Filzen to the conclusion that this class of radical rearrangement would most likely encompass other types of ester. Nitrate and sulfonate esters were considered likely candidates. Accordingly, the esters **237**, **239**, and **241** were prepared and subjected to reaction with tributyltin hydride and AIBN in benzene at reflux. In each case (Schemes 22−24) the migrations were found to occur essentially quantitatively with no indication of products arising from simple reductive debromination observed in the reaction mixture. As indicated, deuterium labeling experiments were used to exclude the possibility that **238** and **240** arose from neophyl rearrangements.[106] Rate constants were not determined for the shifts outlined in Schemes 22−24, but the very high yields of migration product suggests that these will be comparable to the diphenylphosphate shift and probably $\geq 10^5$ s^{-1} at 80 °C.

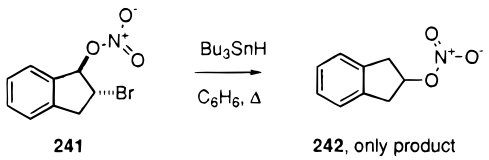
Scheme 22



Scheme 23



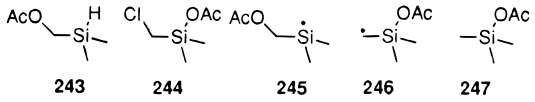
Scheme 24



D. (Acyloxyalkyl)silyl Radical Rearrangement

This uncommon rearrangement, formulated by Wilt, is formally directly analogous to the β-(acyloxy)-alkyl migration.[107] Photolysis of **243** in the presence of di-*tert*-butyl peroxide and tetrachloromethane in hexadecane as solvent provided **244** as the major product. The reaction was inhibited by galvinoxyl and, therefore, most likely involves the transposition of radical **245** to **246**. In the absence of CCl_4, the main product was **247**, suggestive of a chain sequence involving hydrogen atom abstraction from **243**, or from the hydrocarbon solvent, by the rearranged

radical. No detailed kinetic or other studies on the mechanism were conducted; however, it was pointed out that **244** was the major product even in the presence of 5 M CCl_4. As the triethylsilyl radical, somewhat related to **245**, abstracts chlorine atoms from CCl_4 with second order rate constants approaching the diffusion-controlled limit,[108] it can be concluded that the rearrangement is relatively rapid. The absence of examples in the literature is therefore likely simply to be a consequence of the infrequent occurrence of substituted analogues of radical **245**.



243 **244** **245** **246** **247**

III. Fragmentation Reactions

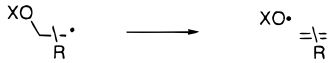
The fragmentation of β-ester substituted alkyl radicals, formally a competition reaction of the β-(ester)alkyl shift, can take place via either a pure radical mechanism (Scheme 25) or a radical−ionic mechanism (Scheme 26). Both are known, but the latter is far more common. This is to be contrasted with the fragmentation of β-(alkyl or arylthio)alkyl radicals and β-halogenoalkyl radicals wherein radical fragmentations to give thiyl radicals, or halogen atoms, is rapid in nonpolar solvents and effectively dictates the chemistry of these species.

A. β-(Acyloxy)alkyl Radicals and Their Thiocarbonyl Analogues

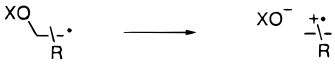
The fragmentation of β-(acyloxy)alkyl radicals by a pure radical mechanism (Scheme 25) is an extremely rare process: the only examples that we know of being described by Barton and co-workers as part of their exploratory work toward a method for reductive radical decarboxylation.[109] When the reaction of the dihydrophenanthrene-derived esters **248** with tributyltin hydride and AIBN was examined in benzene at reflux, it was found that fragmentation occurred to give the carboxyl radical **250** and, following decarboxylation and quenching, the alkanes **252**. The formation of fully aromatic phenanthrene from the dihydrophenanthrene **248** was advanced as the driving force for this fragmenation, and this was supported by the lack of fragmentation observed with the related radical **253** (Scheme 27).

As discussed above, the relatively minor perturbation of substituting carbonyl oxygen by thiocarbonyl sulfur provokes a drastic change in reactivity. The chemistry of β-(thiocarbonyloxy)alkyl radicals is dominated by what appears to be a radical fragmentation reaction (Scheme 10 and Table 4). This dramatic change in behavior must be principally due to the considerable difference in energy of the expelled radicals (RSC═OS· vs RCO_2·) and begs comparison

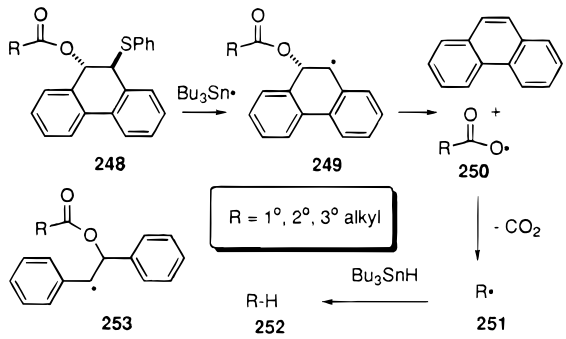
Scheme 25



Scheme 26

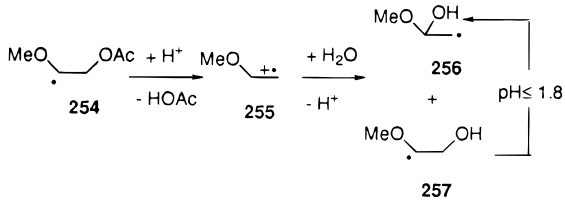


Scheme 27



248 **249** **250** **253** **252** **251**

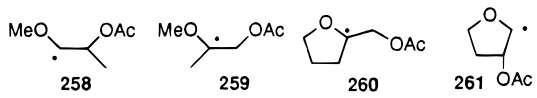
Scheme 28



254 **255** **256** **257**

with the widely disparate chemistries of β-alkoxyalkyl and β-(alkylthio or arylthio)alkyl radicals.

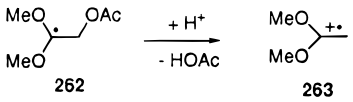
Norman and co-workers were the first to observe the fragmentation of β-(acyloxy)alkyl radicals by the radical-ionic pathway of Scheme 26. These workers generated the β-(acetoxy)alkyl radical **254** in aqueous solution by hydrogen atom abstraction with a hydroxyl radical, which, itself, was formed by the action of titanium(III) chloride on hydrogen peroxide.[110] When the reaction was conducted at pH 5.2 radical **254** was observable by ESR spectroscopy. At pH 1 the intensity of the spectrum attributed to **254** was reduced in favor of a new radical, designated **256**, leading to the suggestion that **254** was undergoing acid catalyzed decomposition to the radical cation **255**: trapping by water and proton loss would then provide **256** (Scheme 28). It is noteworthy in this sequence that the radical cation is quenched regioselectively adjacent to the methoxy group with formation of the less stable primary alkyl radical. Detailed work by Schulte-Frohlinde and co-workers, using their pulsed radiolysis/time resolved conductimetry techique, revealed the half-life for the decomposition of **254** in aqueous solution to be ~350 ms.[111] These workers also studied radicals **258**−**261** and noted their half-lives to be <1 ms in aqueous solution. It was also noted that radicals **254** and



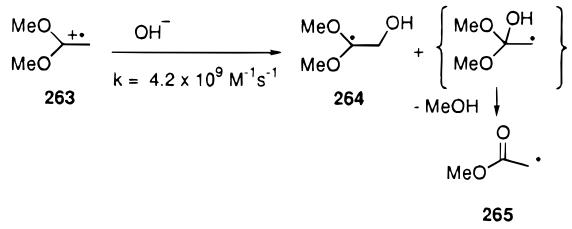
258 **259** **260** **261**

258−**261** could not be observed by ESR spectroscopy in aqueous solution, but that their half-lives were sufficiently extended in acetone solution for spectra to be recorded. Thus, consistent with the S_N1 mechanism, alkyl substitution of the initial radical and polar solvents promote heterolysis. By observing the decomposition of **254** over a range of pH values, the Schulte-Frohlinde group noted that the radical cation **255** is kinetically quenched by water to give a 3:7 mixture of **256** and its regioisomer **257** and that below pH 1.8 rearrangement to **256** occurred, indicating the latter to be the thermodynamic product

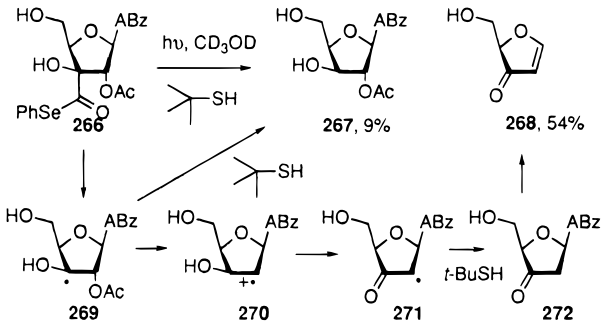
Scheme 29



Scheme 30



Scheme 31



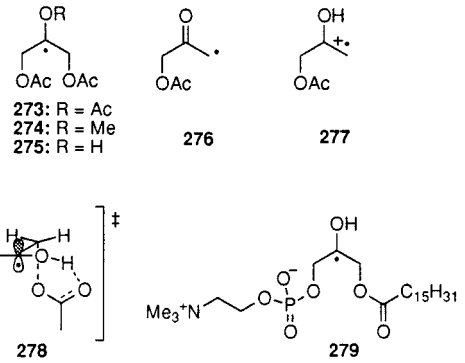
(Scheme 28). This presumably reflects the formation of the anomeric C−O bond as invoked to explain the migration of acyloxy and phosphatoxy groups to anomeric radicals in benzene solution (sections II.A.1 and II.B).

Subsequent work by Schulte-Frohlinde and coworkers, using their pulsed radiolysis/conductivity technique, led to the observation that the more highly oxygenated radical **262** underwent decomposition to the ESR-observable radical cation **263** with a rate constant of $\geq 10^6$ s^{-1} in "slightly acidic" aqueous solution at 20 °C (Scheme 29; Table 7, entry 1).[112]

The relative stability of radical cation **263** in aqueous solution, whether generated from **262** or from corresponding halodimethoxyethyl radicals, enabled the Schulte-Frohlinde group to study its trapping with various nucleophiles.[113] In the presence of hydroxide ion at pH 9−12, the two radicals **264** and **265** were observed by ESR spectroscopy. This is indicative of quenching at both terminii of **263**, followed in the one case by loss of methanol (Scheme 30). By pulse conductimetry, the overall rate constant at 20 °C for the reaction of **263** with OH^- was determined to be 4.2×10^9 M^{-1} s^{-1}.

A recent article from the Giese group[114,115] describes the photolysis of the acyl selenide **266** in CD_3OD in the presence of *tert*-butyl mercaptan resulting in the isolation of the xyloside **267** and the enone **268** in 9 and 54% yields, respectively. The reduction product (**267**) is readily understood in terms of quenching of the 3′-radical **269** by the thiol exclusively on the face opposite the nucleobase. The enone **268** is best understood by the radical ionic fragmentation of **269** to the radical cation **270**, followed by deprotonation to **271** and quenching to the unstable **272**. Elimination of benzoyladenine from **272** then provides the observed product **268** (Scheme 31). No rate constant was determined for this radical-ionic fragmentation, but the low yield of the reduction product **267** suggests that it is relatively large. When tributyltin hydride was employed as hydrogen donor, in place of the thiol, no direct reduction was observed.

In subsequent studies aimed at probing the possible incidence of radical ionic fragmentations in lipids, Giese and collaborators generated radicals **273**−**275** by photolysis of the corresponding *tert*-butyl ketones. When **273** and **274** were generated in benzene solution in the cavity of the ESR spectrometer, no other radicals derived from the glycerol moiety were discernible. Likewise, generation of **273** and **274** in toluene or methanol in the presence of *tert*-butyl mercaptan, as hydrogen source, led only to the isolation of glycerols in very high yield. These two radicals therefore suffer neither rearrangement nor fragmentation in both polar and nonpolar solvents. On the other hand, generation of radical **275** in benzene solution resulted in the observation of **276**, as well as of **275** itself, by ESR spectroscopy.[116] Preparative scale experiments in the presence of *tert*-butyl mercaptan showed the fragmentation of **275** to be more rapid in toluene than in methanol. Standard competition kinetics led to rate constants of 4.0×10^5, 2.1×10^6, and 2.0×10^7 s^{-1} in methanol, dioxane, and toluene, respectively, for this fragmentation. At first sight radical **276** might be thought to arise by the loss of acetate from **275** giving the radical cation **277**, followed by deprotonation. However, as the authors pointed out, neither the large difference in rate of fragmentation between **275** and **274** nor the inverse dependence of rate on solvent polarity can be explained by this stepwise mechanism. It was suggested that the rate acceleration observed with **275** might be a consequence of proton transfer through a cyclic transition state **278**. Replacement of toluene by dioxane or methanol provides the opportunity for hydrogen bonding to the solvent and so retards the fragmentation. The rate constant for the elimination of palmitate from radical **279** was determined to be 3.8×10^5 s^{-1} in methanol at 25 °C.[116]



Other potential examples of the fragmentation of β-(acyloxy)alkyl radicals are found in the work of Tanaka (Table 1, entries 32, 33, 38, and 39) wherein the glycal **89** and the furan **102** are isolated as byproducts from rearrangement reactions. It is not clear at this time whether these products arise from radical or radical-ionic fragmentations. Equally, it is possible that these products arise simply from decomposition of the simple reduction products, similar to the propensity of 2-deoxyglycosyl phos-

phates to undergo decomposition to glycals noted by Crich and Giese (Table 5, entry 9).

B. β-(Phosphatoxy)alkyl Radicals

Arguably, the single most important reaction of β-ester substituted alkyl radicals is the fragmentation suffered by nucleotide C4′ radicals. This fragmentation is implicated in the single- and double-stranded cleavage of DNA and the cleavage of RNA,[117] following hydrogen atom abstraction by hydroxyl and drug based radicals. It is therefore central to the understanding of DNA and RNA cleavage by ionizing radiation and antitumor antibiotics acting through radical mechanisms. The oxidative cleavage of oligonucleotides by radicals has been reviewed many times[118−126] and it is not our intention to reproduce this body of knowledge here. Rather, we attempt to bring together all clear-cut examples of radical ester fragmentations in order to define the prerequisites in terms of conditions and structure and identify the place of these reactions in an overall picture of the free radical chemistry of esters.

1. Anaerobic Conditions

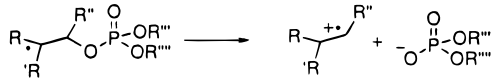
The effects of ionizing radiation on aqueous solutions of nucleic acids, [118−120,124,126] and model carbohydrate systems,[127] have been studied for many years and widely reviewed. Radiolysis of water produces solvated electrons and hydroxyl radicals and it is the later species which are responsible for the oxidative cleavage of oligonucleotides. The hydroxyl radicals predominantly undergo either addition to purine and pyrimidine bases leading ultimately to depurination reactions or intramolecular hydrogen abstraction from the sugar portion. The precise nature and mechanisms of purine base degradation[128] and intramolecuar hydrogen atom abstractions are still under investigation.[129−131] A much smaller proportion of hydroxyl radicals undertake direct hydrogen atom abstraction from the sugar phosphate backbone. This partitioning of hydroxyl radicals between the two pathways is base dependent. Direct abstraction appears to occur mainly, but not exclusively, from C4′ sites in double-stranded DNA. Early studies concentrated on the spectroscopic characterization of the various radicals formed and the identification of the eventual products.

Quantitative studies on the decomposition of phosphatoxy-substituted alkyl radicals were undertaken by the Schulte-Frohlinde group on a series of model compounds.[132] In this ground breaking work radicals were generated by hydrogen abstraction with hydroxyl radicals, generated by pulsed radiolysis of water, and their decomposition to ionic species was monitored by time-resolved conductivity measurements. These authors noted (Table 7, entries 2−8) that the rate of increase in conductivity was a function of the charge on the phosphate ester and of the degree of substitution of the alkyl radical itself. Thus, the distonic radical anions **282** and **283** were hydrolyzed some three orders of magnitude more slowly than the corresponding neutral species **280** and **281**, and the dianion **284** yet ∼10^3 times more slowly again. This pattern of rate constants clearly suggests an ionic reaction with phosphate anions as leaving groups. The contrast in the rates of acid

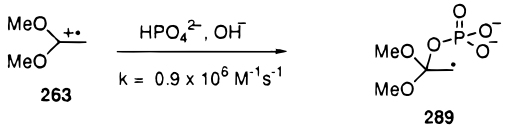
Table 7. First-Order Rate Constants for Fragmentation of β-(Phosphatoxy)alkyl Radicals

entry	radical	solvent	pH	k, s^{-1}	ref
1	**262**	H_2O	slightly acidic	$\geq 10^6$	112
2	**280**	H_2O		$\sim 10^6$	132
3	**281**	H_2O		$\sim 10^6$	132
4	**282**	H_2O		$\sim 10^3$	132
5	**283**	H_2O		$\sim 10^3$	132
6	**284**	H_2O		<1	132
7	**285**	H_2O		$\sim 10^6$	132
8	**286**	H_2O		$\sim 10^6$	132
9	**287**	H_2O	4.5−5	1.4×10^4	163
10	**288**	H_2O	4.5−5	3×10^4	163
11	**295**	MeOH		3.7×10^7	116
12	**296**	MeOH		1.4×10^9	116
13	**279**	MeOH		3.5×10^6	116

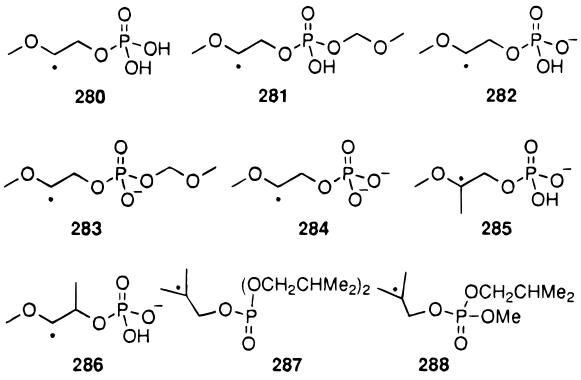
Scheme 32



Scheme 33

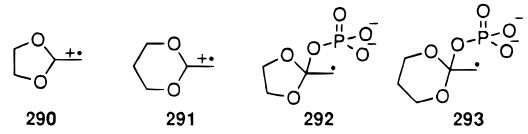


formation between radicals **282** and **283** and the more highly substituted **285** and **286** strongly suggests that the hydrolysis involves an S_N1-like process rather than a bimolecular substitution; the implication being that, in aqueous solution, the β-(phosphatoxy)alkyl radicals **280**−**286** undergo hydrolysis in a unimolecular manner by fragmentation to alkene radical cations and phosphate anions (Scheme 32).



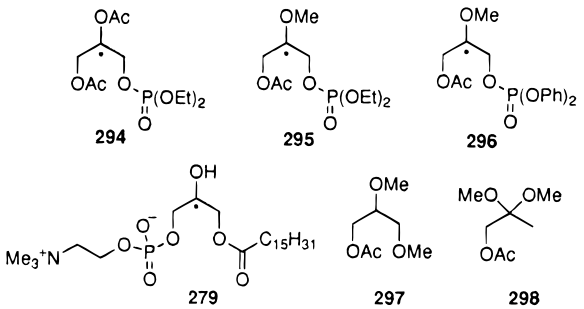
When radical cation **263** was generated in the presence of disodium hydrogen phosphate, an additional ESR signal was observed, corresponding to **289**, which apparently resulted from quenching of **263** by HPO_4^{2-} followed by proton loss (Scheme 33).[113] No evidence was found for the alternative regioisomer. By varying the concentration of HPO_4^{2-} and observing the relative intensities of the signals due to trapping by OH^- and HPO_4^{2-}, the rate constant for the latter addition was estimated to be 0.9×10^6 M^{-1} s^{-1}. However, it was noted that this rate constant is very much a factor of the fine structure of the radical, with k's for addition to the closely related radical cations **290** and **291** being 3×10^8 and 0.8×10^7 M^{-1} s^{-1}, respectively. Evidently, the fragmentation shown in Scheme 32 should be considered as a pH-dependent equilibrium. In the case

of the radicals **289**, **292**, and **293** the process becomes irreversible above pH 10 when they are doubly negatively charged.



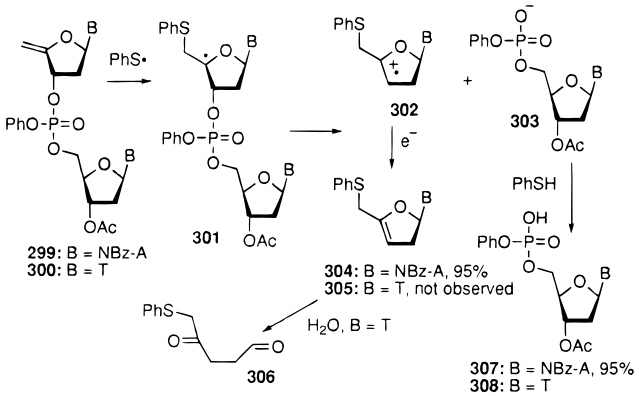
It is of some interest to note the high regioselectivity in the addition of HPO_4^{2-} to **263**, **290**, and **291** and to contrast it with the shifts of acyloxy groups away from the anomeric center in nucleosides in benzene solution as described by Tanaka and Chatgilialoglu (Table 1, entries 29−34, 36−39). Clearly, the regioisomeric equilibrium of such radicals is very finely balanced and significantly altered by relatively small structural differences and solvent effects.

By photolysis of the corresponding *tert*-butyl ketones the Giese group has recently been able to generate radicals **294**−**296** in which acetate and dialkyl phosphate groups compete for elimination.[116] As in the corresponding triacetyl series (**273**, section III.A) no fragmentation or rearrangement of either ester was observed with **294**. However, with **295** and **296** both ESR and preparative scale trapping experiments showed that the phosphate groups were readily eliminated in both toluene and methanol. With **295** very small amounts of competing acetate elimination were observed in toluene but not in methanol. Rate constants for dialkyl phosphate elimination from **295** and **296** in methanol at 25 °C are given in Table 7 (entries 11 and 12) and show the, by now, expected trend. The rate constant for elimination of a monoalkyl phosphate from **279** was also determined (Table 7, entry 13). As expected, elimination of this negatively charged group was less rapid than that of the dialkylphosphates, which enabled competing acetate elimination with a rate constant of 3.8×10^5 s^{-1}. Generation of **295** in methanol in the presence of *tert*-butyl mercaptan resulted in the isolation of the regioisomeric trapping products **297** and **298** in 63 and 14% yields, respectively.

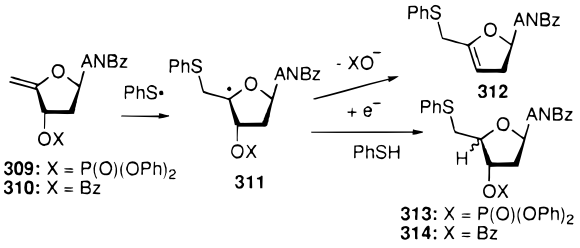


In 1992 Giese and co-workers described studies on the independent generation and reactions of nucleotide C4′ radicals.[133] Model dinucleotides **299** and **300** were irradiated in methanol/water (9/1) mixtures in the presence of a large excess of thiophenol leading to the isolation of strand cleavage products (Scheme 34). In both cases, these were rationalized in terms of addition of PhS• to the methylene group, with formation of a C4′ radical **301**, which then underwent elimination of the phosphate moiety **303** to give a radical cation **302**. In this series of experiments the

Scheme 34



Scheme 35

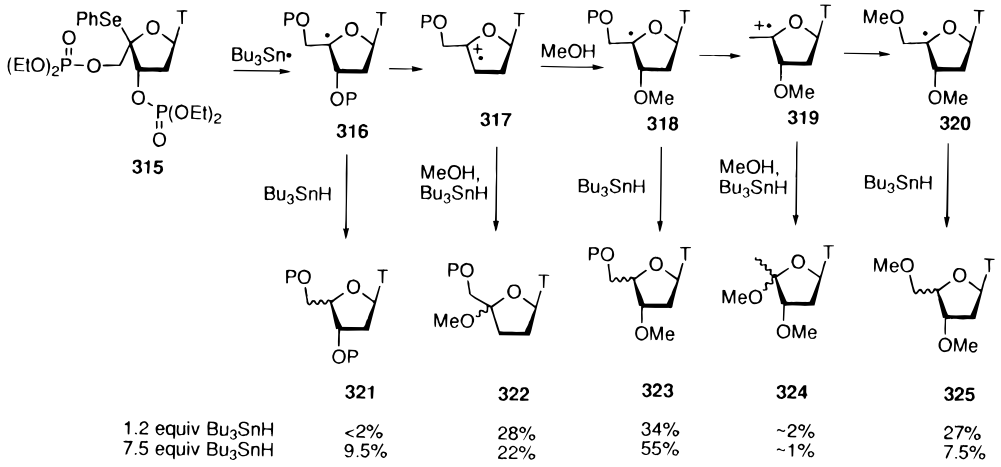


radical cation subsequently accepts an electron, possibly from thiolate, to give the glycal **304**, which is the observed product in the adenosine series. In the thymidine series, the glycal **305** could not be detected but underwent spontaneous hydrolysis to the ketoaldehyde **306**. This compound corresponds to the type of C3′ terminii observed on cleavage of DNA by the Fe-bleomycin complex under anaerobic conditions.[121,123,125] By means of a trapping experiment utilizing a large excess of thiophenol, it was estimated that the rate constant for fragmentation of **301** to **302** and **303** was $>10^8$ s^{-1} in methanol/water (9/1) solution at 30 °C.

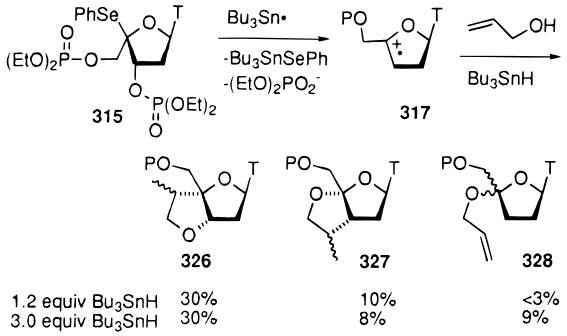
Further experiments with the simple adenosine derivatives **309** and **310** revealed the very significant influence the leaving group has on the chemistry of the C4′ radical. Thus, the diphenyl phosphate **309** furnished mainly the glycal **312** and only a minor amount of the adduct **313**, whereas the analogous benzoate **310** provided only **314** (Scheme 35). Again the fragmentation of **311** [X = P(O)(OPh)$_2$] was estimated to have a rate constant of $>10^8$ s^{-1}.

Subsequently, closely related experiments with a series of dialkyl phosphate esters analogous to **309**, led to Brønsted plots which demonstrated the heterolytic nature of the fragmentation in both ethanol/water (4/1) and toluene.[134] Trapping experiments, impossible with **299**, **300**, and **309** owing to the high rate of electron transfer from the thiol(ate) to the radical cation, were conducted in methanol solution using the reaction of the selenide **315** with tributyltin hydride as the source of C4′ radical. The spectrum of products observed (Scheme 36) is fully consonant with a pathway involving the formation of a C4′ radical **316**, its fragmentation to a radical cation **317**, and trapping by methanol. The dimethoxylated products **324** and **325** are the result of a second fragmentation of **318** to **319** and its trapping by methanol. It is readily deduced from the product ratios that the expulsion of the 5′-phosphate group

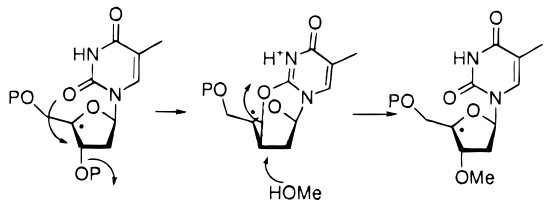
Scheme 36



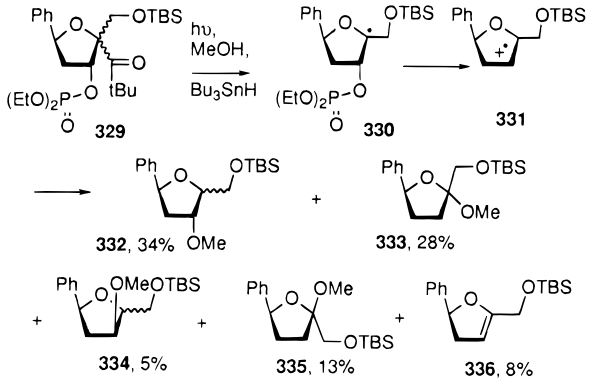
Scheme 37



Scheme 38



Scheme 39



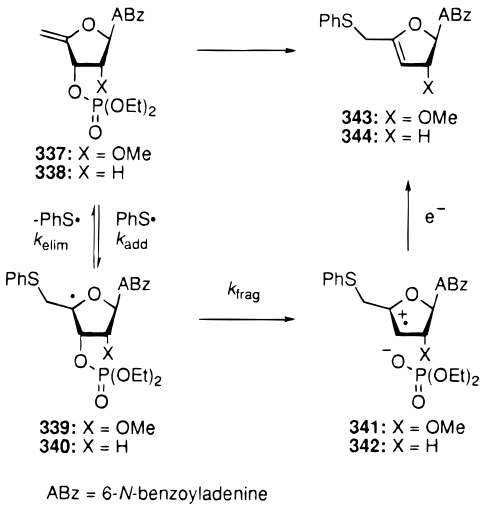
from **318** to give **319** is less rapid by a factor of approximately 60 than the fragmentation of **316** to **317**. This may be understood in terms of the greater stability of the more substituted cationic species **317**. Likewise, it is readily seen from the ratios of **322**:(**323** + **324** + **325**) and of **324**:**325** that nucleophilic attack on **317** occurs with a slight preference for the 3′- over the 4′-site and on **319** preferentially at C5′, presumably to give the more stabilized radical in each case. Again, it is interesting to contrast the regioselectivity of these trapping reactions with that of Scheme 33.

Further experiments in which methanol was replaced by allyl alcohol as solvent resulted in the isolation of three products arising from nucleophilic attack on the radical cation **317** followed by radical cyclization (**326** and **327**) and nucleophilic attack and stannane quenching of the subsequent radical (**328**) (Scheme 37).[134] Again, the preference of radical cation **317** for nucleophilic attack at the C3′ site is evident. Additional evidence for the formation of radical cation **317** was obtained from the observation of a transient photocurrent on photolysis of **315** in acetonitrile, consistent with the formation of charged species. No current was detected in comparable experiments with 3′-O-silyl derivatives or a 3′-O-acetate ester, reinforcing the notion of the requirement for a good leaving group for radical cation formation.[135]

In the above trapping experiments, the radical cation **317** is attacked from the face opposite to the base with very high selectivity. This prompted Zipse to advance an alternative mechanism involving a double inversion with anchimeric assistance by the carbonyl of the thymine residue (Scheme 38).[136] In response to this hypothesis the Giese group prepared the related system **329** and subjected it to photolysis in methanol in the presence of tributyltin hydride. A series of products (**332**−**336**) was isolated and rationalized in terms of Norrish type I cleavage followed by fragmentation of the radical **330** to the radical cation **331**, trapping by methanol and radical quenching by the stannane (Scheme 39). Substitution occurred predominantly anti to the nonparticipating phenyl group, suggesting that both here and in the nucleotides series a radical assisted S_N1 mechanism is operative with face selectivity dominated by steric factors.[137] ESR evidence supporting the formation of radical **330** in the Norrish I cleavage has subsequently been advanced.[138]

The greatly diminished reactivity of RNA, as compared to DNA, with the Fe•bleomycin complex[117,139] inspired Crich and Mo to investigate the reactivity of **337**.[140] In this adaptation of Giese's experiment (Schemes 34 and 35) the RNA and DNA models **337** and **338** were allowed to compete for reaction with benzenethiyl radicals in aqueous methanol. At 40 °C, glycal **344** was formed to the exclusion of **343** and the ribonucleotide **337** recovered essentially quantitatively (Scheme 40). Assuming that

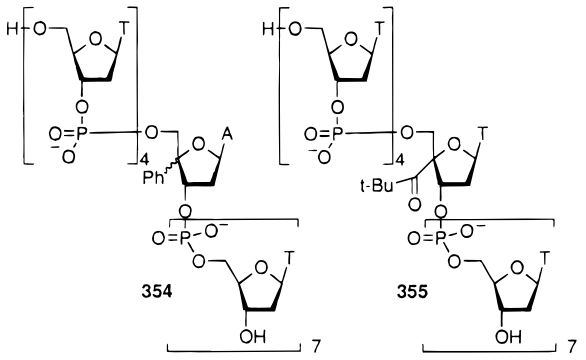
Scheme 40



the methoxy group does not significantly affect the initial equilibrium (**337/338** ⇌ **339/340**) the methoxy group is seen to substantially reduce the rate constant (k_{frag}) for cleavage of the adduct **339** to the radical cation **341** with respect to that seen in the DNA model (**340**→**342**) through inductive destabilization of the polar transition state.

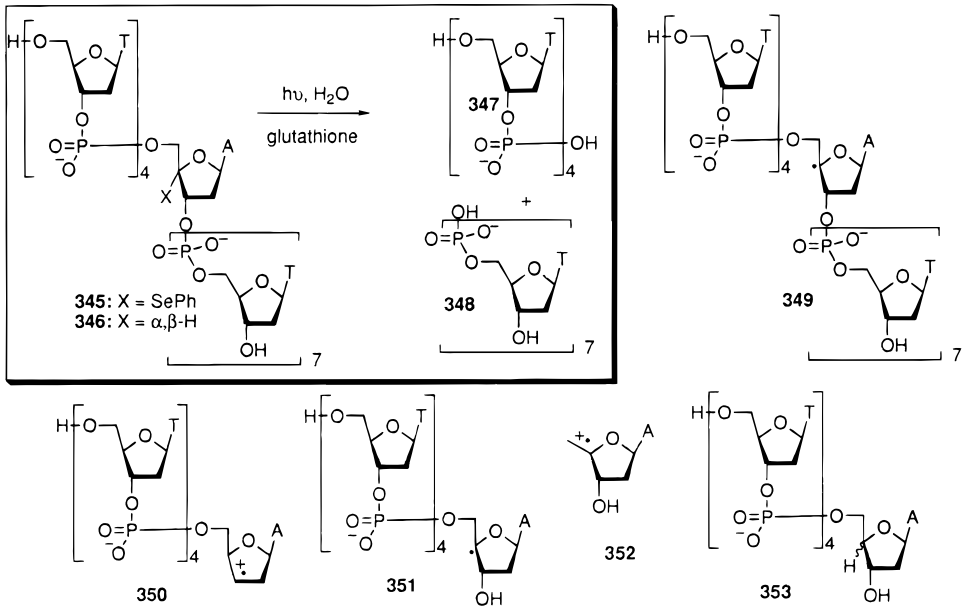
With the basics established, the Giese group proceeded to examine fragmentations of authentic oligonucleotide based radicals. Thus, the dodecamer **345**, bearing a photolabile C4′-radical precursor, was prepared and subjected to photolysis in aqueous solution, in the presence of glutathione as hydrogen atom donor. Analysis of the photolysate by a combination of gel electrophoresis, HPLC analysis, and MALDI-TOF mass spectrometry revealed two principal fragments, **347** and **348**, consistent with the formation of the C4′ radical **349**, its cleavage to the radical cation **350**, trapping by water to give **351**, and further fragmentation to **352** (Scheme 41).[141] When the reaction was conducted in the presence of an excess of glutathione, products **346** and **353** arising from reduction of radicals **349** and **351**, respectively, were also identified in the reaction mixture. Comparable results were obtained with related oligomers.

Subsequent detailed analysis of the reaction mixture from photolysis at low glutathione concentration by MALDI-TOF mass spectrometry revealed the formation of a phenylated product, assigned the structure **354**. This compound is thought to arise from coupling of the initial C4′ radical (**349**) with the *ipso*-position of the phenylselenyl radical in the solvent cage, with subsequent elimination of a selenium atom. This problem is circumvented by use of the alternative radical precursor **355**.[142]

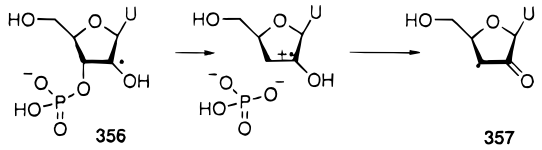


Hydrogen atom abstraction from C2′ of an oligonucleotide (DNA or RNA) also leads to a β-(phosphatoxy)alkyl radicals, raising the possibility of rearrangements and/or fragmentations. This type of radical, which may be formed by direct hydrogen abstraction or indirectly by intramolecular hydrogen abstraction following activation of a purine or pyrimidine base, has been studied much less extensively. Early work in this area, involving direct or indirect hydrogen atom abstraction by HO· and $SO_4^{\bullet-}$, has been reviewed by Schulte-Frohline.[126] The precise mechanisms of intramolecular hydrogen atom abstraction from the carbohydrate framework by radicals derived from activation of base moieties is the subject of intense current investigation most notably by the groups of Greenberg[129,130,143−145] and Saito.[131,146−148] Hydrogen atom abstraction from C2′ of uridine 3′-monophosphate gives a radical **356**, which is too unstable for observation in aqueous solution and decomposes via elimination of the

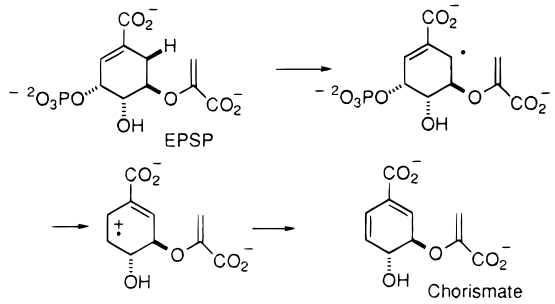
Scheme 41



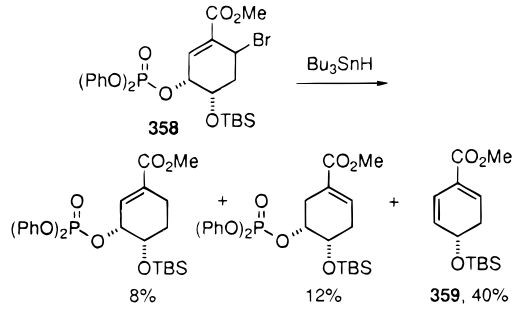
Scheme 42



Scheme 43



Scheme 44



phosphate group and proton loss to give the observed radical **357** (Scheme 42). A similar fate is noted for RNA based C2′ radicals, resulting in strand scission.[126] No such fragmentation appears to have been observed for the corresponding radicals in the 2′-deoxy series, pointing to the importance of the 2′-oxygen substituent in stabilizing the radical cation-like transition state.

The enzyme chorismate synthase catalyses the transformation of enolpyruvylshikimate 3-phosphate (EPSP) to chorismate, for which one mechanistic hypothesis, advanced by Bartlett, involves hydrogen abstraction followed by the loss of phosphate to give a cyclohexadienyl radical cation and eventual reduction to the product (Scheme 43).[149] Thus prompted, Giese and Almstead prepared the bromide **358** and subjected it to tributyltin hydride in benzene at reflux.[150] With slow addition of the stannane and a 10^{-3} M solution of **358**, elimination to **359** was indeed seen to compete with formation of the two regioisomeric reduction products (Scheme 44). A pseudo-first order kinetic study enabled the rate constant for this elimination to be estimated at $\sim 10^2$ s^{-1} at 80 °C in benzene at reflux which the authors deemed to be in accord with Bartlett's proposal. Of course, if this elimination indeed involves loss of a phosphate anion through a polar transition state, it can reasonably be expected to be substantially accelerated in aqueous solution. An alternative radical mechanism, put forward by Abell and co-workers to account for the absolute requirement of chorismate synthase for a reduced flavin cofactor,[151] involves one electron reduction of EPSP to the corresponding radical anion followed by elimination of phosphate to give an allylic

Scheme 45

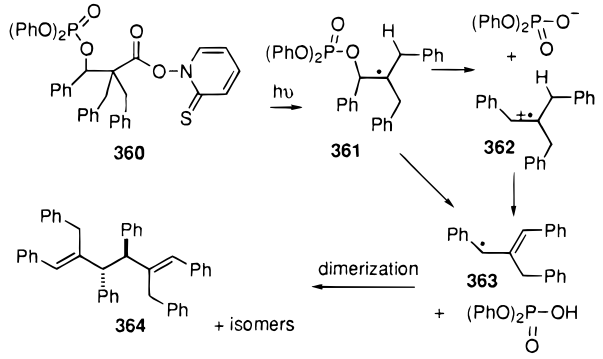


Table 8. Arrhenius Parameters and Rate Constants for Fragmentation of Radical 361

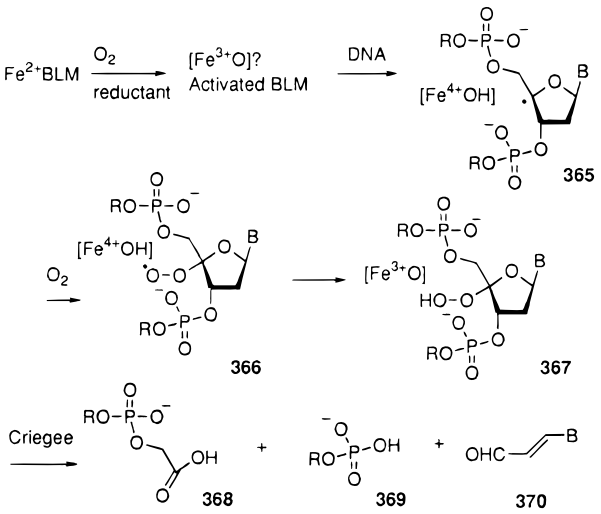
solvent	log(A, s^{-1})[a]	E_a, kcal mol^{-1} [a]	k (19.6 °C) $\times 10^{-4}$, s^{-1} [a]
hexane			<1[b]
benzene			2[b]
THF	13 ± 1	11 ± 1	3.4
acetonitrile	11.6 ± 0.3	8.0 ± 0.4	52
1:1 water/ acetonitrile			300

[a] Errors are at 2σ. [b] Temperature, 22 °C.

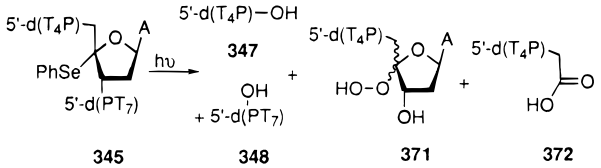
radical. Electrochemical studies with a model system however mitigated against this possibility.[151]

Finally, Crich, Newcomb, and co-workers investigated the photolysis of the *O*-acyl thiohydroxamate **360** in benzene solution in the presence of *tert*-butyl mercaptan. Under these conditions, elimination of the diphenyl phosphate group was complete and the reaction mixture consisted predominantly of an isomeric mixture of hexaphenyloctadienes. The major isomer was isolated pure and shown by X-ray crystallographic analysis to be **364**. One possible explanation for the formation of these products involves fragmentation of the initial β-(phosphatoxy)alkyl radical **361** to give a highly substituted radical cation **362**, which undergoes proton loss to an extensively delocalized allylic radical **363**, whose dimerization provides **364**. Alternatively, radical **361** undergoes a concerted fragmentation to give the allyl radical **363** directly (Scheme 45).[152] This latter process is somewhat akin to that advanced by Giese for the rapid elimination of acetate from radical **275** via transition state **278** (section III.A). Time-resolved laser flash photolytic studies were conducted in a variety of solvents and led to the determination of Arrhenius parameters and rate constants for the formation of the allyl radical **363** (Table 8). The failure to observe the spectrum of the radical cation **362** in these experiments, and the magnitude of the log A values obtained, suggests that the direct, or concerted, elimination pathway is the more likely mechanism for the formation of **363**.[152] The moderate increase in rate with increased solvent polarity is also consistant with this mechanism. The marked difference between this reaction and the rearrangements of very closely related β-(phosphatoxy)alkyl radicals (Table 5, entry 1) further draws attention to the considerable influence of alkyl substitution on the reaction rate and pathway.

Scheme 46



Scheme 47



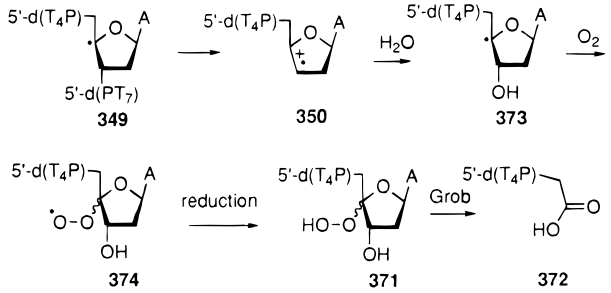
2. Aerobic Conditions

Interest in the interaction of β-(phosphatoxy)alkyl radicals with oxygen has been mainly driven in recent years by the desire to understand Fe-bleomycin-mediated cleavage of DNA and its requirement for oxygen.[117,121,123,125] The discovery of the enediynes and the related neocarzinostatin chromophore[122,153–156] with their diradical mechanisms and the clear demonstration that each species abstracts hydrogen from C4′ sites on DNA following activation have fueled investigations in this area.[157–159]

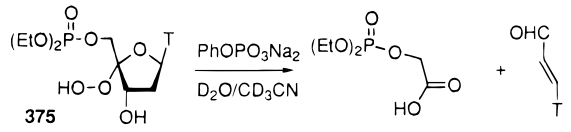
A mechanism for the aerobic cleavage of DNA was advanced by Giloni, the principal features being hydrogen atom abstraction from C4′, trapping of the C4′ radical (**365**) by oxygen to give a peroxy radical (**366**), reduction of this radical to a C4′-hydroperoxide (**367**), and its Criegee rearrangement leading ultimately to the observed products phosphoglycolate (**368**), 5′-terminal phosphate (**369**), and base propenal (**370**).[160] This mechanism, with refinements by Stubbe and others, has stood the test of time[121,125] and is outlined in Scheme 46.

Giese's synthesis of the authentic C4′ single-stranded oligonucleotide precursors **345** and **355**, and their homologues, enabled him to investigate the chemistry of C4′ radicals in the presence of oxygen. Thus, photolysis of **345** in oxygen-saturated water yielded a mixture of products that was investigated by MALDI-TOF and isotopic labeling experiments using $^{18}O_2$ and $H_2{}^{18}O$. The products **347** and **348**, characteristic of the anaerobic cleavage (Scheme 41), were identified together with two new products assigned the structures **371** and **372** (Scheme 47).[161] These were thought to arise from cleavage of the initial radical **349** to the radical cation **350** followed by trapping with water to give a new C4′ radical **373**, which itself was quenched by oxygen, giving a peroxy radical **374**, and after further reduction the hydroperoxide **371**. The phosphoglycolate **372** would then

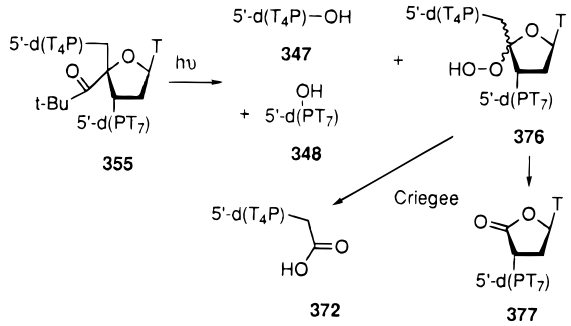
Scheme 48



Scheme 49



Scheme 50

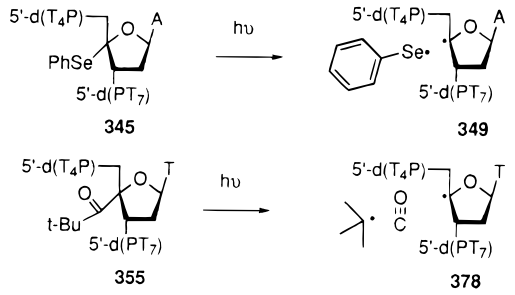


arise by Grob-type fragmentation of **371** (Scheme 48). Indeed, it was subsequently shown with an authentic sample of the hydroperoxy alcohol **375** that treatment with such mild bases as disodium phenyl phosphate provoked decomposition to phosphoglycolate and base propenal in excellent yield (Scheme 49).[161] The implication of these experiments is that, at least for single-stranded DNA, cleavage of the C4′ radical can occur before trapping by oxygen and that alternative pathways to the Giloni mechanism clearly exist for the formation of the standard degradation products of DNA in the presence of bleomycin and presumably the enediynes.

Curiously, subsequent work with the alternative radical precursor **355** gave a different spectrum of products comprised of **347** and **348**, the glycolate **372** (as with **345**), a new hydroperoxide **376**, and a lactone **377** as indicated by MALDI analysis of the photolysate (Scheme 50).[142] Evidently with this precursor, the inital C4′ radical is trapped by oxygen before cleavage can occur as in the Giloni mechanism (Scheme 46). Phosphoglycolate **372** and the lactone **377** were thought to arise from two different modes of Criegee rearrangement of **376**, migration of the 3′- and 5′-carbon atoms, respectively. Unfortunately, the authors did not address the usual requirement for acid catalysis of such migrations to electron deficient oxygen.[142]

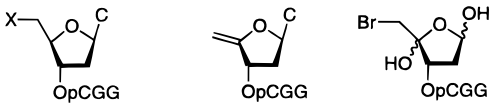
In order to explain the somewhat unexpected outcomes from the two radical precursors, the authors proposed that the phenylselenyl radical generated on photoysis of **345** prevented the approach of oxygen to the C4′ radical **349** and so enabled fragmentation to **350** to compete. With the Norrish-type precursor **355**, it was suggested that the carbon

Scheme 51



monoxide generated in the photolysis sufficiently separated the two radicals for oxygen to enter and rapidly quench **378** (Scheme 51).[142] Whatever the merits of this suggestion, it is evident that different precursors to C4′ radicals lead to different outcomes and, thus, it is not surprising that the controversy over the mechanism of oxidative cleavage of DNA still rages.

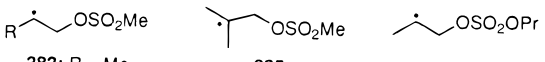
This is further borne out by recent work of Saito and co-workers who, armed with the knowledge that derivatives of Fe-bleomycin selectively hydroxylate the tetranucleotide d($C_1C_2G_3G_4$) at the 5′ terminal cytidine (C_1), prepared the modified bleomycin substrates **379** and **380** bearing 5′-iodo and -bromo groups, respectively, and subjected them to reaction with the antibiotic.[147] Since typical alkyl radicals eliminate β-iodine and β-bromine with rate constants of $>5 \times 10^9$ and 3×10^8 s^{-1}, respectively,[162] it was anticipated that these substrates would serve as suitable probes for the formation of C4′ radicals and of subsequent reactions of these radicals. In this event, incubation of iodide **379** with Fe-bleomycin in aqueous buffer at 0 °C resulted in the formation of the exocyclic glycal **381** as the predominant product, indicating that hydrogen abstraction from the C4′ site of the 5′-terminal residue had occurred and that elimination of iodide was faster than any other degradation pathway. In contrast, under the same conditions, the brominated probe **380** furnished both **381** and a new product assigned as **382**, suggesting that the chemistry undergone by the C4′ radical in the presence of the antibiotic is on the same time scale as elimination of bromine. Saito considered that the most likely competing process was Fe-bleomycin mediated oxidation of the C4′ radical to the corresponding cation and estimated the apparent rate constant for this process to be 2.0×10^8 s^{-1}.



379: X = I
380: X = Br
381
382

C. β-(Sulfonatoxy)alkyl and Related Radicals

Schulte-Frohlinde and co-workers have investigated the fragmentations of three β-(sulfonatoxy)-alkyl radicals (**383**−**385**) and one β-(sulfatoxy)alkyl radical (**386**) by means of their pulsed radiolysis/conductimetry technique. With the exception of **383**, which underwent fragmentation with a rate constant of 2×10^5 s^{-1}, all were found to undergo elimination with rate constants $\geq 10^6$ s^{-1} in aqueous solution at pH 4.5−5.[163] The greater rates of fragmentation of **386**, with the better leaving group, and of **385**, with the higher degree of alkyl substitution, than that of **383** are consistent with the elimination taking place via the radical-ionic mechanism (Scheme 26). A further example of the radical ionic cleavage of a β-(tosyloxy)alkyl radical has been presented recently by Robins.[115]



383: R = Me
384: R = Et
385
386

IV. Mechanism

As is clear from the above compilations of the literature, the chemistry of β-(ester)alkyl radicals is complex and spans a very wide range. At the one extreme we find alkyl radicals which are more or less completely indifferent to the β-ester group for either thermodynamic or stereoelectronic reasons and which are responsible for their transparency in many synthetic schemes. At the other extreme are located fragmentations, without apparent recombination, such as are seen in the chemistry of nucleotide C4′ radicals. In between these two extremes lie the rearrangement reactions and the associated mechanistic puzzle. The purpose of this section is to attempt to define the parameters involved in determining the reactivity of β-(ester)alkyl radicals and in channeling that reactivity toward the fragmentation or rearrangement manifolds. Of particular interest is the mechanism(s) of the ester shift and its relationship to the fragmentation reaction. Insofar as those radicals prone to rearrangement may be considered intermediate between those showing no reactivity with respect to β-ester functions and those undergoing fragmentations, it is appropriate to begin by consideration of these extremes.

A. β-(Ester)alkyl Radicals Susceptible to Neither Rearrangement Nor Fragmentation

β-(Ester)alkyl radicals may be "inert" with respect to fragmentation or rearrangement for either thermodynamic or kinetic reasons. Thus, in the case of the rearrangement, it is readily appreciated that the position of any equilibrium will be dictated by the relative stabilization of the two radicals and the relative strengths of the C−O bonds (Scheme 52). The importance of considering the relative C−O bond strengths, in addition to radical stabilities, is nicely brought home by the various migrations to anomeric radicals (Table 1, entries 13−25, 27, 28; Table 5, entries 9−14), which are driven by the additional stabilization gained from the formation of an anomeric C−O bond.

Scheme 52

However, it is clear, even from the early work of Julia with steroidal β-(acyloxy)alkyl radicals, that thermodynamic factors alone are insufficient to explain the failure of certain radicals to rearrange. Thus, in addition to the migrations listed in Table 1, it was noted that **44** and **46** did not rearrange to **45** and **47**, respectively (Scheme 5).[55,56] Clearly, kinetic

factors must underlie the failure of these rearrangements, which would appear to be more or less thermoneutral or, in the case of **44**, even to slightly favor **45** with its equatorial acetoxy group. The activation energies for these migrations are simply too high for them to occur in benzene at reflux. In these two particular examples the main reason, as will become clear, is probably insufficient substitution to stabilize a partial positive charge on the carbon framework at the transition state.

An example of a kinetically impaired migration is provided by the failure of **172** to undergo rearrangement on treatment with tributyltin hydride and AIBN, in contrast to the facile rearrangments of **170** and **175**, under the same conditions.[71] This may be rationalized in terms of the inability of the derived radical to adopt a conformation in which the scissile C−O bond is near periplanar with the axis of the singly occupied p-orbital for reasons of unfavorable steric and dipolar interactions (Scheme 18), whereas appropriate conformations are readily available to the radicals derived from **170** and **175**. This example also serves to underline a basic stereoelectronic requirement for the migration and, presumably, fragmentation reaction, namely, the approximate coplanarity of the C−O bond to be cleaved and the axis of the free radical.

B. Fragmentation Reactions

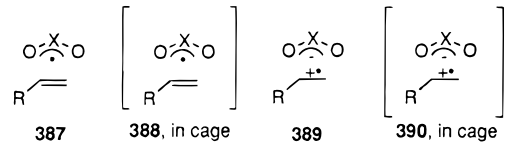
The work of the Schulte-Frohlinde and Sonntag groups with radiolytically generated radicals clearly points to heterolytic fragmentations of β-(acyloxy)-alkyl and β-(phosphatoxy)alkyl radicals into carboxylate, or phosphate, anions and alkene radical cations in polar solvents. In agreement with such a polar mechanism, the fragmentation rate was seen to be significantly enhanced by electron donating groups on the eventual radical cation. Similarly, for formation of a given radical cation, a ranking of leaving group's abilities correlate well with that anticipated for a two electron process (Table 7). However, it should not be forgotten that the rate constants measured by these workers were for increases in conductivity following pulsed γ-radiation of solutions of the precursor, rather than for total fragmentation (or rearrangement). Any radical elimination to alkenes and carboxyl radicals would therefore have passed unnoticed. In this respect the chemical trapping experiments of the Giese group (Schemes 36 and 37), with unambiguously generated nucleotide radicals, are central to the demonstration of the existence of the radical cation/anion fragmentation pathway, at least for phosphate esters. Further strong support is provided by a Brønsted plot from the Giese group correlating pK_a of the leaving group with the rate of fragmentation.[134]

The extremely rapid decarboxylation of acyloxy radicals, at least those derived from aliphatic acids, is usually cited (sections II.A.1 and III.A) as evidence against a mechanism for the (acyloxy)alkyl migration involving fragmentation to a caged carboxyl radical/alkene pair, followed by rapid recombination. Indeed, the purely radical fragmentation of β-(acyloxy)-alkyl radicals is extremely rare and requires a considerable thermodynamic driving force (Scheme 27) such as the formation of an aromatic nucleus, as opposed to a simple alkene, in the course of the fragmentation. It would be of some interest to revisit radicals **249** and **253** in more polar solvents and to ascertain at what stage, if any, the polar fragmentation mechanism takes over. In nonpolar solvents apparently pure radical fragmentations are observed with β-(thiocarbonyloxy)alkyl radicals (Scheme 10, Table 4), and this is attributed to the additional stabilization of the leaving radical by the incorporation of the sulfur atom. However, it is perhaps again prudent and interesting to note the considerably enhanced acidity of thiocarboxylic acids (RCOSH) with respect to carboxylic acids and so to contemplate the possibility of a polar fragmentation in more polar solvents. There is also the possibility that the fragmentations of Scheme 10 occur by the polar mechanism to give a caged radical cation/thiocarboxylate pair followed by rapid electron transfer to give the observed alkene and the thiocarboxyl radical.

The various examples of fragmentation reactions, radical and radical-ionic, presently known do not permit us to draw conclusions about the stereoelectronic requirements of such processes. However, by comparison with traditional two-electron elimination reactions, it would seem reasonable that approximate coplanarity of the scissile C−O bond and the singly occupied p-orbital is required. Consideration of the fragmentation process as an exploded transition state for the migration reaction, with its decidedly polar flavor (section IV.4), suggests that the two processes will have similar stereoelectronic requirements which, as discussed above, maybe be inferred from comparison of the reactivities of **170**, **172**, and **175**.

C. Rearrangement Reactions

The elucidation of the mechanism of the β-ester shift has presented perhaps the greatest challenge to the ingenuity of those working in the area. At the outset a broad spectrum of mechanisms was identified for consideration and investigation. These were (a) fragmentation to an alkene and an ester radical followed by recombination (**387**), (b) the same as (a) with in-cage recombination (**388**), (c) fragmentation to an alkene radical cation and ester anion with subsequent recombination (**389**), (d) the same as for (c) with in-cage recombination (**390**), (e) ring closure to a five-membered cyclic radical intermediate (**391**) with subsequent ring opening, and two open shell concerted pathways, one (f) involving a five-electron−five-center shift (**392**) and the other (g) a three-electron−three-center shift (**393**). Of these seven possibilities three (a, c, and e) have been conclusively eliminated.



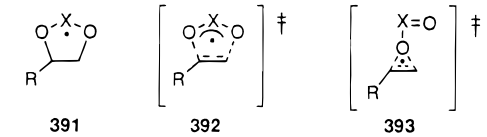


Table 9. Fragmentation of Dioxolanyl Radicals

entry	rearrangement	solvent	temp, °C	k, s^{-1}	ref
1	**394** → **395**	H_2O	rt	$\leq 10^2$	49
2	**394** → **395**	cyclopropane	72	5.8×10^3	166
3	**396** → **397**	hydrocarbon[a]	75	7.6×10^3	53
4	**398** → **399**	cyclopropane	72	7×10^2	166
5	**400** → **401**	hydrocarbon[a]	75	1.0×10^3	53

[a] Undefined hydrocarbon.

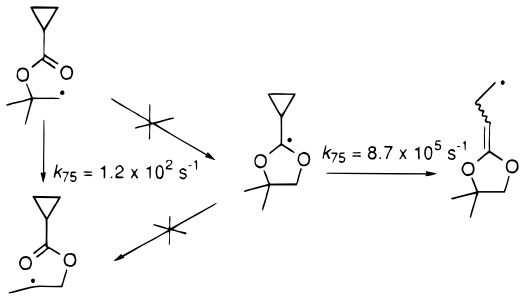
1. Noncage Dissociative Pathways

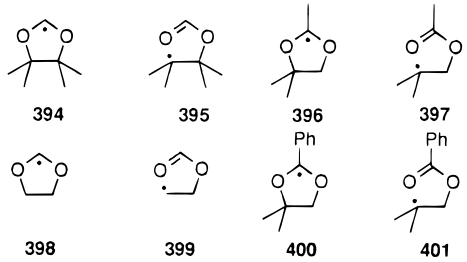
Pathway (a) (**387**) was excluded, at least for the acyloxy shift, on the very reasonable grounds that the rate constant for decarboxylation of the putative intermediate acyloxy radical far surpasses that for the migration in question.[48] For the phosphatoxy and nitroxy shifts, such radical fragmentation/recombination pathways were excluded by simple experiments conducted in the presence of alkenes which failed to show any crossover products.[71,106] Subsequent demonstrations of the highly stereoselective nature of numerous carbohydrate,[60,63] steroidal,[55,56] and even acyclic examples[71] of the acyloxy and phosphatoxy shifts rule out the possibility of radical ionic fragmentation/recombinations of type c (**389**) but not their cage counterparts (d) (**390**). Recent attempts to trap radical cation intermediates with external nucleophiles for both the acyloxy and phosphatoxy shifts have also been unsuccessful.[164,165]

2. Stepwise Pathways via Five-Membered Cyclic Intermediate Radicals

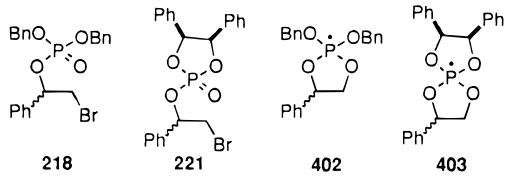
In the case of the acyloxy shift, a formal 5-endo-trig ring closure of the initial radical would lead to a 1,3-dioxolan-2-yl radical (**391**, X = CR). This intermediate radical would then undergo a retro 5-endo-trig fragmentation to the final radical. Beckwith and Tindal[49] first investigated this possibility by the ESR method. In that study, hydroxy radicals were used to abstract hydrogen atoms from 4,4,5,5-tetramethyl-1,3-dioxolane in aqueous solution to give the readily observable tetramethyl-1,3-dioxolan-2-yl radical (**394**). No cleavage of this radical was observed on the time scale of this ESR experiment, prompting the authors to set an upper limit for the rate constant for dioxolanyl radical opening at 10^2 s^{-1} in aqueous solution at room temperature. When the 2-acetoxy-2-methyl-1-propyl radical was generated from *tert*-butyl acetate under the same conditions, it was observed to rearrange with an estimated rate constant of 10^3 s^{-1}. Thus, in aqueous solution, the typical acyloxy migration was demonstrated to occur roughly an order of magnitude more rapidly than dioxolanyl ring opening. In hydrocarbon solvents, Perkins and Roberts,[166] and later Ingold and coworkers,[53] found that the ring opening of authentic dioxolan-2-yl radicals is on a comparable time scale to that of the acyloxy shift. Rate constants for the fragmentation of typical dioxolanyl radicals are given in Table 9.[166] Further experiments, by Ingold, established β-(cyclopropylcarboxy)alkyl radicals to be viable substrates for the migration. Blank experiments indicated that the corresponding 2-cyclopropyl-1,3-dioxolan-2-yl radical suffered the cyclopropylmethyl to homoallylic rearrangement rather than opening of the dioxolane ring and so was not an intermediate in the migration (Scheme 53).[53] The stepwise pathway was therefore conclusively excluded from consideration for the acyloxy shift. Comparison of the work of Beckwith, in aqueous solution, and that of the Ingold and Perkins groups, in hydrocarbon solvents, also hinted for the first time at the acyloxy migration, but not dioxanyl opening, being significantly accelerated in polar solvents.

Scheme 53





In the case of the phosphatoxy shift, the stepwise ring closure/opening mechanism invokes a cyclic phosphoranyl radical [**392**, X = $P(OR)_2$] as intermediate. The rich chemistry[167,168] of these species including fragmentation to phosphorus(III) and (V) species and their well-characterized pseudorotational behavior dictated serious consideration of this possibility. Substrates **218** and **221** were synthesized to probe this possibility. It was anticipated that any phosphoranyl radical intermediates **402** and **403**, respectively, would result in the formation of products from alternative cleavage modes as well as in the standard rearrangement products. As this was not the case (Table 5, entries 15 and 16), this pathway could be eliminated. Corroborating evidence is drawn from the rearrangements of the stereochemically labeled probes **224**, **228**, **230**, and **233** for which the spectrum of products (Table 5, entries 17−20) was inconsistent with a phosphoranyl radical undergoing pseudorotation.



The results of isotopic labeling experiments (section IV.3) for both the nitroxy[169] and sulfonatoxy shifts,[170] which identify high proportions of the 1,2-shift product, are inconsistent with the formation of five-membered cyclic intermediate radicals.

3. Use of Isotopic and Stereochemical Labeling as Probes of Mechanism

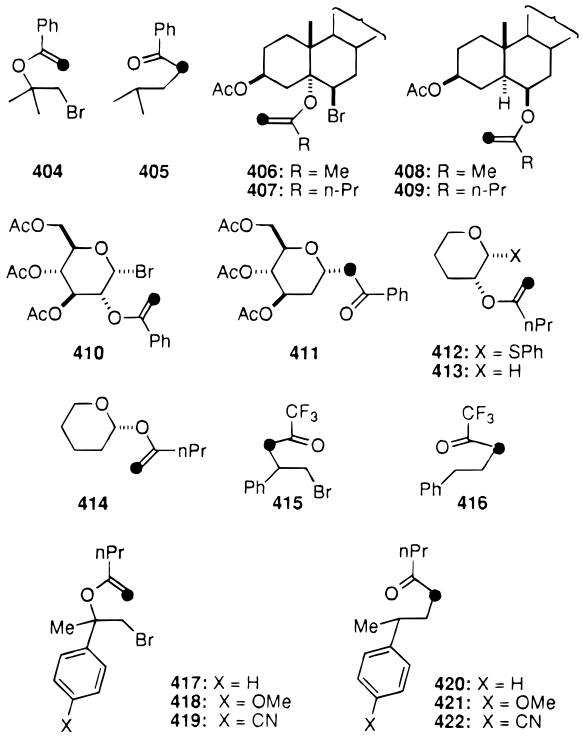
In principle, isotopic and, in the case of phosphate esters, stereochemical labeling may be used to dis-

Table 10. Isotopic and Stereochemical Labeling Experiments

entry	substrate	solvent	rearranged products	temp, °C	% formal 1,2-shift	k, s^{-1} [b]	ref
1	**404**	C_6H_6	**405**	75	~0	2.5×10^2	50
2	**406**	C_6H_6	**408**	80	77		57
3	**407**	C_6H_6	**409**	75	76	1.9×10^6	58
4	**410**	C_6H_6	**411**	75	~0	4.0×10^2	61
5	**412**	C_6H_6	**414**	80	67	1.2×10^4	62
6	**415**	C_6H_6	**416**	80	7		169
7	**417**	C_6H_6	**420**	75	~0	6.2×10^4	164
8	**418**	C_6H_6	**421**	75	39	1.7×10^5	164
9	**419**	C_6H_6	**422**	75	0	1.6×10^4	164
10	**417**	MeOH	**420**	75	25	1.6×10^5	164
11	**224**	C_6H_6	**226** + **227**	80	70		71
12	**228**	C_6H_6	**226** + **227**	80	74		71
13	**230**	C_6H_6	**231** + **232**	80	58		71
14	**233**	C_6H_6	**231** + **232**	80	75		71
15	**423**	C_6H_6	**424**	80	60	8.0×10^5	71
16	**425**	C_6H_6	**426**	80	64 (82)[a]		169
17	**427**	C_6H_6	**428**	80	65 (82)[a]		170

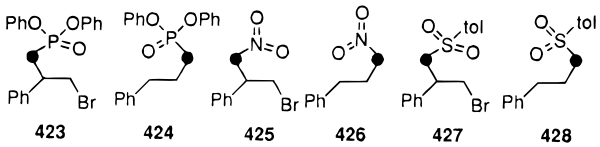
[a] After correction for the 2/1 statistical preference for the 2,3-shift. [b] Taken from Tables 2 and 6.

tinguish between pathways (b) and (d), the radical and radical ion cage mechanisms (**388**) and (**390**), and (f) the five-center−five-electron (**392**) and (g) the three-center−three-electron (**393**) pericyclic shifts. This possibility was recognized early by Beckwith and Thomas who prepared the regiospecifically ^{18}O-labeled substrate **404** and treated it with tributyltin hydride in benzene at reflux.[50] Mass spectral analysis of the rearrangement product **405**, after cleavage of the ester, indicated complete exchange of the carbonyl and carboxyl oxygens (Table 10, entry 1). Thus, the 2,3-shift mechanism (f) through a five-center−five-electron cyclic transition state (**392**) became the paradigm in this area. It was not challenged until 1986, when Kocovsky and co-workers reported the first example of a β-(acyloxy)alkyl rearrangement occuring predominantly without exchange of the two oxygen atoms (**406** → **408**) (Table 10, entry 2).[57] Beckwith and Duggan subsequently repeated the work of Kocovsky using the homologous butyrate ester **407** and obtained closely analogous results (Table 10, entry 3).[58] Giese was also stimulated to conduct a labeling study on the acyloxy migration in carbohydrates and found with **410** → **411**, within the limits of the ^{13}C-NMR isotope shift method employed, complete exchange of the carbonyl and carboxyl oxygens (Table 10, entry 4), compatible with a concerted 2,3-shift of the ester group.[61] In stark contrast to the rearrangement of **410**, Beckwith and Duggan found that **412** gave **414** with 66% of the ^{17}O-label remaining in the carbonyl oxygen, as determined through ^{17}O-labeling in conjunction with ^{17}O-NMR spectroscopy (Table 10, entry 5).[62] Interestingly, some scrambling of the label was also observed in the reduction product **413**. This could be suggestive of either a cage fragmentation pathway with limited readdition at the original position or, alternatively, a reversible migration occurring via the 2,3-pathway in one direction and the 1,2-pathway in the other. Crich and Filzen used ^{18}O-labeling to investigate the rearrangement of the trifluoroacetate **415** in benzene at reflux and found the migration to occur with 93% exchange of the two oxygens (Table 10, entry 6).[169] As part of a recent study, Beckwith and Duggan investigated the rearrangements of the ^{17}O-labeled substrates **417**−**419** and found the 1,2-shift to be promoted (a) by the electron donating *p*-methoxy group and (b) by the use of a polar solvent (Table 10, entries 7−10).[164]



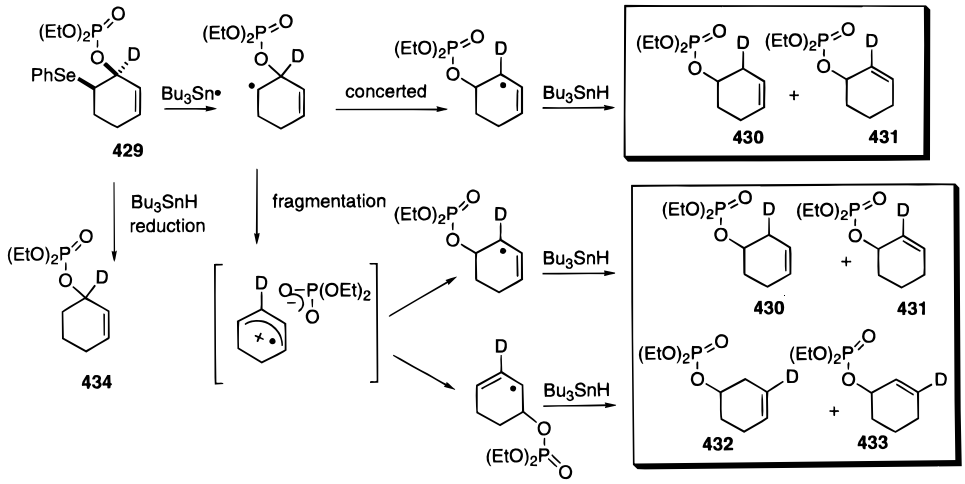
For the phosphatoxy migration, Crich and Yao took advantage of the tetrahedral nature of phosphorus in phosphate esters to design stereochemical probes. Each of the bromophosphates **224**, **228**, **230**, and **233** was treated, separately, with tributyltin hydride and AIBN in benzene at reflux, resulting in the formation of rearranged products with inversion or retention of configuration at phosphorus as indicated in Table 10 (entries 11−14). In each case a significant excess of retention over inversion was observed, possibly suggesting mixed mechanisms with a preponderance of the three-center−three-electron pathway.[71,104] A similar, although less biased, result was obtained with an ^{18}O-labeled diphenylphosphate migration (Table 10, entry 15).[71]

^{18}O-Labeling was also used to demonstrate that the rearrangement of the nitroxy and sulfonatoxy groups in **425** and **427**, respectively, also occurred predominantly by a 1,2-shift (Table 10, entries 16 and 17).[71,170] It should be noted that for both **425** and **427** there is a 2:1 statistical preference in favor of a 2,3-shift and that the preference for the 1,2-pathway, after correction, is actually 82% in both cases.



Thus, for the acyloxy migration there are three clear-cut examples of pure 2,3-shifts and several of mixed mechanisms. Phosphatoxy, nitroxy, and sulfonatoxy shifts take place predominantly in the form of 1,2-shifts although, to date, no examples have been identified of pure 1,2-shifts of any type of ester, the closest being the statistically corrected 82% observed

Scheme 54

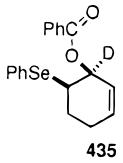


for **425** and **427**. Individually, and overall, the results presented in Table 10 rule out the possibility that any of these radical ester migrations occurs, in benzene solution, via fragmentation to a fully relaxed anion/radical cation cage pair. Indeed, this ensemble of results hints strongly at the existence of two distinct concerted pathways, one via a three-center−three-electron and the other a five-center−five-electron transition state. It is also noted that, of the 17 examples studied so far (Table 10), more than half (10) rearrange predominantly by a 1,2-shift.

In a further attempt to distinguish between concerted and in-cage fragmentation/recombination mechanisms, Crich and Yao designed and studied the deuterium-labeled probe **429**. It was envisaged that a concerted shift, 1,2 or 2,3, would lead to a mixture of the two products **430** and **431**, whereas a fragmentation/recombination pathway would result in the formation of a mixture of the two homoallylic esters **430** and **432** and the two allylic esters **431** and **433**. Thus, for a migration proceeding completely by a concerted pathway, a 1:1 ratio of the olefinic signals for **430** is expected and a 1:0 ratio of those for **431**. On the other hand, for a fragmentation/recombination pathway an uneven ratio in the olefinic signals from the sum of the regioisotopomers **430** and **432** would be expected and an even one for those from the sum of **431** and **433** (Scheme 54).[71] The inevitable formation of **434**, a third regioisotopomer of the allylic ester formed by reduction of the initial radical before migration, complicates analysis of the spectral pattern for **431** and **433**.

In this event, in benzene solution at reflux, reaction of **429** with tributyltin hydride resulted in a product mixture for which the olefinic portion of the ^{1}H-NMR spectrum showed a 1:1 ratio of the two homoallylic olefinic signals and an uneven ratio of those from the allylic products, consistent with a product mixture comprising **430**, **431**, and **434** and so with a concerted shift.[71] In subsequent work, a similar spectrum was obtained when the reaction was run in THF solution, but, when *tert*-butyl alcohol at 80 °C was used, the NMR spectrum clearly showed that this particular migration occurs at least in part by a fragmentation/recombination mechanism in this solvent.[165]

Parallel experiments were conducted with the benzoate ester **435** leading to the conclusion that its migration reaction is non-dissociative in benzene, THF, and in *tert*-butyl alcohol.[71,165]



435

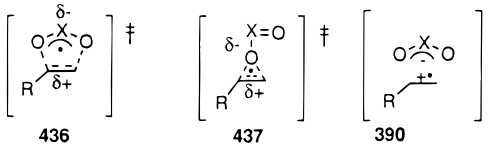
Experiments were also conducted with **429** (and **435**) in *tert*-butyl alcohol in the presence of tetrabutylammonium acetate, but in neither case was the formation of a crossover product observed in the reaction mixture. It is therefore clear that any radical cation intermediates in the rearrangement of **429** in *tert*-butyl alcohol very rapidly recombine with the phosphate anion within the solvent cage excluding any possibility of trapping by external nucleophiles; i.e., a contact or intimate radical cation/anion pair is involved.[165]

This last experiment in no way means that all (acyloxy)- and (phosphatoxy)alkyl migrations take place via a concerted pathway, be it three-center−three-electron or five-center−five-electron, but it clearly demonstrates that such pathways do exist. The change in mechanism of rearrangement of **429** on going from benzene to *tert*-butyl alcohol indicates that there is very fine balance between cage and concerted mechanisms and it is to be expected that only minor changes in substrate and conditions will cause switching between the two possibilities.

4. Quantitative Structure Activity Relationships

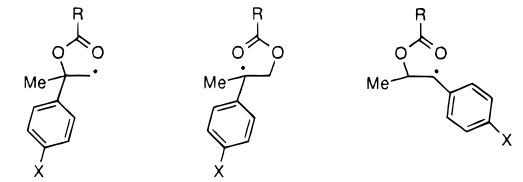
The Crich group prepared a series of *para*-substituted diphenylphosphates and determined their rearrangement rates (Table 6, entries 1−6)[103] using their recently devised stannane−diphenyl diselenide couple clock reaction.[100] The rates at 80 °C showed a strong correlation with the Hammett substituent constant σ_p, giving a reaction coefficient of $\rho = 2.1$. No correlation was found with any of the $\sigma^\bullet$ scales examined. The reaction coefficient of 2.1 versus σ_p is very high for a radical reaction and strongly supports the notion that the (phosphatoxy)alkyl migration proceeds via transition states with substantial polar character, polarized in the way shown

[**436** and **437**, X = $P(OAr)_2$], or, less likely on the basis of the various labeling experiments, the cage ion pair [**390**, X = $P(OAr)_2$].



436 437 390

To gain an insight into the extent of polarization of the acyloxy shift, Beckwith and Duggan determined the rates of rearrangement of three *p*-substituted phenylpropyl butyrate derived radicals (**438**−**440**) and the related **441**, generated from the corresponding bromides, by means of the stannane clock method (Table 2, entries 16−24).[164] At 75 °C in benzene, a Hammett correlation with the substituent constant σ_p^+ was obtained, giving a reaction coefficient of $\rho = -0.71$. The transition state for this reaction is clearly polarized in a similar fashion to the phosphatoxy rearrangement, but to a lesser extent. This series of radicals also possessed an inbuilt test of the experimental method, as it could also undergo a neophyl rearrangement to yield radicals **446**−**449**, a process which is thought to have little if any polar character.[171] As expected, the rates determined for this reaction correlated well with Creary's $\sigma^\bullet$,[172] but not with σ_p^+. Changing to the trifluoroacetate also had a significant effect on the ester migration rate, with the fluorinated radical (**441**) rearranging at a rate >150 times faster than the butyrate (**440**) at 75 °C (Table 2, entries 23 and 24). This is consistent with previous observations by Ingold of trifluoroacetate migrations (section II.A.1) and again suggests a polarized transition state for this reaction. Solvent effects on the rearrangement rate of the unsubstituted phenylbutanoate radical (**438**) were also examined. The results of experiments with six solvents that spanned a broad spectrum of polarities showed a clear dependence of the ester migration rate on solvent polarity (Table 2, entries 16−21). Correlation of the rates with the solvent polarity parameter E_T[173] gave a slope of 0.024, again indicating a mild but discernible polarization in the transition state for the butyrate shift. A similar examination of the neophyl rearrangement enabled the authors to detect what was thought to be a very slight polarization of the transition state for the hydrogen abstraction from tributyltin hydride.[164]



438: X = H, R = n-C_3H_7
439: X = OMe, R = n-C_3H_7
440: X = CN, R = n-C_3H_7
441: X = CN, R = n-CF_3
442: X = H, R = n-C_3H_7
443: X = OMe, R = n-C_3H_7
444: X = CN, R = n-C_3H_7
445: X = CN, R = n-CF_3
446: X = H, R = n-C_3H_7
447: X = OMe, R = n-C_3H_7
448: X = CN, R = n-C_3H_7
449: X = CN, R = n-CF_3

In 1988 Beckwith and Duggan suggested that the acyloxy shift could proceed *via* two competing pathways.[174] One of these, they argued, was the early paradigm—the cyclic five-membered transition state (**392**, X = CR). Due to the unprecedented nature of the three membered cyclic transition state (**393**, X = CR), they suggested that the other would most likely involve an intermediate resembling the cage radical ion pair (**390**, X = CR). They also reflected on the possibility that there was a correlation between rearrangement rate and the extent of involvement of **390** or similar structure, such that environmental factors that stabilised **390** also accelerated the overall reaction. Later, Crich and Filzen came to the conclusion that, in general, the faster rearrangements occurred to a significant extent through the polarized three-center transition state **437**.[169] The polar three-membered transition state (**437**) was preferred over the caged ion pair (**390**) on the basis that the labeling experiments with phosphates and nitrates had shown >50% exchange of label rather than randomization (Table 10) and also that the experiment depicted in Scheme 54 had, for the first time, distinguished between the two possibilities. Unfortunately, these analyses were based on experiments conducted by several groups with a wide variety of substrates and therefore left room for doubt. The recently published study of Beckwith and Duggan[164] in which rate constants were determined for a consistent series of radicals and correlated with labeling studies and solvent effects (Table 2, entries 16−24; Table 10, entries 7−10) provides a much firmer basis for such rationalizations. Thus, it is now well established that factors which favor charge separation in the course of the reaction, be they solvent or substituent effects, accelerate the rearrangement and, at the same time, lead to an increased proportion of the formal 1,2-shift. The transition state for the three-center−three-electron mechanism (**437**) is more polarized than that for the five-center−five-electron shift (**436**) of the same substrate. It is possible, with correctly designed probes (Scheme 54), to distinguish between concerted and ion-pair mechanisms. It has not so far been possible to trap ion pairs with added nucleophiles[164,165] and therefore, in cases where they have been demonstrated, they must be of the contact or intimate kind.

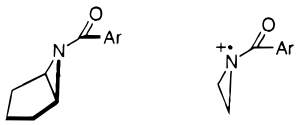
5. Computational Studies and ESR Considerations

Just as benzene is frequently viewed as a first generation model for the transition state of pericyclic reactions proceeding through six-membered−six-electron cyclic transition states,[175−177] the cyclopentadienyl and cyclopropenyl radicals may be thought of as crude approximations for reactions taking place via five-membered−five-electron and three-membered−three-electron cyclic transition states, respectively.[71] A picture of the distribution of electron density in these radicals is available by ESR spectroscopy. The cyclopentadienyl radical (**450**) and its peralkylated analogues have been extensively investigated by Davies. Above 70 K it is a π-radical with D_{5h} symmetry, prompting the Davies group to call it the simplest π-annulene radical which has been prepared. However, below 70 K the ESR spectrum is consistent with a π-radical having C_{2v} symmetry and oscillating between an elongated and a compressed pentagon.[178−182] The ESR spectrum of the trimethylcyclopropenyl radical (**451**), generated by photolysis of di-*tert*-butyl peroxide in the presence of

1,2,3-trimethylcyclopropene, shows it to be an equilibrating mixture of three equivalent σ-radicals at 240 K in cyclopropane and to be a localized σ-radical at 113 K in propane.[183] Parallel phenomena are observed with the tri-*tert*-butylcyclopropenyl radical.[184] Calculations suggest that a three-electron π-cyclopropenyl radical would be antiaromatic.[185,186] The 2,3-di-*tert*-butyl-1-(3,5-di-*tert*-butylphenyl)cyclopropenyl radical has a π-structure, presumably because of the extensive benzylic delocalization.[187]

450 451

Thus, even these very crude models have significant localization of the π-electron density and this can only be accentuated by perturbations resulting from the inclusion of heteroatoms in the bonding framework. The indication is therefore clear: the transition states for the five-center−five-electron and three-center−three-electron migrations will have substantial localization of electron density, i.e., polarization as in **436** and **437**. If we are permitted to take the analogy even further, we reach the conclusion that polarization in the three-center−three-electron transition state will be more substantial than that in its five-center−five-electron counterpart. This, of course, is precisely the conclusion drawn from the study of structure-activity relationships (section IV.C.4). A further hint at the nature of the three-electron−three-center transition state might be gleaned from consideration of the structure and dynamics of *N*-acylaziridines. Aziridine **452** was revealed by X-ray crystallographic structure determination to have a pyramidal nitrogen with the plane of the carbonyl group roughly parallel to the axis of the aziridine C−C bond,[188] rather than perpendicular to it. However, dynamic NMR studies by Anet failed to locate a barrier to rotation about the N−CO bond in a number of *N*-acylaziridines and point to an upper limit of 6 kcal mol^{-1} for this rotation.[189] Analogy suggests that the migrating oxygen in the three-center−three-electron transition state will be pyramidal. The structure of an *N*-acyl aziridine radical cation **453**, as determined by ESR spectroscopy, would be a better analogy but, unfortunately, no such information, to our knowledge, is available at the present time.



452 453

Computational studies have the potential for offering considerable additional insight into the nature of the three- and five-membered transition states. In 1983 Beckwith and Radom carried out *ab initio* calculations on the degenerate migration of the β-(formyloxy)ethyl radical.[190] The initial β-(formyloxy)ethyl radical (**454**) was found to prefer the indicated conformation, namely, the usual syn-ester with the singly occupied p-orbital essentially perpendicular to the axis of the β-C−O bond (Scheme 55). The rearrangement was found to occur, without the involvement of intermediates, via the transition state **456**. Rearrangement through the intermediate dioxanyl radical **457** was also considered. At the highest levels of theory utilized (6 31G* basis set with electron correlation), the transition state **456** and the intermediate **457** were found to be within a few kcal mol^{-1} of each other, but as seen from the energy profile diagram (Figure 1) the unsymmetrical transition states leading to and from **457** are of considerably higher energy and so mitigate against the operation of the stepwise pathway. Although very close in energy, the transition state **456** and the dioxanyl radical **457** are very different. Transition state **456** is best represented as a loose complex between a formyloxy radical and ethylene with long C−O bonds and a partial C−C double bond fully consistent with the polarized transiton state (**436**) originally proposed by Ingold and indicated by structure activity relationships and corresponding, at least geometrically, to the elongated pentagon structure for the cyclopentadienyl radical (**450**). Significant transfer of electron density in the direction $HCO_2^-/CH_2CH_2^{\bullet+}$ is found for **456**, which symmetry considerations suggest should be thought of as an σ-radical with eight electrons of π-symmetry. The dioxanyl radical **457** is best thought of in terms of a fully single bonded structure and as a π-radical having nine electrons of π-symmetry. The interconversion of the energetically similar **456** and **457** is therefore prevented by a symmetry imposed barrier. Calculations on the three-membered-three-electron transition state were not undertaken at the time, as the evidence then indicated that such a mechanism was not operative. However, we note in passing that a three-membered cyclic transition state (**460**) for the rearrangement of the protonated hydroxyethyl radical (section VI.A) had earlier been calculated by Golding

Scheme 55

454: Beckwith and Radom 455: Zipse

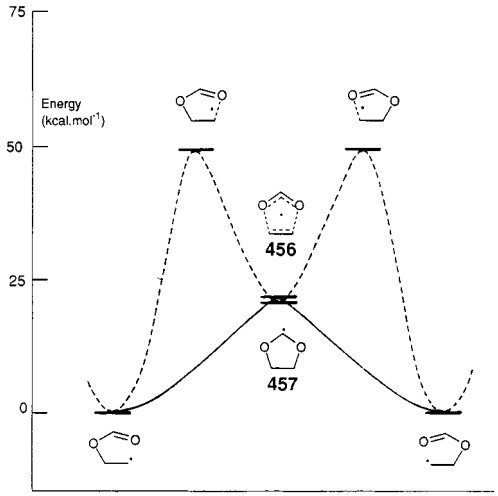
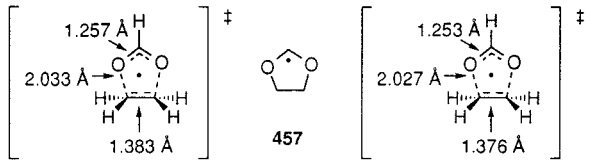
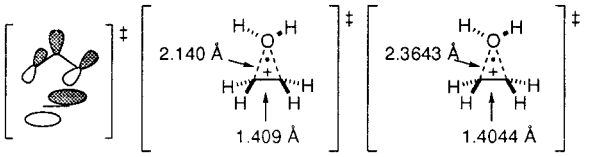


Figure 1. Potential energy profiles for rearrangement of the β-(formyloxyethyl).

and Radom.[191] A related structure (**461**) has also been subsequently located by Zipse.[192]



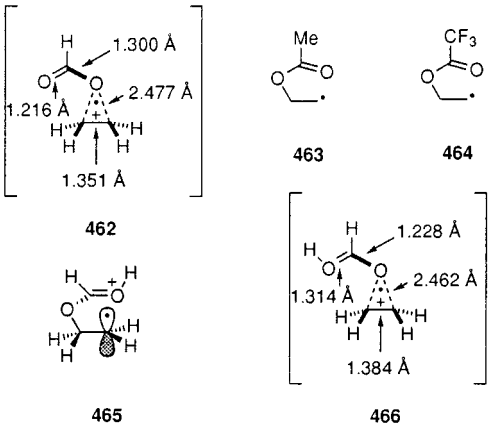
456: Beckwith and Radom **458:** Zipse



459: SOMO **460:** Golding and Radom **461:** Zipse

In pursuit of his "methylenology principle" relating open- and closed-shell pericyclic reactions,[136] Zipse has carried out *ab initio* calculations on the β-(formyloxy)alkyl migration and finds a transition state (**458**) very much akin to that described by Beckwith and Radom (**456**).[193] Analysis of the individual orbitals for the transition state reveals the SOMO at this transition state (**459**) to have little contribution from the formyl carbon atom and similar contributions from the formyl oxygen and ethylene carbon atoms. As in the work of Beckwith and Radom, the formyloxy group was found to carry a partial negative charge. The planar nature of the transition state **458** found by Zipse and the involvement of the formyloxy lone pairs led him to consider the β-(formyloxy)ethyl rearrangement as an intramolecular nucleophilic substitution, which he dubs an $S_{RN}2'$ reaction. Noting the similarly of **458** with the transition state calculated, in parallel, for the degenerate 3,3-sigmatropic shift of allyl formate, Zipse suggested that the radical rearrangment may well be subject to catalysis by acids and also potentially sensitive to the ionic strength of the medium.

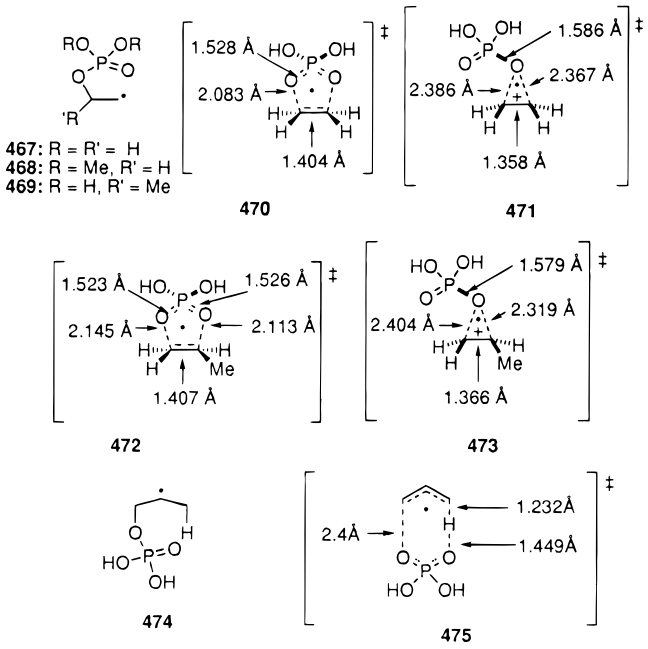
In a subsequent paper, Zipse considered the three-electron−three-membered transition state, the influence of solvent, and that of acid.[194] In the gas phase the three-membered transition state **462** for the migration of the formyloxyethyl radical (**455**) was located and placed some 4 kcal mol^{-1} higher in energy than the corresponding five-membered transition state (**458**). These calculations also revealed that, in the gas phase, the charge separation in both the five- and three-membered transition states was similar with 0.29e and 0.25e, respectively, on the formyloxy group. This was little different from that found in the starting radical (**455**), wherein 0.31e resided on the formyloxy moiety. Thus, the 2,3-shift was predicted to predominate, qualitatively reflecting the experimental result. However, the calculations failed to account for the polarized transition states required by the linear free energy relationships and, especially, for the greater polarization of the three- over the five-membered transition state. Similar calculations were conducted for the acetoxyethyl radical **463** and the trifluoroacetoxyethyl radical **464**, with comparable results. In each case, the five-membered transition state was found to be preferred over the three, and little or no difference in polarity was found between the two. Moreover, the barriers to rearrangement of **455**, **463**, and **464** were found to be remarkably similar, again in contrast to experiment. Zipse was therefore led to incorporate solvent effects in his calculations. When bulk water was included in the system, the barriers to rearrangement of **455** and **463**, via the five-membered cyclic transition states, were lowered, but only by 0.18 and 0.85 kcal mol^{-1}, respectively. With the trifluoroacetoxyethyl radical **464**, a more significant reduction in barrier height of 4 kcal mol^{-1} was noted, corresponding to a sizeable solvent induced charge separation at the transition state (0.63e on CF_3CO_2 in water as opposed to 0.42e in the gas phase). Nevertheless, the predicted solvent effect for the ester migration was much less than that observed experimentally, prompting Zipse to follow up on his earlier suggestion of acid catalysis. Protonation of the formyloxyethyl radical **455** led to **465** as the minimum energy structure. As might be expected, this leads to a lengthening of the C=O bond, a shortening of the O−CO bond, and a considerable stretching of the CH_2−OCO bond (1.640 Å vs 1.478 Å in **455**). The only pathway located for rearrangement of this distonic radical cation passed through the three-membered transition state **466**, with a barrier some 10 kcal mol^{-1} less than for the most favorable rearrangement pathway in the neutral parent system. It is noteworthy that the transition state **466** bears a close resemblence to those calculated by Golding and Radom (**460**) and Zipse himself (**461**) for the rearrangement of a protonated hydroxyethyl radical. The ultimate conclusion drawn from this computational study was that acid catalysis will be at least as important as solvation in accelerating β-(ester)alkyl rearrangements and that such catalysis will be, at least in part, responsible for the "scrambling" observed in isotopically labeled acyloxy groups. These suggestions have yet to be tested experimentally for rearrangement reactions but we note that Giese has recently suggested that intramolecular protonation of acetate groups may be responsible for the acceleration of fragmentation reactions of α-hydroxy-β-acetoxyalkyl radicals sometimes observed (**278**, section III.B.1).



Computational studies on the β-(phosphatoxy)alkyl migration have recently been reported for the first time by Zipse for radicals **467**−**469**.[195] At the Becke3LY/6 31G* level of theory the five- and three-membered transition states **470** and **471**, respectively, were located for the degenerate migration of

radical **467**. It was noted that **470** was qualitatively very similar to **458**, the five-membered transition state computed for migration of the formyloxyethyl radical at the same level of theory. However, charge separation in **470** is computed to be somewhat greater with the phosphate carrying −0.42e overall. The spin density in **470** was located mainly at the ethylene carbons. In the three-membered cyclic transition state (**471**) the phosphate only carried −0.32e of negative charge whereas +0.59 of the spin density was located at the ring oxygen. The calculations therefore suggest that the five-membered cyclic transition state (**470**) is akin to a loose complex of a phosphate anion with an ethylene radical cation, whereas its three-membered counterpart (**471**) is more like a complex of a phosphatoxy radical with ethylene. The barrier heights for rearrangement via **470** and **471** were identical (19.6 kcal mol^{-1}), pointing to the greater importance of the [1,2]-shift in phosphate esters as compared to carboxylate esters, in agreement with experiment. Somewhat surprisingly, however, and in distinct contrast to experiment, the absolute barrier heights for the phosphate shifts were found to be higher than those computed for comparable acyloxy systems. Very similar results were found with the dimethylphosphatoxy system **468**, prompting Zipse to suggest that the discrepancy between theory and experiment must lie in medium effects or in the substitution pattern of the substrate. Accordingly, calculations were conducted with the 2-phosphatoxy-1-propyl radical **469**. The transition states **472** and **473** were located 17.4 and 16.2 kcal mol^{-1}, respectively, above the starting radical, suggesting that, in this more substituted system, the [1,2]-shift would be favored. However, the charge and spin distributions were similar to those found in **470** and **471** with the greater charge separation found in the five-membered transition state. The lowering of the barrier height in **472** and **473** with respect to **470** and **471**, and indeed in **473** with respect to **472**, was attributed to a greater relief of steric strain compared to that found in the starting radicals. The overall conclusion from this study was that the [1,2]-shift will be a much more important pathway for the rearrangement of phosphatoxyalkyl radicals than for that acyloxyalkyl radicals, and that the [1,2]- and [2,3]-phosphate migrations will depend on substituent and solvent effects to differing extents.[195]

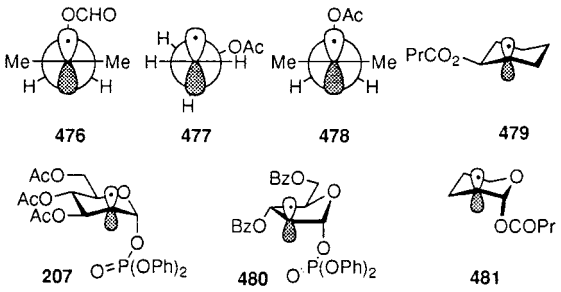
In the same study, Zipse also computed the transition state (**475**) for the direct syn elimination of the β-(phosphatoxy)alkyl radical **474** to H_3PO_4 and the allyl radical. The barrier for this rearrangment was found to be 22.7 kcal mol^{-1} and considerably lower than that for related closed-shell syn-eliminations of phosphate groups. The barrier is higher than that computed for simple 1,2- and 2,3-phosphate migrations (**470**−**473**), which should therefore be expected to predominate. However, any additional substituents which weaken the C−H bond cleaved in this fragmentation process will lower the activation barrier and perhaps render it competitive with the migration reaction. Indeed, Scheme 45 (section III.B) contains an apparent example of such a fragmentation.



One difference between the Beckwith/Radom and Zipse computational studies on the acyloxy rearrangement is the calculated ground-state geometry for the initial β-(formyloxy)ethyl radicals. Thus, Zipse finds a geometry **455** related to that of Beckwith and Radom (**454**) by an approximately 90° rotation about the ethyl C−C bond, with the C−O bond essentially coplanar with the singly occupied p-orbital, and so prealigned for the migration reaction (Scheme 55). This dichotomy is readily resolved by reference to the ESR literature.

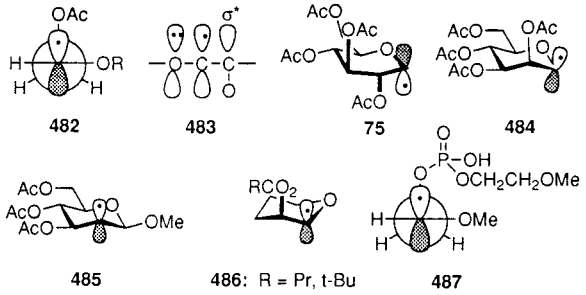
The β-(formyloxy)alkyl radical has been studied by ESR spectroscopy by Smith and collaborators[196] who find the hyperfine coupling to the two β-hydrogens to be 24.59 G, which is consistent with the conformation **454** located computationally by Beckwith and Radom. However, they also discuss conformation **455**, as advanced by Zipse, and suggest that there will be essentially free rotation about the C−C bond. Subsequent semiempirical calculations (INDO) by the same group also point to **454** as the preferred conformation and give a barrier to rotation about the C−C of ≤ 2.98 kcal mol^{-1}.[197] However, the corresponding 1-formyloxy-2-methylprop-2-yl radical, with its two extra methyl groups, only has β-hyperfine splittings of 12.98 G, suggesting a conformation (**476**), readily understood on steric grounds, in which the β-C−O bond eclipses the singly occupied p-orbital.[197] A similar situation is observed for other β-(acyloxy)-alkyl radicals. In their initial paper on the acyloxyalkyl migration, Beckwith and Tindall recorded the ESR spectrum of the β-(acetoxy)ethyl radical in aqueous solution, noted that the β-hyperfine splittings of 25.3 G were slightly smaller than those for the perpendicular β-hydroxyethyl radical (27.6 G), and suggested a conformation comparable to the latter, i.e., an almost perpendicular one (**477**).[49] Edge and Kochi generated the same radical, and the corresponding β-(benzoyloxy)ethyl system, in cyclopropane solution, and also reached the conclusion, on the basis of consideration of hyperfine splittings, that the perpendicular conformation (**477**) is preferred.[198] It was also noted, as with the formyloxyethyl radical, that the introduction of alkyl groups

at the radical center caused a reduction in β-hyperfine splittings, such that the 1-acetoxy-2-methylprop-2-yl radical was considered to have the ecplised conformation (**478**).[198] The conformation of the related cyclohexyl radical (**479**) was found by Beckwith and Duggan to be reminiscent of **477**, but this may simply be a reflection of the acyloxy substituent's overwhelming desire to be equatorial.[199,200] ESR spectra of simple, unsubstituted β-(phosphatoxy)ethyl radicals do not appear to have been recorded. The spectra of two carbohydrate based β-(phosphatoxy)-alkyl radicals, formed by rearrangement, have, however, been reported by Giese. Both **207** and **480** were found to have the β-C−O bond close to eclipsing the axis of the singly occupied p-orbital.[97] The related tetrahydropyranyl (β-acyloxy)alkyl radical (**481**) adopts a similar conformation.[199,200] This conformation in these particular radicals is probably more a reflection of the anomeric nature of the C−O bonds, forcing them to adopt an axial position, rather than of any interaction with the radical. It is likely that simple β-(phosphatoxy)ethyl radicals, like their β-hydroxy, β-chloro, and β-acyloxy counterparts, prefer a more perpendicular conformation.



Therefore, for simple non-heteroatom substituted β-(ester)alkyl radicals the picture is relatively clear: the ground state conformation has the β-C−O bond approximately perpendicular to the axis of the singly occupied p-orbital as in the calculations of Beckwith and Radom. Rotation about the C−C bond to give the eclipsed conformation, as required for migration, will have a minimal barrier of $\leq$3 kcal mol^{-1}, and this barrier will contribute to the activation energy of the rearrangement reaction. It is equally clear that β-(ester)alkyl radicals substituted as in **478** will be preorganized for rearrangement with a lower activation energy.

α-Alkoxy-β-(acyloxy)alkyl and related radicals, unlike the simple β-(acyloxy)alkyl radicals, prefer the eclipsed conformation (**482**).[110,201,202] This conformation was first put forward for α,β-dialkoxyethyl and α-alkoxy-β-(acyloxy)ethyl radicals by Gilbert and Norman from a study of hyperfine splittings. Support was subsequently provided by semiempirical molecular orbital calculations (INDO).[203] Later work by Beckwith and Brumby[204] and the Schulte-Frohlinde group[111] confirmed this observation, which is rationalized in terms of a stabilizing "extended anomeric interaction" between a lone pair on the α-oxygen, the singly occupied p-orbital, and the σ*-orbital of the β-C−O bond (**483**). The same effect is observed in carbohydrate based radicals, wherein the tetraacetyl-1-glucopyranosyl radical has been shown to adopt a flattened, possibly deformed, $B_{2,5}$ boat conformation (**75**) to accommodate this extended anomeric interaction.[205] By the same token, the tetraacetyl-1-mannopyranosyl radical retains the $^4C_1$ chair conformation (**484**).[205] Radicals located at other positions on the pyranose framework, for example, the 3,4,6-triacetyl-1β-methoxy-2-glucopyranosyl radical (**485**), retain the more perpendicular geometry of simple β-acyloxyalkyl radicals and a $^4C_1$ chairlike conformation.[206] The extended anomeric interaction also seems to operate in much less complicated cyclic systems, with the butyrate and even the bulky pivalate esters, (**486**) adopting an axial orientation, coplanar with the SOMO on the adjacent carbon.[199,200] By working in acetone solution, rather than the more polar water where fragmentation was too rapid, the Schulte-Frohlinde group were also able to observe the ESR spectrum of an α-methoxy-β-(phosphatoxy)ethyl radical and conclude that it, too, adopts the eclipsed conformation (**487**).[111] Again, the message is clear: in the absence of other constraints, β-(esteroxy)alkyl radicals bearing an oxygen substituent at the α-position will preferentially adopt a conformation prealigned for fragmentation and/or rearrangement, resulting in a corresponding reduced activation for these processes.

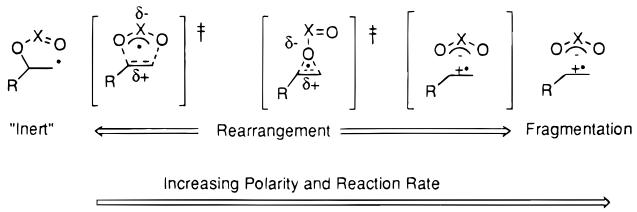


V. Overview of β-(Ester)alkyl Radical Reactions

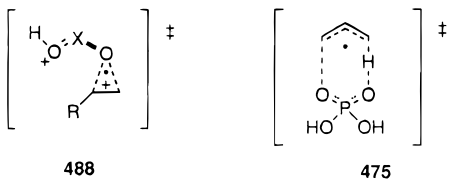
In their most recent discussion of the mechanism of the β-(ester)alkyl rearrangement Crich and Jiao have presented further evidence confirming the validity of their earlier suggestion[71] that the reaction generally proceeds in a nondissociative manner through two parallel competing polarized transition states representing three-electron−three-center and five-electron−five-center shifts.[103] Beckwith and Duggan have reached a very similar conclusion, namely, that a pathway involving a relatively nonpolar five-centered transition structure competes with another that proceeds either through a highly polarized three-centered transition structure or an intimate radical cation/anion pair.[164] Some papers[58,62,104,105] from both groups have been reviewed by Sprecher[207] who has suggested that the experimental results are consistent with a single mechanistic model involving the intermediacy of a contact ion pair or charge-transfer complex.

The picture that now emerges from the background is a satisfyingly comprehensive one which spans the full spectrum of β-(ester)alkyl radical chemistry. At the one extreme we encounter those β-(ester)alkyl radicals that are essentially inert to rearrangement or fragmentation, be it due to an inability to meet the stereoelectronic requirements or to support a polarized transition state or simply for lack of thermodynamic driving force. Moving across the spectrum we first encounter the relatively slow five-

Scheme 56



center−five-electron shift with its planar, somewhat polar transition state, then the more rapid three-center−three-electron shift with its more significantly polarized transition state. As the ability of the reactive system or medium to stabilize charge increases, we then encounter rearrangement by an intimate or contact radical ion pair as intermediate. Finally, at the other end of the continuum, we find separation of the radical ion pair such that the radical cation is susceptible to trapping by external nucleophiles, or deprotonation, so preventing recombination, i.e., the fragmentation reaction (Scheme 56). This general concept is related to, but not the same as, the continuum of more or less tightly associated ion pairs advocated by Sprecher.[207] There is, indeed, a continuum but one that includes three- and five-center open-shell pericyclic mechanisms. In protic solvents, in the light of the recent computations of Zipse,[194] this spectrum should probably be extended to include protonated three-membered ring transition states **488**. Concerted fragmentation processes leading directly to allylic radicals, via transition states like **475**, also have to be taken into account with certain substituent patterns.



488 **475**

Examples of alkyl radicals indifferent to the presence of a β-ester group are provided by **44** and **46** in Scheme 5 and by **172** in Scheme 18. The two examples of Scheme 5 lack any significant thermodynamic driving force for rearrangement and consequently would have to follow a more or less symmetric reaction profile with a relatively high activation barrier. In addition the low degree of substitution of the alkyl framework and the comparatively low acidity of the migrating group provide little opportunity to accommodate charge separation at the polarized transition. The radical derived from **172** provides an example with ample thermodynamic driving force and ability to sustain the charge-separated transition state for rearrangement but which is unable to proceed as the stereoelectronic needs of the migration require it to adopt a prohibitively high energy conformation.

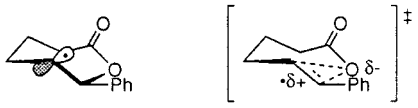
The five-center−five-electron pathway is followed by many β-(acyloxy)alkyl radicals, as exemplified by **404**, **410**, and **417**, in nonpolar media. Examples of rearrangements proceeding substantially by the three-center−three-electron mechanism, even in nonpolar solvents, are given by the stereochemically labeled phosphates **224**, **228**, **230**, and **233** and by the ^{18}O-labeled nitrate and sulfonate **425** and **427**. Phosphate, nitrate, and sulfonate esters are better able to accommodate negative charge on the migrating group at the transition state than carboxylate esters. Hence a greater proportion of the more polar three-electron−three-center mechanism is seen with these species. Steroidal systems **406/7** are examples of carboxylate esters rearranging predominantly through the three-center−three-electron mechanism. This is most probably due to the more substituted nature of the carbon framework, which is therefore able to carry the more substantial partial positive charge. Rearrangement through the three-center−three-electron pathway is entropically much less demanding than that by the five-center−five-electron route and hence, when the greater charge separation can be sustained, usually has the higher rate constant. Nowhere is this better illustrated than by the internal competition of Scheme 19, wherein phosphate migration, with its preference for the more polarized 1,2-shift, occurs to the exclusion of acetate migration.

Examples of rearrangements proceeding at least in part by caged, contact radical ion pairs are provided by **429** in *tert*-butyl alcohol (Scheme 54) and most likely by **412** with the partial scrambling of the label in the corresponding reduction product **413**. The change in mechanism with **429** on going from benzene or THF to *tert*-butyl alcohol (Scheme 54) serves to illustrate the delicate balance of the system. The change in mechanism between the rearrangement of **412** and of the comparable carbohydrate system (**410**), visible from the labeling studies (Table 10, entries 4 and 5) and the kinetic parameters (Table 2, entries 13 and 14), illustrates the effect of remote substituents. In effect, the additional acetoxy groups in **410** (and the corresponding radical **75**) inductively withdraw positive charge from the carbon framework and so retard rearrangement by the more polar three-electron−three-center and ion pair mechanisms. This is simply a more subtle manisfestation of the effect of a 2′-methoxy group on the fragmentation of a 4′-nucleotide radical as seen in Scheme 40.

Many examples of fragmentation reactions are provided by the nucleotide reactions (Schemes 34−37, 39, and 40). In these examples separation of the initial contact radical ion pairs is permitted by the stability of the negatively charged leaving group, the extensive delocalization of the radical cation, and the ability of the medium to individually support both charged species. Once separated, the radical cation rapidly undergoes attack by external nucleophiles.

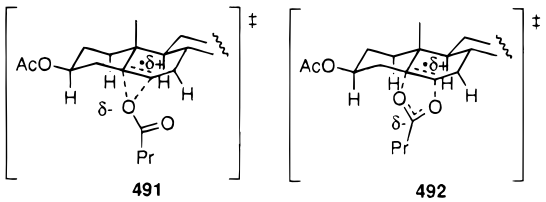
As noted above, those β-(ester)alkyl radicals in which the C−O bond is prealigned coplanar to the singly occupied p-orbital will have a reduced activation energy for rearrangement. This, as well as the three-membered transition state discussed above, doubtless helps account for the rapidity of the rearrangement of steroidal systems **406/7**. Similarly, we propose[86] that the apparent rapidity of contraction of lactone **113** (Scheme 9, Table 3, entry 3) may be accounted for by the initial radical adopting a conformation **489** prearranged for rearrangement via transition state **490**.

In the case of **406/7** there is also the possibility that the three-center−three-electron transition state **491** is additionally favored over the five-center equivalent



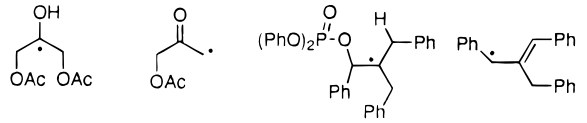
489 490

(**492**) due to steric compression,[58] i.e., the minimization of 1,3-diaxial type interactions with the axial hydrogens at C1, -3, -7, and -9.



491 492

Probable examples of concerted fragmentation reactions leading directly to allylic or heteroallylic radicals are provided by the fragmentations of radicals **275** to **276** and of **361** to **363** (Scheme 45).



275 276 361 363

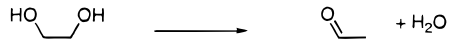
The above all-encompassing hypothesis removes the need for the rationalization promulgated earlier by two of us[71] for the three-center−three-electron/five-center−five-electron mechanistic dichotomy based on the syn/anti conformational equilibrium of esters and a Curtin−Hammett kinetic scheme. At the present time there is no further need to invoke rearrangement through higher energy anti-ester conformers except, of course, where they are imposed as in lactones such as **113** and the corresponding radical **489**.

VI. Related Reactions Involving Radical C–O Bond Shift and Cleavage

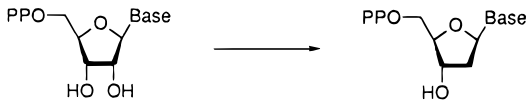
A. Rearrangement and Fragmentation of *β*-Hydroxyalkyl Radicals

In preparative free radical chemistry hydroxy and/or alkoxy substituents β to α-radicals, as with β-ester groups, are normally considered innocuous and devoid of rearrangements. Indeed, there are many examples of radical reactions in which such β-substituents are merely spectators. Occasionally,[208] β-alkoxy groups accelerate the formation of radicals by fragmentation of xanthate esters and related species, but experiment has shown[39] that this small effect is best rationalized in terms of the relief of steric or dipolar repulsions rather than of any interaction between the alkoxy group and the forming radical center. Evidence has begun to accumulate that hydroxy,[209,210] and other,[211] substituents may play a role in determining the stereochemistry of radical cyclizations through conformation-limiting hydrogen bonds. β-Methoxyalkyl radicals undergo 6-exo-trigonal cyclizations almost an order of magnitude faster than simple unsubstituted analogues, but this acceleration is readily rationalized in terms of a conformation effect and does not require a specific interaction of the oxygen group with the radical.[212] Comparable α,β-dimethoxy radicals, however, cyclize more slowly, and this is attributed to an extended anomeric effect (section IV.C.5, **483**).[202,212] However, as is often the case, nature provides the exceptions to the rule and so generates the need for further reflection and experiment: β-hydroxyalkyl radicals and, more especially, α,β-dihydroxyalkyl radicals are of considerable interest because of their apparent rearrangement and/or fragmentation in several enzymic processes. Pertinent among these are diol dehydrase,[213−216] which converts glycols into aldehydes (Scheme 57), and the ribonucleotide reductases,[216−218] responsible for the biosynthesis of deoxyribonucleotides from ribonucleotides (Scheme 58).

Scheme 57



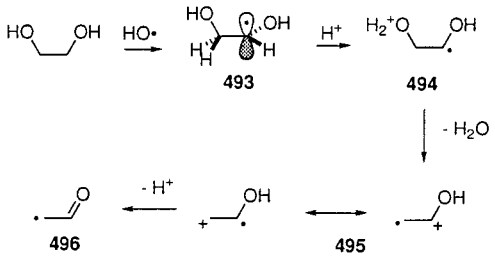
Scheme 58



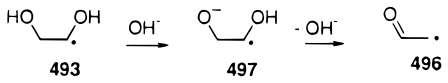
There is an extensive literature on both classes of enzymes covering the contributions of many groups and which we do not attempt to survey here. Rather, this section simply outlines the basic chemistry of β-hydroxyalkyl radicals as ascertained from model experiments and computational studies in order to permit identification of parallels with that of the β-ester substituted alkyl radicals, and to provide guidelines for synthetic applications.

ESR spectroscopic investigations were conducted by several groups using various techniques. After some initial confusion, it was recognized that the spectral parameters of the α,β-(dihydroxy)ethyl radical (**493**) generated from ethylene glycol by hydrogen atom abstraction with alkoxy radicals were the same whether these latter were obtained with a Ti(III)/hydrogen peroxide system[110] or by simple photolysis of hydrogen peroxide.[219] This radical (**493**) adopts an eclipsed conformation (**483**) owing to the extended anomeric interaction.[202] Both groups of workers recognized that the intensity of the signal for **493** was a function of the acidity of the medium and that under more strongly acidic conditions **493** rapidly rearranged to the formylmethyl radical **496**. Similar observations were made by other groups using the γ-radiolysis technique for the generation of the initial, hydrogen-abstracting, hydroxyl radical.[220−222] Using Fenton's reagent as a source of hydroxyl radical, Walling and Johnson carried out product studies over a range of pHs and confirmed that the formation of acetaldehyde (and so radical **496**) was indeed subject to acid catalysis.[223] The rough consensus of opinion among the various groups (Scheme 59) was that radical **496** was formed by protonation of the initial radical (**493**) on the β-hydroxy group, giving **494**, followed by expulsion of water giving a radical cation (**495**),[224] and eventual deprotonation. Walling perspicaciously pointed out that the fragmentation step would not only be accelerated by protonation of the leaving group but also by substituents capable of stabilizing the radical cation.[223]

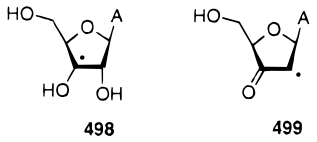
Scheme 59



Scheme 60



The fragmentation is also accelerated under basic conditions. It has been suggested that this is due to deprotonation of the α,β-dihydroxyalkyl radical (Scheme 60).[222] Indeed, Lenz and Giese have recently found that the rate constant for elimination of water from radical **498**, giving **499**, increases by approximately two orders of magnitude in going from pH 5 to 8 in buffered aqueous acetonitrile. The rate of elimination was also found to increase with increasing concentration of triethylammonium acetate buffer. These authors were therefore led to conclude that the elimination is subject to general base catalysis and occurs most readily from the radical anion.[114]

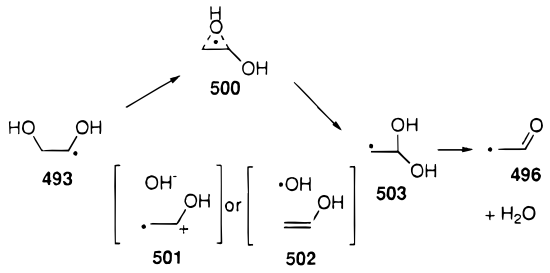


It is readily appreciated that in the absence of acid or base catalysis fragmentation/rearrangement will therefore usually not be observed. This nicely explains the absence of such reactions in most preparative schemes involving β-hydroxy and α,β-dihydroxyalkyl radicals which are normally conducted in neutral, aprotic solutions. However, numerous examples of related dehydrative rearrangements of α,β-dihydroxyalkyl radicals and hydroxyalkoxylalkyl radicals are to be found in the ESR literature in both simple model systems and complex carbohydrates and nucleosides. These examples are characterized by the use of protic solvents, usually water, and acidic media.[111,127,224−228]

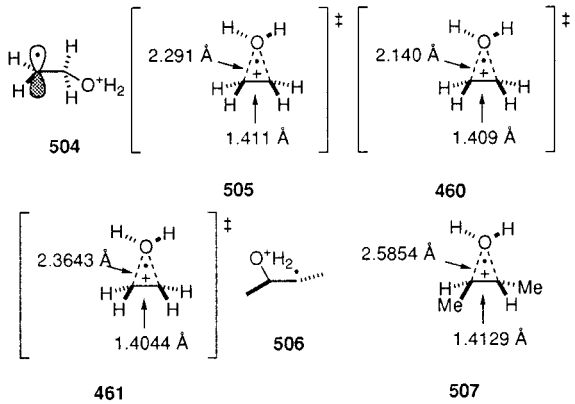
These entirely reasonable, acid- or base-catalyzed mechanisms, however, do not account satisfactorily for the diol dehydrase promoted version of this same reaction. Labeling studies indicated that, in the enzyme catalyzed reaction, up to 50% of the oxygen from the hydroxy group β to the radical is retained in the carbonyl group of the product.[213] Thus, the notion arose of a migration through a three-centered transition state (**500**) or by a fragmentation followed by a rapid in-cage recombination (**501** or **502**), both giving a β,β-dihydroxyalkyl radical (**503**) followed by expulsion of water (Scheme 61).

The problem was addressed computationally by Golding and Radom who could find no cyclic structure, transition state, or intermediate lower in energy than the sum of the separate ethylene and hydroxyl radical moieties that might account for the degenerate rearrangement of the β-hydroxyethyl radical.

Scheme 61



They therefore concluded that if this (uncatalyzed) rearrangement does occur it must do so by a fragmentation recombination pathway.[191] These authors next considered the possibility that the rearrangement might be acid catalyzed. The preferred conformation of the protonated β-hydroxyethyl radical was found to be the perpendicular one **504**, not unlike that found experimentally for β-hydroxy and β-alkoxyethyl radicals in polar and nonpolar solvents.[229,230] The barrier to rotation about the C−C bond was estimated to be 2−3 kcal mol^{-1}. Two cyclic structures (**505** and **460**), of similar energy and resembling complexes of water with the ethylene radical cation, were located as possible transition states. These structures were approximately 17.4 kcal mol^{-1} more stable than water and the ethylene radical cation, which suggests that, were this rearrangement to occur, it would do so via one of the two cyclic structures as transition state rather than via a polar fragmentation recombination process. The activation barrier for such a rearrangement in the gas phase was found to be 8 kcal mol^{-1}. Golding and Radom therefore came to the conclusion that "whereas 1,2-shifts in simple radicals are likely to occur via a dissociation−recombination process mechanism, an intramolecular rearrangement is favored when the radicals are protonated".[191] Zipse has recently revisited the interaction of water with the ethylene radical cation, using higher levels of theory. This author located a bound structure (**461**) similar to Golding and Radom's **460**, although with somewhat longer partial C−O bonds, lying 21.7 kcal mol^{-1} below the separate water and ethylene radical cation and 4.39 kcal mol^{-1} above the protonated hydroxyethyl radical.[192] The influence of substituents was emphasized when it was found that the cyclic structure **507** is actually a minimum, lower in energy than the protonated 3-hydroxy-2-butyl radical **506**.[192]

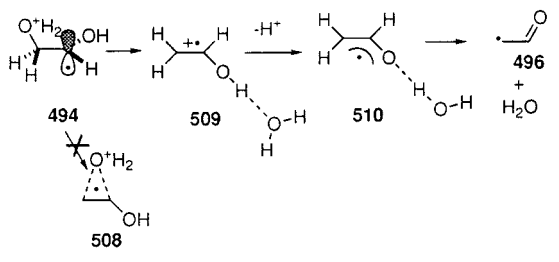


Ab initio calculations have also been undertaken recently on the protonated α,β-dihydroxyethyl radical

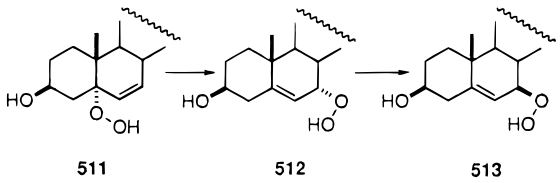
(**494**). In this study, Glusker and co-workers found no three-membered ring structure (**508**), either as an intermediate or transition state, along the reaction coordinate for rearrangement.[231] Rather, the initial radical **494** was transformed without activation to a hydrogen bonded hydrate of the vinyl alcohol radical cation (**509**), a local minimum on the energy surface. In this calculation, the system then evolves by loss of a proton to give a hydrate (**510**) of the formylmethyl radical, which may dissociate to the formyl methyl radical (**496**) and water or, after hydrogen transfer, to acetaldehyde and water (Scheme 62).[231] The significance of this study, aside from the lack of a three-membered transition state, is the absence of formation of a hemiacetal, or gem-diol, type species, of the formylmethyl radical, prompting the authors to speculate about alternative, nonradical mechanisms for the diol dehydrase enzyme.

With the exception of the computational results depicted in Scheme 62, the parallels between the chemistry of β-hydroxyalkyl radicals and β-esteralkyl radicals are striking. β-Esteralkyl radicals rearrange and/or fragment through highly polarized transition states that resemble carboxylates (or phosphates, nitrates or sulfonates, etc.) loosely bound to alkene radical cations with the faster shifts preferring the more polarized 1,2-transposition. β-Hydroxyalkyl radicals, after protonation, either fragment to water and the alkene radical cation or rearrange through a protonated three-membered transition state. As pointed out by Walling,[223] the reactions will be accelerated by the ability of the carbon framework to support positive charge. It would seem entirely reasonable to suggest that, as in the case of the β-(ester)alkyl radicals, there is a continuum of mechanisms ranging from (i) protonated three-membered cyclic transition states, such as those calculated by Golding and Radom and Zipse, to (ii) mechanisms involving fragmentation to an actual alkene radical cation and a water molecule in a solvent cage followed by recombination, to (iii) dissociation of the cage pair and interception of the alkene radical cation by external nucleophiles. Increasing ability of the alkene-like moiety to support positive charge would lead to greater radical cation character, then the cage mechanisms, and eventually cage leakage. Clearly, the medium will also have a considerable effect on the precise location of a given system within this spectrum of mechanisms. This will be all the more so for reactions taking place within the microenvironment of an enzyme active site. Thus, it is readily envisaged that the active site of diol dehydrase is such as to support the concerted, three-membered shift, or a cage pair mechanism, but is devoid of nucleophiles suitably placed to intercept the charged intermediates. On the other hand, the ribonucleotide reductases, with active site cysteine residues, promote the fragmentation mechanism and divert the mechanism to the overall reduction observed.

Scheme 62



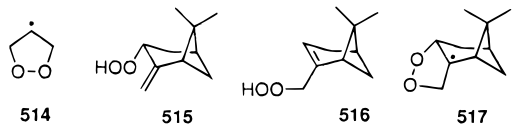
Scheme 63



B. Schenck or Allylperoxy Radical Rearrangement

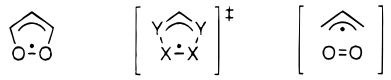
In 1958 Schenck described a novel rearrangement of a steroidal allylic hydroperoxide (**511**) to its regioisomer (**512**).[232,233] Subsequently, it was shown by Smith that a second, slower rearrangement provides the stereoisomer (**513**) of the product (Scheme 63).[234] Over the years, numerous examples of this apparent [2,3]-allylic hydroperoxide rearrangement have been recorded in both acyclic and cyclic systems.[235−245] Further examples of epimerization, as in **512** → **513**, have also been described.[246] Aspects of the rearrangement have been reviewed[247,248] and approximate rate constants determined by competition reactions.[249,250]

From the beginning it was noted by the various groups in the area that the rearrangement frequently required an initiation period, could be facilitated by the use of typical radical initiators, and was inhibited by 2,6-di-*tert*-butyl-4-methylphenol. This led, naturally enough, to the formulation of the reaction as a radical chain sequence. The first concrete mechanistic proposals were put forward by Brill, who suggested a stepwise mechanism involving 5-endo-trig ring closure of an initial hydroperoxy radical to give a 1,2-dioxolan-4-yl radical (**514**), followed by a ring-opening step.[236] Subsequent work, by the same author, with the pinene hydroperoxides **515** and **516**, mitigated against such a mechanism as the anticipated intermediate radical **517** neither was trapped by oxygen nor underwent cleavage of the strained cyclobutane ring.[241] Shortly thereafter, the final nail in the coffin of this stepwise mechanism was driven by Porter and Zuraw, who demonstrated that unambiguously generated 1,2-dioxolan-4-yl radicals could be readily trapped by oxygen and did not suffer ring opening to allylperoxyl radicals.[251]



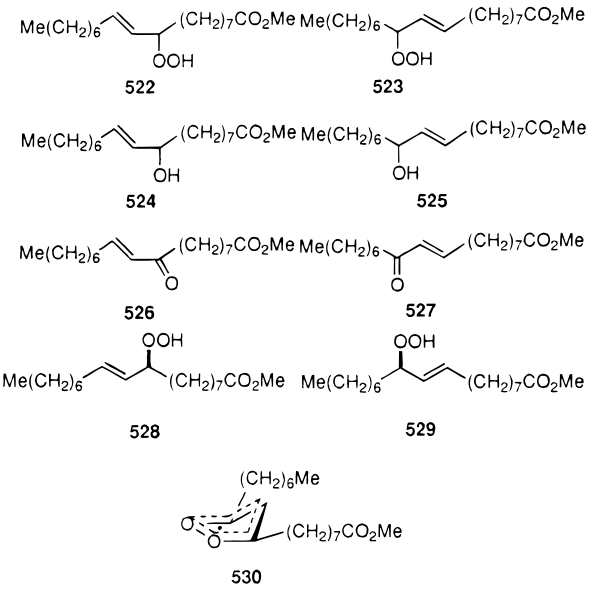
Alternative hypotheses were therefore advanced. Brill suggested that allylic hydroperoxy radicals might best be regarded as ring-closed species with the single electron located in an O−O π*-orbital (**518**),[241] whereas Porter and Zuraw considered the possibility of a concerted mechanism through a transition state (**519**) not unlike Brill's intermediate.[251] Both groups also recognized the possibility of a stepwise mechanism involving fragmentation of the initial allylperoxyl radical to a cage pair of oxygen and an allyl radical (**521**). Hence, the unifying

mechanistic hypothesis arose that the β-(acyloxy)-alkyl rearrangement and the allylperoxyl rearrangement represent different facets of the same basic mechanisms and indeed present the same conundrum—both reactions involve either intimate cage pairs or concerted 2,3-shifts proceeding via the closely related transition structures **519** and **520**.



518 **519**: X = O, Y = C; **520**: X = C, Y = O **521**

In an attempt to distinguish between concerted and cage pathways Davies and Beckwith conducted the rearrangement of **511** to **512** under an atmosphere of $^{36}O_2$ and observed no incorporation of the label in the product. On the other hand, the rearrangement of **512** to **513**, under the same conditions, did lead to the incorporation of labeled oxygen.[252,253] Parallel oxygen labeling experiments by Porter and Wujek with the oleate hydroperoxide **522** provided a series of products (**523**−**527**) with no discernible exchange with atmospheric oxygen.[254] Both groups were therefore led to conclude that the rearrangement most likely took place by a concerted [2,3]-shift, although the cage pathway could not be conclusively excluded. Subsequent experiments by the Porter group with the resolved methyl oleate hydroperoxide **528**, in hexane solution at 40 °C, resulting in the formation of **529** with essentially complete retention of stereochemical integrity, were fully consistent with the labeling studies. A cyclic transition state (**530**) was thought to best accommodate the results.[255]



522 **523** **524** **525** **526** **527** **528** **529** **530**

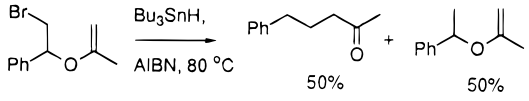
A subsequent computational study by Boyd and coworkers, however, cast doubt on this hypothesis. By use of high level molecular orbital calculations, it was shown, in agreement with experiment, that while the 1,2-dioxolan-4-yl radicals (**514**) are minima on the energy surface, the barrier to their formation by closure of an allylperoxyl radical, and their opening, is prohibitively high. More importantly, it was determined that structures such as **519** and **530** were neither minima nor maxima on the energy surface and consequently neither transition states nor intermediates in the allylperoxy rearrangement. The lowest energy pathway was determined to be fragmentation to give an allyl radical and oxygen within a solvent cage (**521**).[256] Thus stimulated, in the seminal work, Porter and co-workers reinvestigated the rearrangements of **528** and **529** in solvents of different viscosity, at different temperatures, and in the presence of $^{36}O_2$. It was found that the use of higher temperatures and/or less viscous solvents led to an erosion of stereochemical integrity, both in the recovered substrate and the product, and that this epimerization was paralleled by the uptake of atmospheric oxygen.[257] However, even the results of these sophisticated experiments do not by themselves preclude unambiguously the possibility of the rearrangement proceeding by two concurrent competing pathways, one a fast concerted process involving the transition structure and the other a slower dissociation−recombination.[258] Indeed, very recent work by Porter and Lowe with a regiospecifically monolabeled allyl hydroperoxide provides convincing evidence for the existence of the concerted five-center−five-electron pathway under some, but not all, reaction conditions.[259]

Thus, in the final analysis, it seems apparent that the allylperoxy rearrangement exhibits, if not a continuum of mechanisms, at least dual reaction pathways. Furthermore, it seems that there will be a very fine line dividing the five-center−five-electron shift and the fragmentation/in cage recombination mechanism and that switching between these two manifolds will be a subtle function of substituents and conditions. The parallel rearrangement of pentadienyl radicals also occurs via a fragmentation/recombination mechanism but, as expected for the more extensively delocalized pentadienyl radical intermediate, allows much more facile exchange with atmospheric oxygen.[260−262] Finally, it may be pertinent that computational scrutiny of rearrangements proceeding through a four-membered cyclic transition state or through an intimate allyl carbocation−superoxide ion pair appears not to have been conducted, nor has the possibility of oxygen scrambling through a three-membered transition structure.

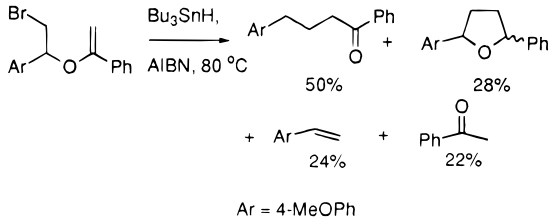
C. β-(Vinyloxy)alkyl to 4-Ketobutyl Rearrangement

In a quest for synthetically useful C−C bond-forming reactions, Crich and Yao studied the rearrangements of 2-(vinyloxy)alkyl radicals, reactions superficially related to the β-(ester)alkyl radical rearrangements.[263] The precursor bromides were readily prepared by application of the Tebbe or related reactions to β-(acyloxy)alkyl bromides. A number of such derivatives were synthesized and treated dropwise with tributyltin hydride and AIBN in benzene at reflux. In a number of cases, as in the example of Scheme 64, the anticipated rearrangement was observed, although yields never exceeded 50%. In other cases, particularly those derived from

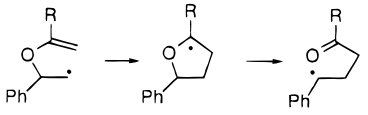
Scheme 64



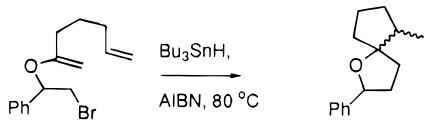
Scheme 65



Scheme 66



Scheme 67



application of the Tebbe reaction to benzoate esters, tetrahydrofurans were found to be significant byproducts (Scheme 65). Intriguingly, with the same substrates an apparent radical fragmentation was also a side reaction.

The isolation of tetrahydrofurans naturally aroused the suspicion that these rearrangements take place via a two step mechanism (Scheme 66) in which the initial radical (**531**) undergoes 5-endo-trigonal ring closure to a tetrahydrofuranyl radical (**532**) followed by a retro-5-endo-trigonal ring opening to **533**. Such 5-endo-trigonal processes are usually considered to be stereoelectronically disfavored,[264,265] very slow, and of little preparative value. As with all such rules, exceptions are known,[266−271] but few of these are sufficiently rapid to be synthetically useful. Recent work from the laboratories of Ishibashi,[272−275] Malacria,[276] Clive,[277] Chatgilialoglu,[278] and Tanaka,[279] however, serves to illustrate the potential of such processes. Also of note is the work of Ingold,[280] and the related precedent from Janzen,[281,282] illustrating the very rapid ($k = 2 \times 10^8$ s^{-1} at 45 °C) 5-endo-trig cyclization of 2-formylbenzoyl and related radicals.

Subsequent work with a 5-hexenyl-substituted derivative **534** resulted in complete suppression of the rearrangement reaction and the isolation of a spirocyclic product **535** (Scheme 67).[283] The stepwise pathway, via the tetrahydrofuranyl radical intermediate, was therefore firmly established, and the rate constant for the migration was demonstrated to be very significantly less than that of a typical 5-hexenyl cyclization.

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