The Mechanism of the β-(Acyloxy)alkyl Radical Rearrangement: Substituent and Solvent Effects

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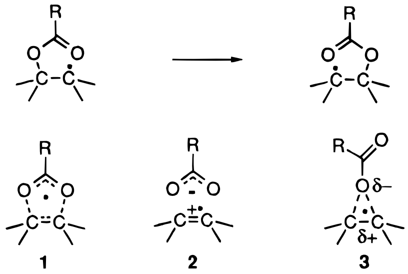
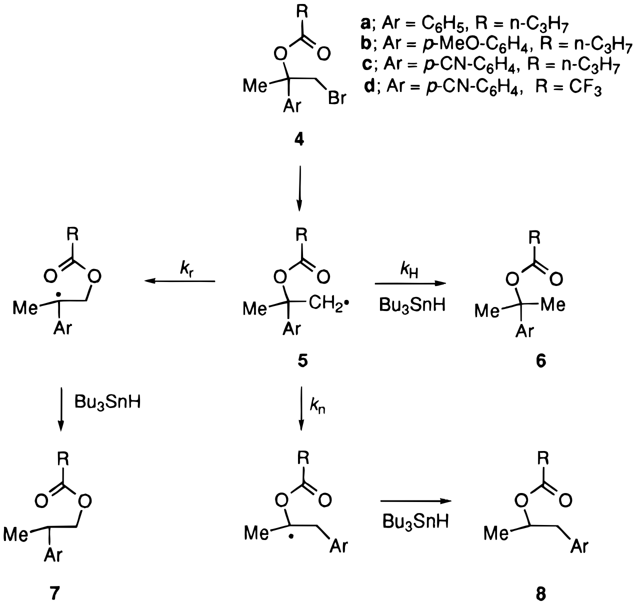
Ever since it was first reported,[2] the β-(acyloxy)alkyl radical rearrangement (Scheme 1), an intramolecular process that has no intermolecular analog, has attracted almost continuous mechanistic investigation. Early results indicated that it involves a five-membered cyclic transition structure (**1**) and hence can be regarded as an open shell pericyclic process.[3] However, more recent work on this and related rearrangements[3,4] has supported the view that the mechanism might sometimes involve a tight radical-cation/anion pair (**2**) and/or a three-membered cyclic transition structure **3**.[3,4c,5] These conclusions have been based on the comparison of results from widely different systems. In order to obtain a more cohesive set of data, we have now examined the substituent effects, the solvent dependence, and the product distribution of an ^{17}O label for a single type of β-(acyloxy)alkyl radical.

The 2-(butanoyloxy)-2-phenylpropyl radical **5a** was chosen as the parent system (Scheme 2) because (a) the rearrangement of the corresponding acetate is known to proceed smoothly;[6] (b) it has a molecular weight amenable to labeling studies that employ ^{17}O NMR spectroscopy;[3] (c) the rearrangement rate was expected to be in a range suitable to be measured accurately by the tributyltin hydride method;[3,5] (d) substituent effects could be readily examined by changing substitution on the phenyl ring; and (e) it undergoes a neophyl rearrangement that is relatively insensitive to polar effects[7] and hence can be used as a kinetic yardstick for calibration of the rates of rearrangement of **5a** and its substituted derivatives.

Scheme 1



Scheme 2



In the usual way,[3,5,8] the bromide **4a**[9] was treated with Bu$_3$SnH (0.0156−0.125 M) and AIBN (2,2′-azobisisobutyronitrile) in benzene at various temperatures (11.5−100.0 °C), and the yields of **6a**, **7a**, and **8a**[9] were accurately determined by GC. The usual treatment of the data[10] gave $\log[(k_r/k_H)/\mathrm{M}] = (3.24 \pm 0.36) - (8.34 \pm 0.55)/2.3RT$ and $\log[(k_n/k_H)/\mathrm{M}] = (1.37 \pm 0.72) - (7.35 \pm 1.2)/2.3RT$ where k_r and k_n are the rate constants for the β-(acyloxy)alkyl and the neophyl rearrangements, respectively. Substitution of the Arrhenius parameters for k_H, the rate constant for the reaction of Bu$_3$SnH with neopentyl radical[11] gave the temperature dependence for k_r and k_n (eqs 1 and 2).

$$\log[(k_r)/\mathrm{s}^{-1}] = (11.7 \pm 0.5) - (11.0 \pm 1.3)/2.3RT \quad (1)$$

$$\log[(k_n)/\mathrm{s}^{-1}] = (9.9 \pm 0.8) - (10.1 \pm 2.0)/2.3RT \quad (2)$$

The log A terms for k_r and k_n are both somewhat smaller than those previously reported for these types of reactions[3,5,12] but the rate constant k_r at 75 °C ($6.2 \times 10^4\ \mathrm{s}^{-1}$) is mid-range for a β-(acyloxy)alkyl rearrangement.[3] However, the neophyl migration rate constant k_n at 75 °C ($3.6 \times 10^3\ \mathrm{s}^{-1}$) for **5a** is somewhat smaller than usual.[12]

Solvent effects were determined by measuring the relative rate constants k_r/k_H and k_n/k_H at 75 °C in six solvents.[13] Correlation of the results (Table 1) with the solvent polarity parameter E_T[14] gave $\log[(k_r/k_H)/\mathrm{M}] = 0.020E_T - 2.793$ and $\log[(k_n/k_H)/\mathrm{M}] = -0.004E_T - 3.135$. Since k_n is virtually independent of solvent polarity,[7] k_H must show a weak solvent dependence. Normalization against the value of log k_H[11] in

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[2] Surzur, J. M.; Teissier, P. *C. R. Acad. Sci., Ser. C* **1967**, *264*, 1981. Surzur, J. M.; Teissier, P. *Bull. Soc. Chim. Fr.* **1970**, 3060. Tanner, D. D.; Law, F. C. P. *J. Am. Chem. Soc.* **1969**, *91*, 7535.

[3] Beckwith, A. L. J.; Duggan, P. J. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1673 and references cited therein.

[4] (a) Wilt, J. W.; Keller, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 1395 (ester migration onto a silyl radical). (b) Crich, D.; Filzen, G. F. *J. Org. Chem.* **1995**, *60*, 4834 (rearrangement of β-(nitroxy)alkyl and β-(sulfonatoxy)alkyl radicals). (c) Crich, D.; Yao, Q.; Filzen G. F. *J. Am. Chem. Soc.* **1995**, *117*, 11455. Crich, D.; Jiao, X.-Y. *J. Am. Chem. Soc.* **1996**, *118*, 6666 (phosphate ester migration). (d) Crich, D.; Yao, Q. *Tetrahedron* **1994**, *50*, 12305 (rearrangement of β-(vinyloxy)alkyl radicals).

[5] Beckwith, A. L. J.; Duggan, P. J. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1777.

[6] Beckwith, A. L. J.; Thomas, C. B. *J. Chem. Soc., Perkin Trans. 2* **1973**, 861.

[7] Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, pp 170 −174.

[8] Second-order conditions were employed (0.95 equiv of Bu$_3$SnH). The following equations were also used: $[\mathbf{7}]_{\mathrm{final}}/[\mathbf{8}]_{\mathrm{final}} = k_r/k_n$; $k_R = k_r + k_n$; $[\mathbf{7}]_{\mathrm{final}} + [\mathbf{8}]_{\mathrm{final}} = (k_R/k_H)\ln\{([\mathrm{Bu_3SnH}]_{\mathrm{init}} + k_R/k_H)/([\mathrm{Bu_3SnH}]_{\mathrm{final}} + k_R/k_H)\}$.

[9] All new compounds were characterized by ^{1}H and ^{13}C NMR, IR, MS, and HRMS or microanalysis.

[10] Product ratios were determined at four different stannane concentrations at each of four temperatures for the ester migration and at each of three temperatures for the neophyl rearrangement.

[11] Johnston, L. J.; Lusztyk, J.; Wayner, D. D. M.; Abeywickreyma, A, N.; Beckwith, A. L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 4594.

[12] Lindsay, D. A.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1984**, *106*, 7087.

[13] The rate constants for reactions in benzene at 75 °C were calculated from the Arrhenius parameters. The others were averages of three to five determinations, each at different stannane concentrations.

[14] Reichardt, C. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 29.

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Table 1. Kinetic Data for the Rearrangement of **5a** in Various Solvents at 75 °C

solvent	E_T	$10^{-6}\,k_H$ ($M^{-1}\,s^{-1}$)	$10^{-4}\,k_r$ (s^{-1})
C_6H_{12}	30.9	6.17	3.7
C_6H_6	34.5	6.37	6.4
DME	38.2	6.60	5.8
DMF	43.8	6.95	8.4
EtOH	51.9	7.48	13.0
MeOH	55.5	7.74	16.4

benzene gave $\log[k_H/M^{-1}\,s^{-1}] = 0.004E_T + 6.667$. Values of k_H determined from this equation were used to determine the values of k_r given in Table 1. A plot of the data for k_r gave $\log[k_r/s^{-1}] = 0.024E_T + 3.882$ ($r = 0.978$). This indicates a weak dependence of k_r on solvent polarity by comparison with purely ionic reactions but a substantial one for a radical reaction.

For a limited survey of substituent effects the rate constants k_r and k_n for the *p*-methoxy- and *p*-cyano-substituted radicals **5b**[9] and **5c**[9] were determined at 75 °C[15] by the stannane method and compared with those for **5a**. As expected for a reaction with little polar character, k_n for **5b**, **5a**, and **5c** (7.6, 3.8, and $100 \times 10^3\ s^{-1}$, respectively) correlated well with Creary's radical substituent parameter[16] ($\sigma_c^\bullet$) but not with σ_p^+. However, in accord with the view that the ester migration involves a polar transition structure, k_r for **5b**, **5a**, and **5c** (16.9, 6.0, and $1.6 \times 10^4\ s^{-1}$, respectively) showed a good correlation ($r = 0.985$) with σ_p^+, the ρ value (−0.71) being substantial for a radical reaction. As expected for a substrate (**5d**) containing the highly electron-attracting trifluoroacetoxy group, k_r at 75 °C ($2.5 \times 10^6\ s^{-1}$) was relatively large (cf., butyrate **5c** $k_r = 1.6 \times 10^4\ s^{-1}$).[17]

Although the solvent and substituent effects clearly support the hypothesis that the β-(acyloxy)alkyl radical rearrangement of **5a** involves a polarized transition state and/or intermediate, the key question remains of whether the mechanism changes with change of solvent or substitution.

In an attempt to resolve this question, the three radical precursors **4a**−**c** labeled with ^{17}O mainly in the carbonyl group[18] were treated with Bu_3SnH and AIBN.[3,5] The labeling patterns in the bromides and the rearranged products **6a**−**c** were determined by the ^{17}O NMR method.[3] The results (Table 2) reveal that under conditions that do not greatly favor a highly polarized transition state or an intermediate similar to **2** (e.g., the rearrangements of **5a** and **5c** in benzene), complete transposition of the ester oxygens occurs. Under conditions that do favor such a polarized transition state or intermediate (e.g., rearrangement of **5b** in benzene and of **5a** in methanol), considerable scrambling of the ester oxygens occurs. However, attempts to trap intermediate radical-cation/anion pairs such as **2** with methanol or with benzoate or azide anions were unsuccessful.

Table 2. Rearrangement of ^{17}O-Labeled Substrates

		^{17}O distributions in % (^{17}O NMR chemical shift)[a]			
		substrate[b]		rearranged[c]	
solvent	radical	-C=O	-O-	-C=O	-O-
C_6H_6	**5a**	84 (370)	16 (160)	14 (346)	86 (162)
C_6H_6	**5b**[d]	100 (368)		39 (346)	61 (160)
C_6H_6	**5c**[e]	100 (375)			100 (160)
CH_3OH	**5a**	84 (370)	16 (160)	33 (346)	67 (162)

[a] The ppm values are relative to external ^{17}O H_2O. [b] Compound **4**. [c] Compound **7**. [d] Heating of **4b** in benzene for an extended period did not result in any detectable scrambling of the ester oxygens. [e] The labeling pattern in **7c** was determined from a mixture of **6c**, **7c**, and **8c**, the ratios of which were determined accurately by GC.

The significance of the present work is that it clearly establishes a relationship between electronic environment, rearrangement rate, and the degree of oxygen scrambling in a *single system*. Conditions expected to favor the formation of dipolar transition states or intermediates accelerate the rate of the rearrangement and increase the degree of scrambling of the ether and carbonyl oxygen atoms in the migrating acyloxy group.

The most straightforward interpretation is that radicals such as **5** can undergo an acyloxy shift by more than one mechanism. One of these must be relatively nonpolar in nature and involves a five-membered transition state similar to **1**.[19] Another must be relatively dipolar and may involve a radical-cation/anion pair similar to **2** or a highly polarized version of **3**. Indeed, **2** and **3** can reasonably be regarded as variations of the same contact radical-cation/anion pair arising from differing degrees of tightness. It has recently been suggested[20] that all of these reactions proceed by essentially one mechanism involving the collapse of an intermediate contact radical-cation/anion pair. However, until this hypothesis can be further explored experimentally, we believe that the concept of a dichotomy of mechanism agrees best with all the available evidence, both experimental and computational.[21]

Supporting Information Available: Details of the synthesis of substrates and products and descriptions of kinetics and analytical methods (14 pages). See any current masthead page for ordering and Internet access instructions.

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(15) Rate constants were calculated from an average of four determinations, each at a different stannane concentration.

(16) Creary, X.; Mehrsheikh-Mohammadi, M. E.; McDonald, S. *J. Org. Chem.* **1987**, *52*, 3254.

(17) A similar difference in rates for the rearrangement of radicals containing the acetate or trifluoroacetate group has been previously recorded: Barclay, L. R. C.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1984**, *106*, 1793.

(18) ^{17}O-Butyryl chloride was prepared as described previously[5] and heated with the appropriate bromohydrin in dimethylaniline at 50−70 °C. The labeled product was isolated by means of flash chromatography.

(19) The five-membered transition state **1** is thought to have *some* polar character: Beckwith, A. L. J.; Radom, L.; Saebo, S. *J. Am. Chem. Soc.* **1984**, *106*, 5119.

(20) Sprecher, M. *Chemtracts*: *Org. Chem.* **1994**, *7*, 120.

(21) Zipse, H. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1797.