# Dichotomy of Mechanism in the Rearrangment of β-(Acyloxy)alkyl Radicals

**Athelstan L. J. Beckwith* and Peter J. Duggan**

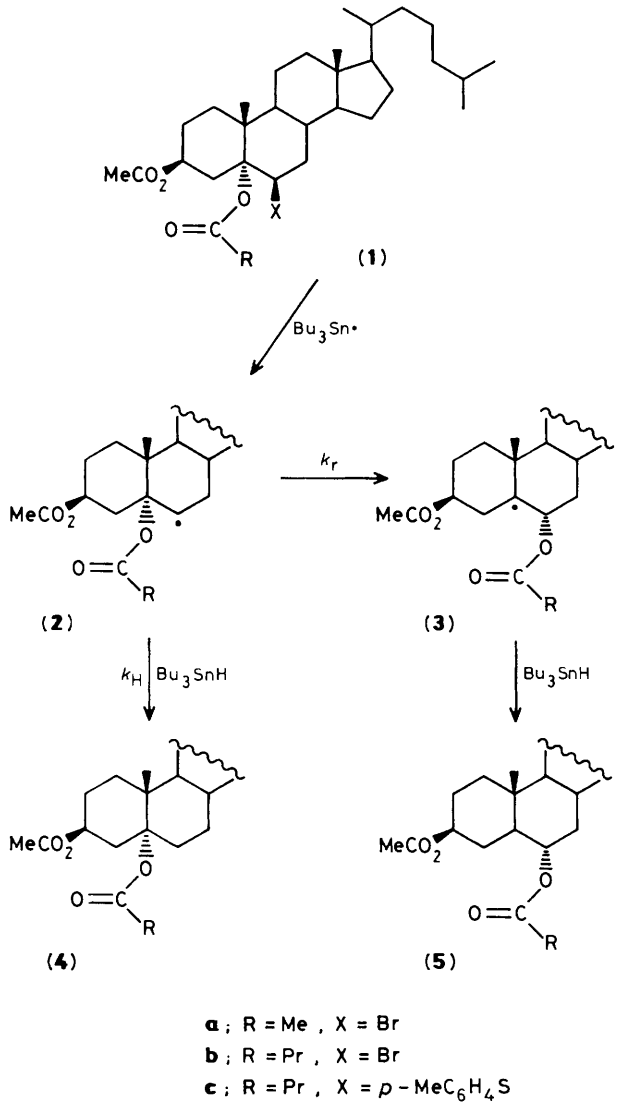
*Research School of Chemistry, Australian National University, GPO Box 4, Canberra, A.C.T. 2601, Australia*

Differences between the rate constants and $^{18}O$ distribution for the rearrangements of the β-(acyloxy)alkyl radicals (**2b**) and (**7b**) suggest that the first is a pericyclic reaction whereas the second proceeds through an anion–radical cation ion pair.

Suitably constituted β-(acyloxy)alkyl radicals undergo 1,2-migration of the acyloxy group.[1—10] All earlier mechanistic studies[4—8] indicated that the reaction is concerted and proceeds through a five-membered cyclic transition state to afford products in which the carbonyl and ether oxygen atoms of the starting material become interchanged. However, in the most recent study[9] the radical generated from an $^{18}O$-labelled sample of the cholesterol derivative (**1a**) gave products with a labelling pattern incompatible with this mechanism. In an attempt to resolve this discrepancy we have conducted further kinetic and $^{18}O$-labelling experiments: the results indicate that the rearrangement can occur by at least two different mechanisms.

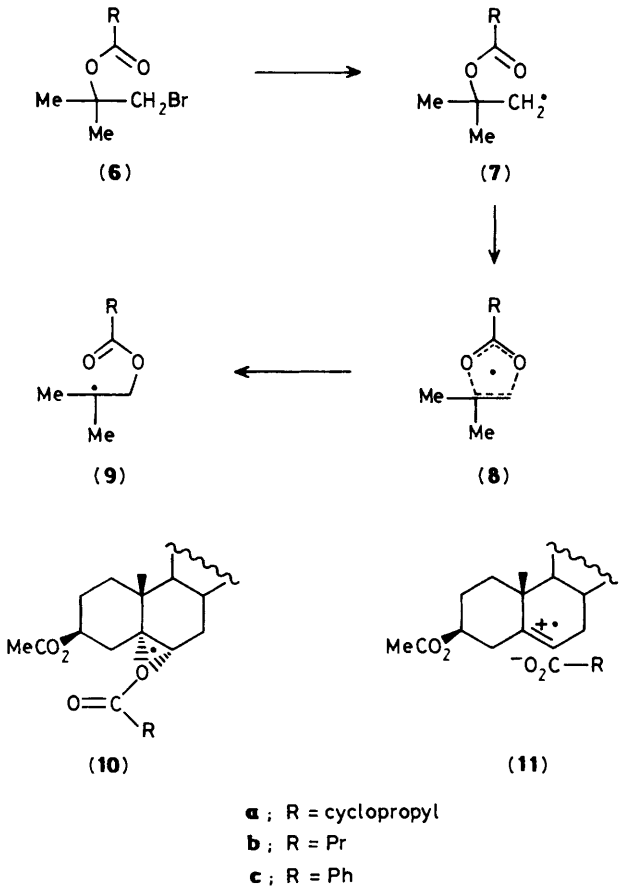
Heating of the bromo ester (**1b**)† with tributylstannane and azoisobutyronitrile (AIBN) in benzene gave a mixture of unrearranged and rearranged esters (**4b**) and (**5b**) which was accurately analysed by h.p.l.c. Values of $k_r/k_H$ were obtained

† All new compounds gave spectral and analytical data consistent with the assigned structures.




**a**; R = Me, X = Br
**b**; R = Pr, X = Br
**c**; R = Pr, X = *p*-$MeC_6H_4S$

**Scheme 1**




**a**; R = cyclopropyl
**b**; R = Pr
**c**; R = Ph

by substitution of the data into the kinetic equation $k_r/k_H$ = $[Bu_3SnH]P/U$, obtained by steady-state treatment of the proposed mechanism (Scheme 1), where $P/U$ is the ratio of yields (**5b**) (%)/(**4b**) (%) and $[Bu_3SnH]$ is the concentration of stannane (used in large excess). Experiments were conducted at four different temperatures with three different concentrations at each temperature (*e.g.* at 60 °C $[Bu_3SnH]$ = 0.108, 0.203, and 0.404 mol $dm^{-3}$). Typical values of $k_r/k_H$ were 0.012, 0.055, 0.176, and 0.410 mol $dm^{-3}$ at 8, 33.5, 60, and 80 °C, respectively. Linear regression analysis of the data gave $\log(k_r/k_H) = (5.58 \pm 0.38) - (9.64 \pm 0.56)/2.3RT$ (mol $dm^{-3}$). Addition of the Arrhenius parameters for hydrogen atom transfer from tributylstannane to cyclohexyl ($\log A/s^{-1}$ mol$^{-1}$ $dm^3$ = 9.24 ± 0.03; $E_{act}$ = 3.97 ± 0.04 kcal $mol^{-1}$)[11] gave $\log k_r/s^{-1} = (14.82 \pm 0.38) - (13.6 \pm 0.56)/2.3RT$, from which $k_r = (1.9 \pm 1.1) \times 10^6\ s^{-1}$ at 75 °C. These data are very different from those ($\log k_r = 13.2 - 16.8/2.3RT$; $k_r = 5.1 \times 10^2\ s^{-1}$ at 75 °C) previously determined for rearrangement of the acyclic radical (**7a**).[7]

Identical results were obtained when the sulphide (**1c**) was used as the precursor of the radical (**2b**); clearly the mechanism of the rearrangement does not involve loss of the bromo or the arylthio substituent in a kinetically significant step. In none of these experiments was the 6β-epimer of the rearranged product detected.

For comparison with the earlier work, the butyrate (**6b**) was treated with tributylstannane in the usual way. The values of $k_r$ for the rearrangement (**7b**) → (**9b**) were very similar to those reported for the rearrangement of the radical (**7a**).[7]

When the bromo ester (**1b**) specifically enriched (35%) in the butyrate carbonyl group with $^{18}O$ was treated under appropriate conditions with tributylstannane it gave products (**4b**) and (**5b**) in which all the label was retained. In accord with the recent report,[9] $^{13}C$ n.m.r. spectroscopy detected the label in only the butyrate carbonyl oxygens of both products. Similarly, reduction of the labelled product (**4b**) with lithium aluminium hydride afforded only unlabelled cholestane-3β,5α-diol. However, reduction of (**5b**) gave cholestane-3β,6α-diol containing (by accurate mass spectrometry) about 23% of the label present in the starting material. It thus appears that n.m.r. spectroscopy is not sufficiently sensitive for the accurate determination of $^{18}O$ in such samples.

As an additional check on earlier work[5] in which the distribution of $^{18}O$ in products from the labelled ester (**6c**) was determined by mass spectrometry, the butyrate (**6b**) enriched with $^{18}O$ (*ca.* 35%) at the carbonyl oxygen was treated with tributylstannane. $^{13}C$ N.m.r. spectroscopy detected $^{18}O$ at only the carbonyl oxygen of the unrearranged product and at only the ether oxygen of the rearranged product. These results are in full agreement with the earlier results and support the mechanism previously suggested[5] for rearrangement of β-(acyloxy)alkyl radicals.

However, both the isotopic labelling studies and the fact that the rate constant is more than three orders of magnitude greater than that for the acyclic radical (**7b**) indicate that the

rearrangement of the steroid-derived radical (**2b**) proceeds by a different mechanism. One possibility is that the rearrangement proceeds by a direct 1,2-shift of the acyloxy group through a three-membered cyclic transition structure (**10**). There is, however, no precedent for such a process. Alternatively, the mechanism may involve the intermediacy of an anion–radical cation ion pair (**11**) which is sufficiently tight to prevent complete randomisation of the ether and carbonyl oxygen atoms, or migration of the acyloxy group to the β-face of the molecule. Such a mechanism is compatible with the kinetics of rearrangement of strongly electron-attracting acyloxy groups,[7] and has some similarity to the mechanism of rearrangement of radicals derived from 1,2-diols.[12]

In summary, there are two mechanisms for the rearrangement of β-(acyloxy)alkyl radicals. Simple acyclic systems such as (**7**) undergo slow rearrangement through a five-membered transition structure. Like the recently reported rearrangement of allylperoxyl radicals[13] this is formally a pericyclic reaction‡ of an open-shell system. The steroid radical (**2**), possibly because of steric compression, undergoes rearrangement much more rapidly, either through a three-membered cyclic transition structure, or more probably *via* a tight anion–radical cation ion pair.

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‡ A referee has suggested that the term 'mesopericyclic' would be more appropriate for an open-shell reaction.

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