form if a cis vacancy is present, a trans vacancy being too remote to allow such interaction. Since 405-nm photolysis also leads to **3** within the laser pulse duration but via the lower LF state (expected to give trans CO dissociation), it appears that trans to cis interconversion of the vacant site must occur within a few nanoseconds. These conclusions are summarized in Scheme II. Our resonance Raman results, however, permit no definitive conclusions about the rate of internal conversion[11] (IC) between the two $^1B_2$ states shown. If IC were too slow to compete with CO dissociation induced by 360-nm photolysis, species **3** would form rapidly from the cis CO loss entity within the duration of the laser pulse. If IC were fast enough to compete with CO loss, this would result in population of the lower lying LF state which, as the experiments at 405 nm suggest, would again lead to formation of **3** within the laser pulse duration. Thus no unequivocal statement can be made about the rate of IC between the two LF states.

Summary

Laser flash photolysis at 354.7 nm in the ligand field absorption region of $(CO)_5W{=}C(OMe)Ph$ in solution results in prompt formation of a transient with a microsecond lifetime. Evidence for primary photodissociation of CO is presented, in agreement with earlier steady-state photolysis studies,[8] but the transient decay is independent of CO concentration in solution. It is concluded on the basis of both kinetic and resonance Raman spectroscopic evidence that the transient is the result of rapid intramolecular rearrangement, within the laser pulse duration, in the primary CO-dissociated photofragment. This rearrangement "blocks" the vacant coordination in the latter, by way of a proposed two-electron, three-center interaction between the electron-deficient tungsten and the C-H bond of the OMe group. The interaction distinguishes the chemical and kinetic behavior of the transient from that of the initial, coordinatively unsaturated entity, $[(CO)_4W{=}C(OMe)Ph]$, while at the same time allowing the carbene ligand skeleton effectively to retain its integrity. Although the mechanism for decay of the transient remains a matter for speculation, its essential nature as expressed in the previous sentence is an important conclusion. A significant part of the evidence for it derives from a central feature of resonance Raman spectroscopy, namely, that the observed pattern of enhancement in vibrational modes can be linked to resonance with a particular electronic transition, hence enabling well-founded identification of a key chromophore in the scattering species. The present study shows that this "localization" of structural information, which is a natural feature of RR spectroscopy, can be turned to substantial advantage in elucidating the nature of transient species.

We are currently extending the RR and kinetic investigations to analogues of the Fischer complex and are also examining the possibility of probing the carbonyl vibrational modes as a complement to transient IR methods.

Acknowledgment. We thank the SERC for equipment grants for the Nd/YAG laser and optical multichannel analysis system at Queen's University of Belfast, for a postdoctoral research assistantship (to S.E.J.B.), and for access to the Laser Support Facility. The assistance of the staff at the Facility in setting up the resonance Raman experiments is also gratefully acknowledged. K.C.G. thanks the Department of Education (N. Ireland) for a postgraduate studentship and the Queen's University of Belfast for the award of an Andrews Studentship. We also wish to thank Professor J. J. Rooney for several very useful discussions.

Registry No. 1, 37823-96-4; **1**-d_3, 109388-47-8; **2**, 85221-50-7; CH_2Cl_2, 75-09-2; *n*-hexane, 110-54-3; benzene, 71-43-2; acetonitrile, 75-05-8.

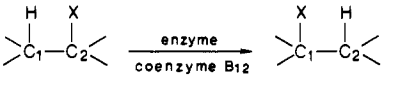
1,2-Migrations in Free Radicals Related to Coenzyme B_{12} Dependent Rearrangements

Susan Wollowitz and Jack Halpern*

Contribution from the Department of Chemistry, The University of Chicago, Chicago, Illinois 60637. *Received August 26, 1987*

Abstract: The free radicals $XC(CH_3)(COOR)CH_2^{\bullet}$, where X = C(=O)Me (**1**), C(=O)SEt (**2**), C(=O)OEt (**3**), $C(=CH_2)Me$ (**4**), and C_6H_5 (**5**), were generated by reaction of the corresponding bromides with $(n\text{-}Bu)_3SnH$. The rates of rearrangement involving 1,2-migration of X (to form $^{\bullet}C(CH_3)(COOR)(CH_2X)$) were measured in competition with trapping by $(n\text{-}Bu)_3SnH$. The measurements yielded the following rearrangement rate constants, k_r, and activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$: (**1**) 1.2×10^4 s^{-1} at 45 °C, 11.0 kcal/mol, −4 cal/mol·K; (**2**) 23.5 s^{-1} at 60.5 °C, 13.8 kcal/mol, −11 cal/mol·K; (**3**) <10 s^{-1} at 113 °C; (**4**) 3.0×10^5 s^{-1} at 45 °C, 10.0 kcal/mol, −2 cal/mol·K; (**5**) 5.0×10^3 s^{-1} at 61 °C. From the results of crossover experiments it is concluded that the rearrangements of **1** and **2** are intramolecular processes, probably proceeding through cyclopropyloxy radical intermediates or transition states. The carbanions corresponding to **1**–**5** (i.e., $XC(CH_3)(COOR)CH_2^-$, generated by reduction of the corresponding bromides with sodium naphthalene) also rearrange rapidly but, in each case, with some contribution from migration of the ester group. This represents the first demonstration of spontaneous 1,2-migration of a thioester group in a free radical and models the coenzyme B_{12} dependent methylmalonyl-CoA mutase rearrangement. The results support a free-radical rearrangement mechanism for the latter reaction.

Coenzyme B_{12} (5′-deoxyadenosylcobalamin, abbreviated $AdCH_2{-}B_{12}$) serves as a cofactor in several enzymatic reactions, a common feature of which is the interchange of a hydrogen atom and another substituent [X = OH, NH_2, C(=O)S–coenzyme A, $C(=CH_2)COOH$, or $CH(NH_2)COOH$] on adjacent carbon atoms, as depicted schematically by eq 1.[1,2]



(1)

Several lines of evidence have provided persuasive support for a mechanistic scheme, the minimal features of which are depicted by eq 2 and 3.[2-5]

$$AdCH_2{-}B_{12} \overset{\text{enzyme}}{\rightleftharpoons} AdCH_2^{\bullet} + B_{12_r} \qquad (2)$$

An aspect of the mechanism that continues to be controversial is whether the rearrangement step itself, i.e., the 1,2-migration of X, actually occurs at the free-radical stage (i.e., $S^{\bullet} \rightarrow P^{\bullet}$, directly), as depicted in eq 3, or via additional intermediates (for

(1) For leading references, see: (a) Dolphin, D., Ed. *B_{12}*; Wiley: New York, 1982. (b) "Vitamin B_{12}", *Proc. Eur. Symp., 3rd* **1979**.
(2) Halpern, J. *Science (Washington, D.C.)* **1985**, *227*, 869, and references cited therein.
(3) Babior, B. M. *Acc. Chem. Res.* **1975**, *8*, 376.
(4) Golding, B. T. Reference 1a, Vol. 1, p 543, and references cited therein.
(5) Abeles, R. H. Reference 1b, p 373.

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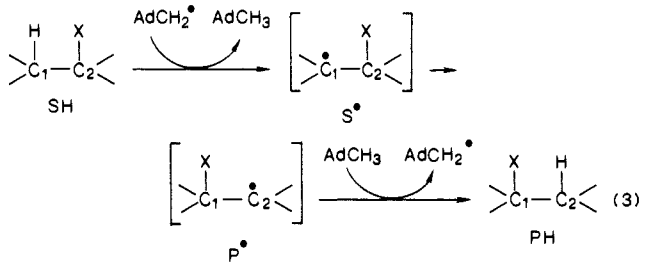
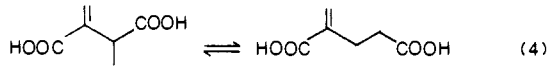
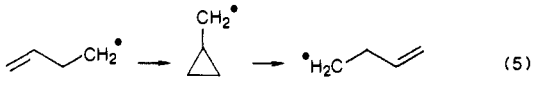


(3)

example, carbanions, carbonium ions, or organometallic adducts). Only in the case of the α-methyleneglutarate mutase reaction (eq 4) has the corresponding 1,2-migration, i.e., of a vinyl group, previously been observed directly in model radicals (eq 5).[6]

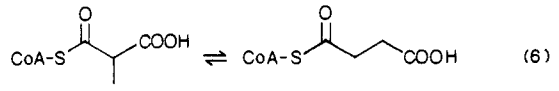


(4)



(5)

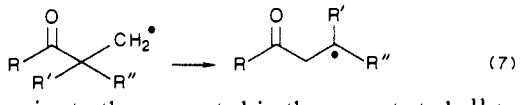
Accordingly, alternative rearrangement mechanisms involving additional intermediates, including carbanions, carbonium ions, or organometallic species, have been proposed (e.g., $S^{\bullet} \rightarrow S^{-} \rightarrow P^{-} \rightarrow P^{\bullet}$; $S^{\bullet} \rightarrow S^{+} \rightarrow P^{+} \rightarrow P^{\bullet}$; or $S^{\bullet} + B_{12r} \rightarrow S\text{-}B_{12} \rightarrow P\text{-}B_{12} \rightarrow P^{\bullet} + B_{12r}$).[7] There have been several reports of attempts to identify such paths, for example for the methylmalonyl-CoA mutase reaction (eq 6), by independently generating such putative



(6)

intermediates or analogues thereof, notably organocobalt adducts such as ["Co"$CH_2C(CH_3)$(COSEt)(COOEt)] (where "Co" = cobalamin or a related cobalt complex).[8] Decomposition of such adducts under a variety of conditions (thermal, photochemical, reductive) yielded, after workup, products that included some derived from 1,2-migration of the thioester group,[8] a result of possible relevance to the coenzyme B_{12} dependent methylmalonyl-CoA mutase reaction. However, the results of such studies have failed to identify conclusively the mechanism of the migration step.

A few examples of 1,2-migrations of carbonyl substituents in radicals (eq 7) have previously been reported,[9] including one recent kinetic study involving migration of the $C(=O)C(CH_3)_3$ group.[10] Such rearrangements have been limited to migrations of acyl or aroyl groups [C(=O)R, R = alkyl or aryl].



(7)

Attempts, prior to those reported in the present study,[11] to demonstrate unequivocally the corresponding 1,2-migration of an ester or thioester group [C(=O)OR or C(=O)SR] were unsuccessful,[6,9d,12-14] raising questions about whether migration of the thioester group in the methylmalonyl-CoA mutase reaction (eq 6) actually occurs at the free-radical stage. In this connection it is noteworthy that the methylmalonyl-CoA mutase reaction is relatively slow (k_{cat} = ca. 10^2 s^{-1} at 30 °C)[16] compared with typical free-radical lifetimes in prior studies on model radical rearrangements. Accordingly, failure to observe thioester group migration in such studies does not convincingly argue against a free-radical rearrangement mechanism for the methylmalonyl-CoA mutase reaction.

To probe whether a substrate free radical (or appropriate model thereof) would rearrange spontaneously on the time scale of the enzymic reaction calls for generating the free radical unambiguously, under conditions where its lifetime is fairly long ($\geq 10^{-2}$ s) and, preferably, susceptible to measurement and systematic variation. Furthermore, it is desirable to accomplish this in the absence of any cobalt complexes to eliminate the issue, which has complicated previous studies, of possible cobalt participation in such rearrangements. This paper describes such studies involving migration of a thioester group in a free radical that models that derived from the substrate of the methylmalonyl-CoA mutase reaction. Also reported are the results of related studies on the migrations of other carbonyl groups and on rearrangements of corresponding carbanions.

Results

General Procedures. Our method for measuring the rates of free-radical rearrangements parallels that previously used in related studies by Walling and others.[17] The radicals of interest (R•) were produced by reaction of the parent bromides with $(n\text{-Bu})_3Sn^{\bullet}$, generated in a chain reaction initiated by oxidation of $(n\text{-Bu})_3SnH$ with AIBN (2,2′-azobisisobutyronitrile). The rate of radical rearrangement to R′• (k_r) was then measured in competition with that of trapping by $(n\text{-Bu})_3SnH$ (k_t, eq 8–10).

$$(n\text{-Bu})_3SnH \xrightarrow{\text{AIBN}} (n\text{-Bu})_3Sn^{\bullet} \quad (8)$$

$$RX + (n\text{-Bu})_3Sn^{\bullet} \rightarrow R^{\bullet} + (n\text{-Bu})_3SnX \quad (9)$$

$$R^{\bullet} \xrightarrow[k_t]{(n\text{-Bu})_3SnH} RH + (n\text{-Bu})_3Sn^{\bullet} \quad (10a)$$

$$R^{\bullet} \xrightarrow[k_r]{} R'^{\bullet} \xrightarrow{(n\text{-Bu})_3SnH} R'H \quad (10b)$$

According to this scheme,

$$d[RH]/d[R'H] = k_t[(n\text{-Bu})_3SnH]/k_r \quad (11)$$

Previously measured values of k_t, ca. 2.5×10^6 M^{-1} s^{-1} at 25 °C, have been found to be relatively insensitive to the identity of R•.[18] Assuming this value for k_t permits k_r to be deduced from eq 11.

For fast radical rearrangements, it is permissible for $[(n\text{-Bu})_3SnH]_i$ to be much larger than $[RX]_i$ and, hence, $[(n\text{-Bu})_3SnH]$ remains essentially constant ($=[(n\text{-Bu})_3SnH]_i$) during the course of reaction. Under these conditions, we obtain eq 12 (where i = initial and f = final).

(6) (a) Beckwith, A. L. J.; Ingold, K. In *Rearrangements in the Ground State and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980; Vol. 1, p 161, and references cited therein. (b) Effio, A.; Griller, D.; Ingold, K. U.; Beckwith, A. L. J.; Serelis, A. K. *J. Am. Chem. Soc.* **1980**, *102*, 1734.

(7) Halpern, J. Reference 1a, Vol. 1, p 502, and references cited therein.

(8) (a) Scott, A. I.; Kang, K. *J. Am. Chem. Soc.* **1978**, *99*, 1977. (b) Scott, A. I.; Kang, J.; Dalton, D.; Chung, S. K. *J. Am. Chem. Soc.* **1978**, *100*, 3603. (c) Scott, A. I.; Hanson, J. B.; Chung, S. K. *J. Chem. Soc., Chem. Commun.* **1980**, 388. (d) Scott, A. I.; Kang, J.; Dowd, P.; Trivedi, B. K. *Bioinorg. Chem.* **1980**, *9*, 227. (e) Grate, J. H.; Grate, J. W.; Schrauzer, G. N. *J. Am. Chem. Soc.* **1982**, *104*, 1588.

(9) For example: (a) Karl, C. L.; Maas, E. J.; Reusch, W. *J. Org. Chem.* **1972**, *37*, 2834. (b) Tada, M.; Miura, K.; Okabe, M.; Seki, S.; Mizumi, H. *Chem. Lett.* **1981**, 33. (c) Okabe, M.; Osawa, T.; Tada, M. *Tetrahedron Lett.* **1981**, *22*, 1899. (d) Tada, M.; Akinaga, S.; Okabe, M. *Bull. Chem. Soc. Jpn.* **1981**, *55*, 3939. (e) Bertini, F.; Caronna, T.; Grossi, L.; Minisci, M. *Gazz. Chim. Ital.* **1974**, *104*, 471.

(10) Lindsay, D. A.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1984**, *106*, 7087.

(11) A preliminary account of some of the work reported in this paper has previously appeared: Wollowitz, S.; Halpern, J. *J. Am. Chem. Soc.* **1984**, *106*, 8319.

(12) Retey, J. Reference 1b; p 439.

(13) Lewis, S. N.; Miller, J. J.; Winstein, S. *J. Org. Chem.* **1972**, *37*, 1478.

(14) Prior attempts to observe 1,2-migration of a thioester group in a free radical include studies by Aeberhard et al.[15] on the photolysis and thermolysis of the perester $(CH_3)_3CO_3CCH_2CH(COOEt)(COSEt)$, a potential precursor of the $^{\bullet}CH_2CH(COOEt)(COSEt)$ radical. No rearranged product resulting from thioester migration was observed when the perester was photolyzed in hexane at room temperature. Thermolysis in cumene at 140 °C yielded only a trace (ca. 0.1%) of the rearranged thiosuccinate ester, $EtS(CO)CH_2CH_2COOEt$.

(15) Aeberhard, U.; Keese, R.; Stamm, E.; Vogeli, V. R.; Lau, W.; Kochi, J. K. *Helv. Chim. Acta* **1983**, *66*, 2740.

(16) (a) Kellermeyer, R. W.; Allen, S. H. G.; Stjernholm, R.; Wood, H. G. *J. Biol. Chem.* **1964**, *239*, 2562. (b) Overath, E. R.; Kellerman, G. M.; Lynen, F. *Biochem. Z.* **1962**, *336*, 77. (c) Canata, J. J. B.; Focesi, A.; Mazumder, R.; Warner, R. C.; Ochoa, S. *J. Biol. Chem.* **1965**, *240*, 3249.

(17) Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1972**, *94*, 6059.

(18) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739.

$$[RH]_f/[R'H]_f = k_t[(n\text{-Bu})_3SnH]_i/k_r \quad (12)$$

For slow radical rearrangements, the $(n\text{-Bu})_3SnH$ concentration must be kept as low as possible to slow the trapping rate and increase the radical lifetime. Under these conditions, i.e., with $(n\text{-Bu})_3SnH$ as the limiting reagent ($[RX]_i > [(n\text{-Bu})_3SnH]_i$), the $(n\text{-Bu})_3SnH$ concentration no longer remains approximately constant during the course of the reaction, and eq 11 must be integrated to take account of its variation. The resulting expression is[19] eq 13.

$$[R'H]_f = \frac{k_r}{k_t} \ln \left[\frac{k_t[(n\text{-Bu})_3SnH]_i}{k_r} + 1 \right] \quad (13)$$

Most of the measurements reported in this paper were made under these conditions, k_r/k_t being deduced from eq 13 by an iterative procedure. In practice this permitted rearrangement rate constants (k_r) as low as 5 s^{-1} (25 °C) to be determined. For the case of migration of $-C(CH_3)=CH_2$, k_r was measured under both limiting conditions to demonstrate consistency.

Particularly when k_r is small, it is appropriate to consider the error introduced into such determinations of k_r by contributions from *unrecognized additional* competing reactions of R·. If a third reaction of R·, e.g., eq 14, competes with those of eq 10a

$$R\cdot \xrightarrow{k_p} ? \rightarrow \rightarrow \text{stable products (P)} \quad (14)$$

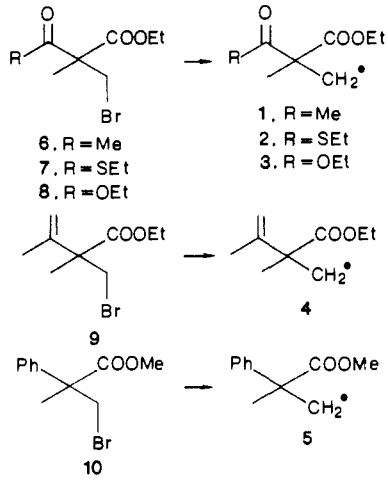
and 10b, then the concentrations of final products, R'H and P, will be given by eq 15, which yields eq 16.

$$[R'H]_f + [P]_f = \frac{k_r + k_p}{k_t} \ln \left[\frac{[(n\text{-Bu})_3SnH]_i k_t}{k_r + k_p} + 1 \right] \quad (15)$$

$$[R'H]_f = \frac{k_r}{k_t} \ln \left[\frac{[(n\text{-Bu})_3SnH]_i k_t}{k_r + k_p} + 1 \right] \quad (16)$$

Thus, if an unrecognized third reaction is occurring, the value of k_r/k_t calculated iteratively (see below) from eq 13 will be in error. In fact the contribution from k_p must be substantial ($k_p \geq k_r$) before this error becomes significant. The following example refers to a case where $k_r = 100$ s^{-1} at 25 °C, i.e., sufficiently slow that unpredicted side reactions might become competitive. At 25 °C, $k_r/k_t = 4.3 \times 10^{-5}$ M. If $k_p = k_r$, the value of k_r/k_t *calculated* from eq 13 would be 5.0×10^{-5} M, i.e., in error by only ca. 15%. If $k_p = 10k_r$, the value of k_r/k_t calculated from eq 13 would be 7.3×10^{-5} M, i.e., less than a factor of 2 in error. The influence of such a side reaction on the material balance would be apparent long before the error in k_r/k_t became significant.

Our studies encompass the free radicals **1–5**, generated from the corresponding bromides, **6–10**.



(19) Equation 6 in ref 17 contains a typographical error. The correct form is given by our eq 13. We are grateful to Professor C. Walling for confirming this.

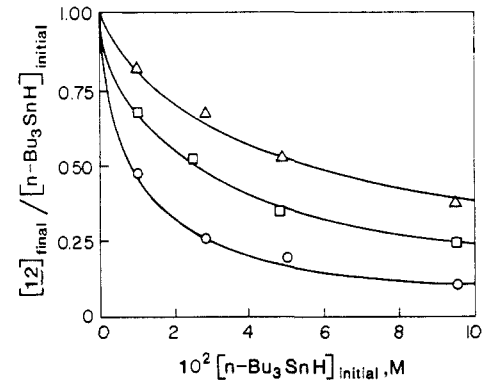
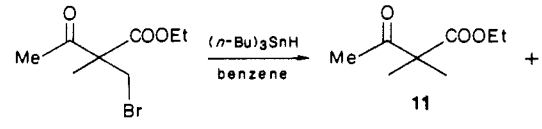
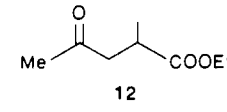


Figure 1. Plots of $[12]_f/[(n\text{-Bu})_3SnH]_i$ vs $[(n\text{-Bu})_3SnH]_i$ in benzene at 45 °C (△), 71 °C (□), and 96 °C (○). The points denote experimental values. The curves are calculated with eq 13 and the "optimal fit" values of k_r/k_t from Table I (3.2×10^{-3}, 9.6×10^{-3}, and 21.9×10^{-3} M, respectively).

1–3 were selected to explore the migratory aptitudes of various carbonyl groups; **2** serves as a model for the methylmalonyl-CoA mutase substrate. **4** serves as a model for the radical derived from α-methyleneglutarate (eq 4). **5** was examined in the context, discussed below, of differentiating between radical and anionic rearrangement pathways. The carbonyl-containing radicals **1–3** have previously been invoked in model studies on coenzyme B_{12} dependent enzymic rearrangements. Methyl substitution adjacent to the radical site eliminates disproportionation as a side reaction.

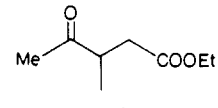
Rearrangement of the Me(C=O)C(CH$_3$)(COOEt)CH$_2$· Radical (1). The β-acetyl radical **1**, generated from the bromide **6**, was found to undergo rearrangement involving 1,2-migration of the acetyl group in accord with eq 17.



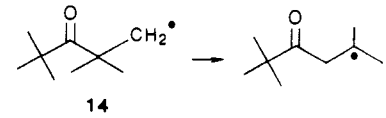


(17)

The results of our measurements on this system are summarized in Table I and Figure 1. The rearrangement is fast ($k_r = 1.6 \times 10^4$ s^{-1} at 45 °C), and even with $[(n\text{-Bu})_3SnH]_i$ as high as 0.1 M, the rearranged species **12** accounted for 13% of the total product. Figure 1 depicts the experimental data for the yields of **12** vs $[(n\text{-Bu})_3SnH]_i$ at several temperatures together with calculated curves representing the optimal fits to the data of eq 13 from which the values of k_r/k_t in Table I are derived. There is no indication that an equilibrium between the radical **1** and the rearranged radical is being approached since no deviation from eq 13 is observed even when **12** is the predominant product. None of the product that would result from migration of the ester group (i.e., **13**) was detected.



The value of k_r for **1** at 25 °C, extrapolated from our data, is only about one-tenth that determined by Ingold for the corresponding rearrangement of **14** (eq 18).[10] The discrepancy may be due to steric (i.e., methyl vs *tert*-butyl) or electronic (i.e., methyl vs carbethoxy) influences.



(18)

Table I. Results for the Reaction of $CH_3(C{=}O)C(COOEt)(CH_3)CH_2Br$ (**6**) with $(n\text{-}Bu)_3SnH$ in Benzene

temp, °C	$10^2[Bu_3SnH]_i$, M	$[\mathbf{11}]_f$:$[\mathbf{12}]_f$		$10^3(k_r/k_t)$, M	$10^{-4}k_r$,[a] s^{-1}
45	9.5	89.3:10.7		2.88	1.05
45	4.9	81.0:19.0		3.41	1.24
45	2.8	74.1:25.9		3.17	1.15
45	1.0	53.1:46.9		3.44	1.25
			mean	3.20 ± 0.30	1.17 ± 0.09
61	9.5	79.4:20.6		7.47	3.59
61	4.9	71.7:28.3		6.45	3.09
61	2.8	63.7:36.3		5.74	2.76
61	1.0	34.5:65.4		8.25	3.96
			mean	6.98 ± 1.10	3.35 ± 0.53
71	9.5	76.0:24.0		9.52	5.37
71	4.8	66.1:33.9		8.67	4.89
71	2.5	48.2:51.8		10.8	6.11
71	1.0	32.0:68.0		9.38	5.28
			mean	9.59 ± 0.89	5.41 ± 0.51
82	9.7	71.0:29.0		13.3	8.84
82	4.9	61.6:38.4		11.2	7.44
82	2.8	43.1:56.9		15.3	10.2
82	0.94	26.4:73.6		11.8	7.86
			mean	12.9 ± 1.8	8.58 ± 1.2
96	9.5	62.3:37.7		20.8	16.9
96	4.9	47.4:52.6		22.0	17.8
96	2.8	33.1:66.9		24.7	20.0
96	0.99	18.5:81.5		20.3	16.5
			mean	21.9 ± 2.0	17.8 ± 1.6
96	0.99[b]	18.3:81.7		20.6	16.7
112	2.8	36.4:63.6		21.1	21.0
112	1.0	12.5:87.5		33.6	33.5
			mean	27.4 ± 6.3	27.3 ± 6.3

[a] Based on k_t calculated from $\log k_t = 9.06 - 3.65/RT$.[24] [b] 1 equiv of methyl methacrylate was added before initiation (see text).

Table II. Results for the Reaction of $EtS(C{=}O)C(COOEt)(CH_3)CH_2Br$ (**7**) with $(n\text{-}Bu)_3SnH$ in Benzene

temp, °C	$10^3[Bu_3SnH]_i$, M	$[\mathbf{15}]_f$:$[\mathbf{16}]_f$		$10^6(k_r/k_t)$, M	$10^{-1}k_r$,[a] s^{-1}
61	2.7	98.7:1.3		5.62	25.7
61	1.1	97.7:2.3		4.67	21.3
			mean	5.15 ± 0.55	23.5 ± 2.2
70	5.1	98.9:1.1		8.68	46.0
70	2.1	98.0:2.0		7.46	41.0
70	2.1	98.0:2.0		7.61	40.3
70	2.1	97.8:2.2		8.68	46.0
70	1.1	96.2:3.7		8.44	44.7
			mean	8.17 ± 0.59	43.2 ± 2.7
80	5.1	98.6:1.3		11.5	70.5
80	3.5	98.2:1.8		10.6	65.0
80	2.7	97.5:2.5		13.0	80.0
80	2.1	96.9:3.1		13.0	80.0
80	2.1	97.0:3.0		12.1	78.9
			mean	12.0 ± 1.0	74.9 ± 6.8
95	9.9	98.7:1.3		20.3	162
95	0.9	90.3:9.7		23.9	191
			mean	22.1 ± 1.8	177 ± 15
96	10.0	98.4:1.6		27.5	224
96	7.9	97.8:2.2		31.6	240
96	5.0	97.3:2.7		25.8	196
96	4.6	97.1:2.9		25.4	193
96	2.1	94.8:5.2		24.9	189
96	1.1	91.0:9.0		26.4	215
			mean	26.9 ± 2.5	209 ± 20
114	5.1	95.7:4.3		45.9	451
114	5.1	94.2:5.8		68.8	676
114	3.5	93.9:6.1		49.7	488
114	2.4	91.7:8.3		51.6	507
114	2.1	94.3:5.7		27.8	273
			mean	48.8 ± 14.6	479 ± 144

[a] Based on k_t calculated from $\log k_t = 9.06 - 3.65/RT$.[24]

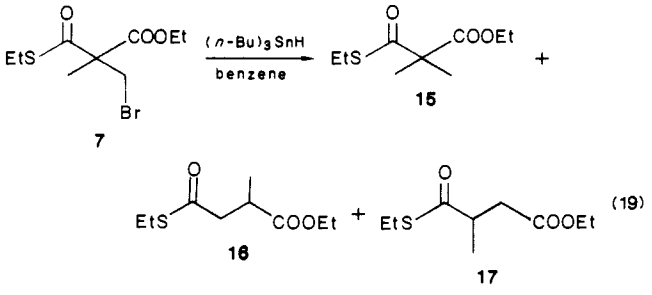
Rearrangement of the $EtS(C{=}O)C(CH_3)(COOEt)CH_2^\bullet$ Radical (2) in Benzene.[11] Because the migration of a thioester group in a free radical had not previously been detected and because of its relevance to the methylmalonyl-CoA mutase reaction, we were particularly interested in the rearrangement of **2**. While no rearranged product could be detected under the conditions employed to study the rearrangement of **1**, lowering $[(n\text{-}Bu)_3SnH]_i$ to the range 1.0×10^{-1}–1.0×10^{-3} M resulted in reproducible yields of

Table III. Results for the Reaction of EtS(C=O)C(COOEt)(CH_3)CH_2Br (7) with (n-Bu)$_3$SnH in Toluene

temp, °C	$[(n\text{-Bu})_3\text{SnH}]_i$, M	$[\mathbf{15}]_f$:$[\mathbf{16}]_f$	$10^{-2}k_a$,[a] M^{-1} s^{-1}	$10^{-1}k_r$,[b] s^{-1}	10^{-1}"k_r",[c] s^{-1}
61	1.8	99.4:0.6	1.15	2.4	0.71
61	3.5	99.5:0.5	0.56		1.1
61	5.1	99.6:0.4	0.58		1.2
61	5.1	99.6:0.4	0.53		1.2
76	1.8	98.7:1.3	1.33	6.3	2.3
92	1.8	97.9:2.1	2.70	16	5.2
92	3.5	98.4:1.6	2.11		7.1
92	5.1	98.8:1.2	2.43		7.2
105	3.5	98.1:1.9	1.94	31	18
120	1.1	94.7:5.3	7.56	66	15
120	1.8	95.5:4.5	7.27		19
120	1.8	96.0:4.0	8.96		16
120	3.5	97.5:2.5	11.8		18
120	5.1	97.1:2.9	5.38		32

[a] Calculated from eq 15 and 16 (see text for details) and k_r values measured in benzene. [b] k_r values measured in benzene taken from Table II. [c] k_r values calculated directly from product ratios, assuming that $k_a = 0$ (i.e., using eq 13).

16 ranging from 1 to 9% (eq 19; Table II and ref 11; Figure 1). No rearrangement product involving migration of the ester group (i.e., **17**) was detected.



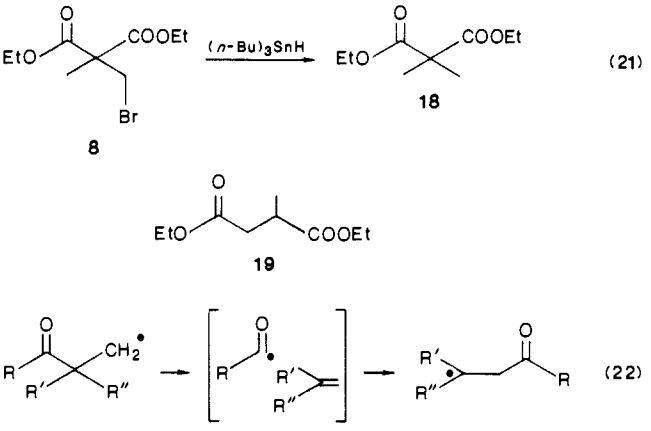
Rearrangement of 2 in Toluene. Because of the higher temperatures required to observe the slow rearrangement of **2** and obtain appreciable yields of **13**, we attempted to use toluene as the solvent. In contrast to the reaction in benzene, the values of k_r/k_t deduced from the results in toluene using eq 16 were found to decrease with decreasing $[(n\text{-Bu})_3\text{SnH}]_i$ (Table III). This is attributable to hydrogen abstraction from toluene by **2** (eq 20).

$$\mathbf{1} + C_6H_5CH_3 \xrightarrow{k_a} \mathbf{15} + C_6H_5CH_2^{\bullet} \qquad (20)$$

Substituting our calculated values of k_r, determined in benzene, together with the experimental toluene values of $[\mathbf{16}]_f$ vs $[(n\text{-Bu})_3\text{SnH}]_i$ into eq 16 yielded the values of k_a (k_p in eq 16) in Table III. Although the values of k_a yielded by this treatment are subject to considerable error, the resulting kinetic parameters ($\Delta H^{\ddagger}$ = 9.7 ± 2 kcal/mol; $\Delta S^{\ddagger}$ = −22 ± 6 cal/mol·K) are in good accord with those determined for the reaction of methyl radicals with toluene in the gas phase ($\Delta H^{\ddagger}$ = 8.8 kcal/mol; $\Delta S^{\ddagger}$ = −25 cal/mol·K).[20] It is possible that similar competitive reactions at high dilution might be employed to determine rates of abstraction from other solvents.

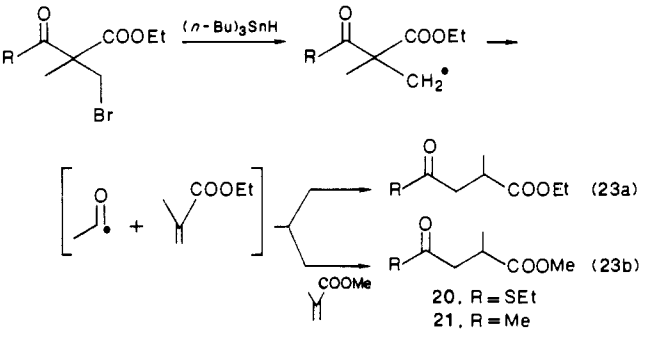
Reaction of the Diester 8 with (n-Bu)$_3$SnH. Reduction of the diester **8** with (n-Bu)$_3$SnH in benzene (eq 21) under the most extreme attainable experimental conditions (113 °C, $[(n\text{-Bu})_3\text{SnH}]_i = 1.1 \times 10^{-3}$ M) yielded less than 0.3% of the rearranged product **19**. Thus, k_r for the migration of the ester group in **3** is less than 10 s^{-1} at 113 °C.

Reduction of 6 and 7 in the Presence of Methyl Methacrylate. Since a dissociation–recombination mechanism (eq 22) had been proposed for the 1,2-migration of carbonyl groups in radicals,[9e]



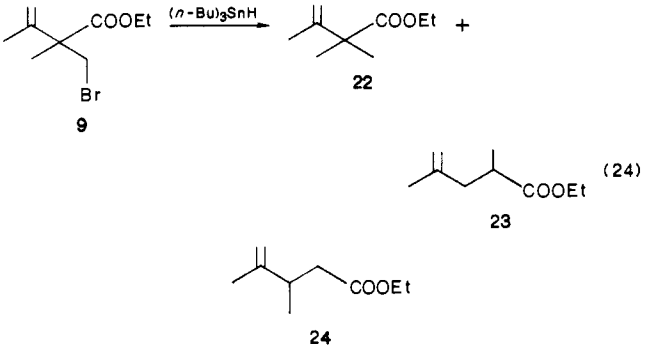
crossover experiments were conducted to test this possibility.

The ketone **6** and thioester **7** each were reduced with (n-Bu)$_3$SnH under standard conditions in the presence of 1 equiv of methyl methacrylate (eq 23). At GC detection limits of 0.3%



of product, no crossover product **20** could be detected from the reduction of **7**. The crossover product **21** could not be distinguished by GC from the direct reduction product of the ketone **6**; however, no methyl ester **21** was detectable in the NMR spectrum of a sample of the product **11** that was isolated by preparative GC.

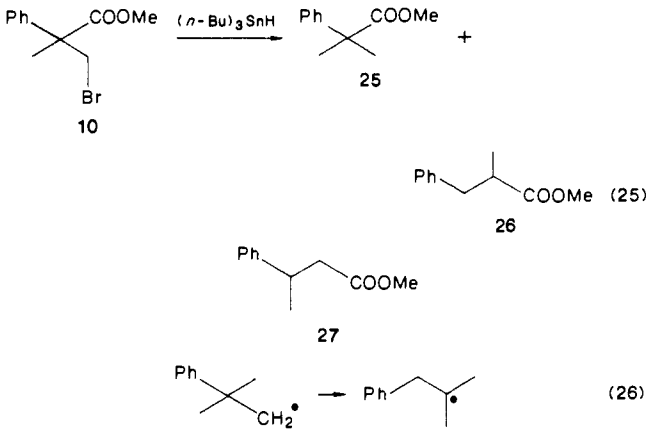
Rearrangement of the Me(C=CH_2)C(CH_3)(COOEt)CH_2· Radical (4). The rearrangement of **4** (eq 24) was anticipated to be very fast and, indeed, at 45 °C in the presence of 0.1 M (n-Bu)$_3$SnH, 52% of the product was the rearranged isomer **23**.



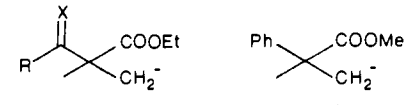
The reduction of **9** by (n-Bu)$_3$SnH was examined both under pseudo-first-order conditions ((n-Bu)$_3$SnH in excess) and with (n-Bu)$_3$SnH as the limiting reagent. Results are listed in Table IV. As with the other radicals studied, no product resulting from migration of the ester group (i.e., **24**) was detected.

Rearrangement of the PhC(CH_3)(COOMe)CH_2· Radical (5). This reaction (eq 25) was examined only briefly at 61 °C, with the results reported in Table V. 1,2-Migration of the phenyl group occurred readily under the reaction conditions, but no ester migration (i.e., formation of **27**) was observed. Reduction of **10** with (n-Bu)$_3$SnH in benzene has previously been reported[9d] with results that yield $k_r = 2 \times 10^5$ s^{-1} at 83 °C. Our own measurements yield a value of $(5.0 \pm 0.4) \times 10^3$ at 61 °C in reasonable agreement with the rate constant recently determined for migration of the phenyl group in the neophyl radical (eq 26).[10]

(20) Cher, M.; Hollingsworth, C. S.; Sicillio, F. *J. Phys. Chem.* **1966**, *70*, 877.



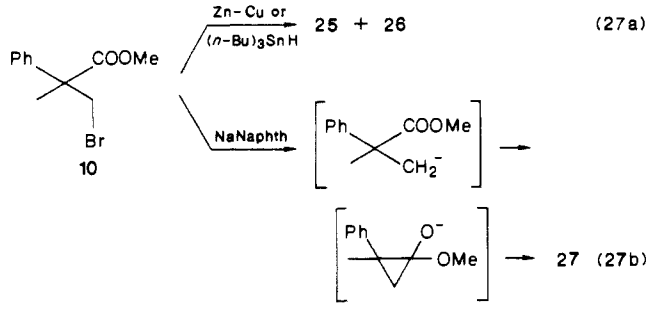
Generation and Rearrangement of Model Carbanions. Having unambiguously generated model radicals **1–5** and measured their rearrangement rates, we were interested in examining the corresponding carbanions **1′–5′**.



1′, R = Me, X = O
2′, R = SEt, X = O
3′, R = OEt, X = O
4′, R = Me, X = CH_2
5′

It has been shown that, upon treatment of alkyl halides with sodium naphthalenide (NaNaphth) in dimethoxyethane (DME), two rapid one-electron transfers occur to yield the corresponding anions.[21] This procedure was used to generate the carbanions **1′–5′** from **6′–10′**. Reduction of the bromides by the Zn–Cu couple in methanol also was examined, although there is literature precedent that this results only in a single electron transfer to yield radicals.[22] The latter reaction was of interest because Zn–Cu has been employed to reduce **6** in a previous study of the rearrangement of **2** without clarification of the reaction mechanism.[8e]

The phenyl compound **10** was found to be diagnostic for distinguishing between radical and carbanion formation. Addition of **10** to a NaNaphth solution (2–2.5 equiv of NaNaphth, DME, −78 °C) yielded only the ester migration product **27**, presumably formed from the anion via a Favorskii-type rearrangement (eq 27b). On the other hand, reduction with the Zn–Cu couple (2–3



equiv in MeOH, 5% NH_4I, 20 °C) yielded **26** (i.e., the phenyl migration product) as the only rearrangement isomer, as in the case of reduction with $(n\text{-Bu})_3SnH$ (eq 27a). Thus, it is concluded, contrary to earlier assertions,[8e] that rearrangement induced by the Zn–Cu couple proceeds via free-radical intermediates.

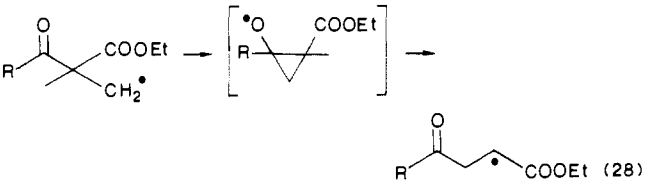
The other bromides were reduced with NaNaphth and with Zn–Cu, and the results of the comparisons are reported in Table VI. For the butenyl species formed from **9**, the rearrangements were again very selective as anticipated; reduction with Zn–Cu (as with $(n\text{-Bu})_3SnH$) yielded the propenyl migration product whereas reduction with NaNaphth yielded the ester migration product. On the other hand, rearrangements of anions **1′** and **2′** were nonspecific and yielded products resulting from migration, in each case, of both carbonyl functionalities.

The Zn–Cu reactions were very clean, yielding only the bromide reduction products in high yields. On the other hand, the NaNaphth reductions also yielded considerable amounts of high molecular weight materials.

Discussion

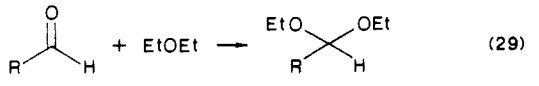
The activation parameters for the radical rearrangement reactions that we have identified are summarized in Table VII, together with those for the cyclization of the 3-butenyl radical.[6]

From the results of our methyl methacrylate crossover experiments on **6** and **7**, we conclude that these radical rearrangements are intramolecular processes. By analogy with the vinyl migration mechanism depicted by eq 5, it is plausible to interpret the carbonyl group migration reactions as proceeding via cyclopropyloxy intermediates or transition states according to eq 28.



The uniformly negative entropies of activation (Table VII) are consistent with this parallel. The much lower migratory aptitudes of the carbonyl group, compared with that of vinyl, are not surprising since the stabilities of oxygen radicals are expected to be lower (by ca. 10–20 kcal) than those of corresponding carbon radicals.

This interpretation also is consistent with the sequence of migratory aptitudes for the different carbonyl groups [i.e., $C(=O)CH_3 > C(=O)SEt > C(=O)OEt$]. The enthalpy of activation corresponding to formation of the cyclopropyloxy intermediate (eq 28) is expected to correlate with the enthalpy for saturation of the C=O bond. The latter value (kilocalories per mole in parentheses)[23] derived for a model reaction (eq 29) does indeed increase along the following sequence: $C(=O)CH_3$ (−4.8) < $C(=O)SEt$ (1.8) < $C(=O)OEt$ (5.1). This trend is attributable to increasing stabilization of the carbonyl group by π-conjugation with R.



Our demonstration of spontaneous 1,2-migration of a thioester group in a model free radical lends support to the view that the rearrangement step in the methylmalonyl-CoA mutase reaction does indeed occur at the free-radical stage. Extrapolation of our results yields a value of $k_r = 2.5\ s^{-1}$ for the migration of the thioester group in **2** at 30 °C. While this falls short of the value of ca. $10^2\ s^{-1}$ that has been estimated for k_{cat} for the methylmalonyl-CoA mutase reaction,[16] the discrepancy would seem to lie within the range of influences associated with the differences involved in the comparison of the model and enzyme substrate radicals. Such influences that might operate to enhance the rate of thioester migration in the enzyme substrate radical include conformational effects associated with the binding of the substrate and product radicals to the enzyme and stabilization of the cyclopropyloxy radical intermediate by hydrogen bonding to the sulfur and/or oxygen atoms. Rearrangement may also be favored for steric reasons by the bulky coenzyme A group compared with SC_2H_5 in the model radical. On the other hand, the presence of the additional methyl group in the model radical **2** is expected to enhance the rate of migration (Thorpe–Ingold effect).[24]

(21) Garst, J. F. *Acc. Chem. Res.* **1971**, *4*, 400.
(22) Brace, N. O.; van Elswyck, J. E. *J. Org. Chem.* **1981**, *41*, 766.

(23) (a) $\Delta H_f°$(l) for diethyl ether and acetaldehyde from: Cox, J. D.; Pilcher, G. *Thermochemistry of Organic and Organometallic Compounds*; Academic: London, 1970. (b) $\Delta H_f°$ for ethyl formate and triethyl orthoformate from: Hine, J.; Klueppel, A. *J. Am. Chem. Soc.* **1974**, *96*, 2924. (c) $\Delta H_f°$ for *S*-ethyl thioformate and triethyl monothioorthoformate, from: Guthrie, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 5892.
(24) Chatgilialoglu, C.; Ingold, K. U.; Tse-Sheepy, I.; Warkentin, J. *Can. J. Chem.* **1983**, *61*, 1077.

Table IV. Results for the Reaction of $CH_3C(=CH_2)C(COOEt)(CH_3)CH_2Br$ (**9**) with $(n\text{-}Bu)_3SnH$ in Benzene

temp, °C	$[Bu_3SnH]_i$,[a] M	$[22]_f$:$[23]_f$		$10^{-1}(k_r/k_t)$, M	$10^{-5}k_r$,[b] s^{-1}
45	0.92 xs	92.5:7.5		0.756	2.75
45	0.097 xs	51.1:48.9		0.932	3.39
45	0.089 lim	34.2:65.8		0.745	2.71
			mean	0.81 ± 0.11	2.95 ± 0.38
54	0.92 xs	91.1:8.9		0.911	3.89
54	0.097 xs	44.2:55.8		1.23	5.26
54	0.097 lim	25.6:74.4		1.28	5.47
			mean	1.14 ± 0.20	4.87 ± 0.85
67	0.94 xs	85.8:14.2		1.55	8.22
67	0.097 xs	36.0:64.0		1.73	9.17
67	0.095 lim	19.2:80.8		1.86	9.86
			mean	1.71 ± 0.16	9.08 ± 0.82
77	0.94 xs	79.0:21.0		2.49	15.4
77	0.108 xs	30.7:69.3		2.49	15.4
	0.096 lim	15.1:84.9		2.53	15.6
			mean	1.50 ± 0.02	15.5 ± 0.1
87	0.94 xs	79.9:20.1		2.35	16.8
87	0.097 xs	22.3:77.7		3.39	24.2
87	0.104 lim	15.8:84.2		2.62	18.7
			mean	2.79 ± 0.54	19.9 ± 3.8
97	0.67 xs	63.4:36.6		3.88	31.9
97	0.097 xs	18.8:81.2		4.19	34.4
			mean	4.04 ± 0.16	33.1 ± 1.3

[a] Key: xs, at least 8 equiv of Bu_3SnH was used; lim, Bu_3SnH was used as limiting reagent (about 0.8 equiv). [b] Based on k_t values calculated from $\log k_t = 9.06 - 3.65/RT$.[24]

Table V. Results for the Reaction of $PhC(COOMe)(CH_3)CH_2Br$ (**10**) with $(n\text{-}Bu)_3SnH$ in Benzene at 61 °C

$10^2[Bu_3SnH]_i$, M	$[25]_f$:$[26]_f$[a]		$10^4(k_r/k_t)$, M	$10^{-3}k_r$,[b] s^{-1}
1.0	76.2:23.8		9.9	4.8
0.5	61.5:38.5		11.4	5.5
0.2	45.0:55.0		10.0	4.8
		mean	10.5 ± 0.9	5.0 ± 0.4

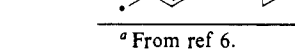
[a] Assuming $[25]_f + [26]_f = [(n\text{-}Bu)_3SnH]_i$. [b] Based on k_t calculated from $\log k_t = 9.06 - 3.65/RT$.[24]

Table VI. Reductions of Various Bromides with NaNaphth and with Zn–Cu

bromide	reductant	yield,[a] % direct product	ester mign product	other mign product
6	Zn–Cu	**11** (45)[b]	**13** (0)[b]	**12** (57)[b]
6	NaNapth	**11** (<0.2)	**13** (7)	**12** (17)
7	Zn–Cu	**15** (92.6)	**17** (0)	**16** (7.4)
7	NaNapth	**15** (<0.2)	**17** (4)	**16** (42)
8	Zn–Cu	**18** (100)[b]	**19** (0)[b]	
8	NaNapth	**18** (0)	**19** (100)[b]	
9	Zn–Cu	**22** (75)[b]	**24** (0)[b]	**23** (25)[b]
9	NaNapth	**22** (0.5)	**24** (14)	**23** (<0.2)
10	Zn–Cu	**25** (60)[b]	**27** (0)	**26** (30)[b]
10	NaNapth	**25** (0)	**27** (50)	**26** (0)

[a] Yields are GC yields based on unreacted starting material unless otherwise noted. [b] Product ratios determined by NMR.

Table VII. Activation Parameters for Radical Rearrangements

reaction	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, cal/mol·K
1 → $\cdot C(CH_3)(COOEt)C(=O)Me$	11.0 ± 0.3	−3.6 ± 0.8
2 → $\cdot C(CH_3)(COOEt)C(=O)SEt$	13.8 ± 0.2	−11.0 ± 0.7
4 → $\cdot C(CH_3)(COOEt)C(=CH_2)CH_3$	10.0 ± 0.3	−2.1 ± 1.0
	9.1[a]	−11.0[a]

[a] From ref 6.

Anionic rearrangement clearly also is sufficiently rapid to accommodate the thioester migration step in the enzymic reaction. However, we consider the formation of such a substrate carbanion (presumably by electron transfer from the initially formed B_{12r} to the substrate radical) to be highly unfavorable and, on balance, much less likely than the alternative free-radical pathway that we now have demonstrated to be chemically viable. Thus, we conclude that, while contributions from pathways involving carbanions or organocobalt intermediates cannot be definitively excluded, there is no plausible rationale for invoking such additional intermediates at this stage in the case of the methylmalonyl-CoA mutase reaction. The case for a free-radical rearrangement pathway for the α-methyleneglutarate mutase reaction, which involves the 1,2-migration of a vinyl group, is even more compelling. On the other hand, free-radical rearrangement pathways for the other coenzyme B_{12} dependent reactions that involve migrations of *saturated* substituents [OH, NH_2, and $CH(NH_2)COOH$] remain unprecedented in model systems.[35]

Experimental Section

General Procedures. THF, DME, ether, benzene, and toluene were distilled from Na–benzophenone just prior to use. Tri-*n*-butyltin hydride ($(n\text{-}Bu)_3SnH$) was prepared from tin chloride,[25] distilled from CaH_2, and stored under N_2.

Preparative GC was performed on a Varian 920 instrument with a 5 ft × $^1/_4$ in. 20% SE-30 column. Analyses were performed with a Perkin-Elmer Sigma 300-Sigma 15 system with a 30 m × 0.25 mm DB1 Durabond column. NMR spectra were recorded on a 500-MHz spectrometer in $CDCl_3$ with TMS as standard. Elemental analyses were performed by Galbraith Laboratories.

Ethyl *S*-ethyl 2-(bromomethyl)-2-methylmonothiomalonate (7) was prepared according to literature procedures.[26]

Ethyl 2-(bromomethyl)-2-methyl-3-oxobutanoate (6) was prepared from ethyl 2-(hydroxymethyl)-2-methyl-3-oxobutanoate.[27] The alcohol (3.35 g, 29.2 mmol), anhydrous K_2CO_3 (4.15 g, 30 mmol), and Ph_3P (5.08 g, 29.4 mmol) were stirred in 50 mL of dry $CHCl_3$. Bromine (1.0 mL, 20.0 mmol) in 4 mL of $CHCl_3$ was added dropwise over 15 min. After stirring overnight, the solid was filtered and rinsed with ether. The organic solutions were concentrated and rediluted with ether. After several hours the solution was filtered, concentrated, and distilled by bulb-to-bulb distillation (0.1 mmHg, 60–90 °C) to give 1.37 g of a 1:3 mixture of ethyl 2-methyl-3-oxobutanoate and **6**. ^1H NMR: δ 1.28 (t, J = 7.1 Hz, 3 H), 1.51 (s, 3 H), 2.20 (s, 3 H), 3.67 (d, J = 10.6 Hz, 1 H), 3.79 (d, J = 10.6 Hz, 1 H), 4.23 (m, 2 H). Anal. Calcd for $C_8H_{13}BrO_3$: C, 40.53; H, 5.53. Found: C, 40.60; H, 5.59.

Ethyl 2-(bromomethyl)-2,3-dimethyl-3-butenoate (9) was prepared from ethyl 2,3-dimethyl-2-butenoate, which was synthesized following a modified literature procedure[28] by treating ethyl 2-bromopropionate (2.60

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mL, 20.0 mmol) in 25 mL of benzene with activated zinc dust[29] (1.35 g, 21 mmol) and acetone (1.50 mL, 20.4 mmol, distilled from $CaSO_4$). The mixture was heated to 65 °C until initiation of reaction. After 30 min, Zn (0.2 g, 3 mmol) and acetone (0.4 mL, 5 mmol) were added, and the mixture was refluxed for 30 min. The addition and heating were repeated following which the mixture was cooled and poured into enough 1.2 M HCl to dissolve the resultant salts. The organic layer was separated, and the aqueous layer was extracted with 10 mL of ether. The combined organic layers were dried and concentrated. The resultant alcohol was dehydrated by refluxing in 20 mL of benzene with 3.5 g of P_2O_5 for 2 h. Upon cooling, the solutions were decanted, and the solid was rinsed with 3 × 10 mL of ether. The combined organic solutions were shaken with 3 × 10 mL of 1.2 N HCl and saturated aqueous NaCl, dried, and concentrated. Distillation (50 mmHg, 95–105 °C) gave 1.74 g (60%) of the 2,3-double-bond isomer. ^{1}H NMR: δ 1.29 (t, J = 7 Hz, 3 H), 1.79 (s, 3 H), 2.00 (s, 3 H), 4.17 (q, J = 7.2 Hz, 2 H). About 10% of the 3,4-double-bond isomer also was formed. Partial NMR: δ 3.13 (q, J = 7 Hz, 1 H), 4.85 (s, 2 H).

The bromide **9** was prepared by adding the isomer mixture (0.582 g, 4.1 mmol) at −78 °C to a solution of hexamethylphosphoramide (0.82 mL, 4.70 mmol) and lithium diisopropylamide (4.30 mmol) in 10 mL of THF that had previously been stirred for 30 min at −78 °C. After another 30 min, dibromomethane (0.60 mL, 8.3 mmol) was added, and the solution warmed to 0 °C during 40 min. Workup gave a mixture of the starting material and **9**, which was separated by distillation and preparative GC. ^{1}H NMR: δ 1.26 (t, J = 7.1 Hz, 3 H), 1.46 (s, 3 H), 1.75 (s, 3 H), 3.57 (d, J = 10.0 Hz, 1 H), 3.81 (d, J = 10.0 Hz, 1 H), 4.17 (m, 2 H), 4.91 (s, 1 H), 5.00 (s, 1 H). Anal. Calcd for $C_9H_{15}BrO_2$: C, 45.98; H, 6.43. Found: C, 46.23; H, 6.49.

Methyl 2-(bromomethyl)-2-phenylpropionate (10) was prepared by a literature procedure.[9d]

Reductions with Tri-*n*-butyltin Hydride. The bromides were purified by preparative GC to ≥99% purity. A weighed amount of the bromide (1.1–1.5 equiv, 0.05–0.20 mmol) was placed in a flask equipped with a rubber septum backed by a Teflon seal (a Wheaton cap or a Teflon vacuum stopcock or regular Teflon stopcock depending on the reaction scale and temperature). A known volume of benzene was added under N_2. The stopcock was closed and the flask heated in a thermostated bath (±0.5 °C). After equilibration for 5–10 min, $(n\text{-Bu})_3$SnH (0.004–1.00 mmol), followed by 0.5–1.00 mL of a solution of 2,2′-azobisisobutyronitrile (AIBN) in benzene (0.003 M), was added. After 3–10 h, the reaction was cooled and concentrated if necessary, and dodecane was added as standard. The samples were analyzed by GC. Results were consistent over several preparations of alkyl halide and $(n\text{-Bu})_3$SnH. Generally, 85–100% of the bromide was accounted for as starting material or reduction products. Representative raw data are reported in Table VIII (supplementary material). Samples of all products were isolated by preparative GC and identified by NMR comparison with authentic samples or known NMR spectra.

Reductions of **9** with an excess of $(n\text{-Bu})_3$SnH were performed similarly, but at least an 8-fold excess of $(n\text{-Bu})_3$SnH was added to the bromide.

Reductions with $(n\text{-Bu})_3$SnH in the presence of methyl methacrylate (MMA) were performed as above except that 1.0 equiv of MMA was injected before $(n\text{-Bu})_3$SnH was added. Authentic samples of the possible methyl ester products **20** and **21** were prepared so that their presence in the reaction mixture could be recognized.

Product Identification. Reduction products of 7 were prepared by literature procedures.[8a]

Reduction Products of 6. Ethyl 2,2-Dimethyl-3-oxobutanoate (11). ^{1}H NMR: δ 1.26 (t, J = 7 Hz, 3 H), 1.36 (s, 6 H), 2.15 (s, 3 H), 4.19 (q, J = 7 Hz, 2 H).

Ethyl 2-methyl-4-oxopentanoate (12) was prepared by esterification of 2-methyl-4-oxopentanoic acid.[30] ^{1}H NMR: δ 1.18 (d, J = 6.6 Hz), 1.25 (t, J = 7.2 Hz), total of 6 H, 2.15 (s, 3 H), 2.45 (m, 1 H), 2.90 (m, 2 H), 4.20 (q, J = 7.1 Hz, 4 H).

Ethyl 3-methyl-4-oxopentanoate (13) was prepared by esterification of the acid.[30] ^{1}H NMR: δ 1.15 (d, J = 7.2 Hz, 3 H), 1.24 (t, J = 7.1 Hz, 3 H), 2.21 (s, 3 H), 2.28 (dd, J = 16.7, 5.6 Hz, 1 H), 2.74 (dd, J = 16.7, 8.5 Hz, 1 H), 2.99 (m, 1 H), 4.11 (q, J = 7.1 Hz, 2 H).

Possible Methyl Esters Sought after Reduction in the Presence of Methyl Methacrylate. Ester **20** was prepared similarly to **16**. ^{1}H NMR: δ 1.21 (d, J = 6.9 Hz), 1.24 (t, J = 7.5 Hz), total of 6 H, 2.63 (m, 1 H), 2.88 (q, J = 7.5 Hz, 2 H), 2.97 (m, 2 H), 3.68 (s, 3 H).

Ester **21** was prepared similarly to **12**. ^{1}H NMR: δ 1.18 (d, J = 6.8 Hz, 3 H), 2.14 (s, 3 H), 2.46 (m, 1 H), 2.92 (m, 2 H), 3.67 (s, 3 H).

Reduction of 9. Ethyl 2,2,3-trimethyl-3-butenoate (22) was prepared by a literature procedure.[31] ^{1}H NMR: δ 1.23 (t, J = 7.1 Hz), 1.32 (s), total of 9 H, 1.73 (s, 3 H), 4.12 (q, J = 7.1 Hz, 2 H), 4.84 (s), 4.86 (s), total of 2 H. Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.19; H, 10.08.

Ethyl 2,4-Dimethyl-4-pentenoate (23). Sodium metal (0.22 g, 9.8 mmol) was dissolved in 20 mL of anhydrous EtOH. After it was cooled to room temperature, ethyl 2-methylacetoacetate (1.27 mL, 9.0 mmol) and 3-chloro-2-methylpropene (1.17 mL, 12.0 mmol) were added, and the mixture was refluxed for 3 h. After cooling, KOH (2.0 g) was added and stirring continued for 3 h. The mixture was concentrated and redissolved in 20 mL of H_2O. After it was rinsed with 5 mL of ether, the aqueous solution was acidified with concentrated HCl (cooling required) and the resultant oil extracted with 3 × 10 mL of ether. After the oil was dried and concentrated, 2,4-dimethyl-4-pentenoic acid was obtained [1.13 g (98%)]. Esterification gave the ester. ^{1}H NMR: δ 1.15 (d, J = 7.0 Hz, 3 H), 1.26 (t, J = 7.0 Hz, 3 H), 1.72 (s, 3 H), 2.09 (dd, J = 14.1, 7.4 Hz, 1 H), 2.42 (dd, J = 14.1, 7.4 Hz, 1 H), 2.64 (m, 1 H), 4.13 (q, J = 7.0 Hz, 2 H), 4.71 (s, 1 H), 4.77 (s, 1 H). Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.23; H, 10.12.

Ethyl 3,4-dimethyl-4-pentenoate (24) was prepared from 2-propenylmagnesium bromide and ethyl crotonate. Mg turnings (0.260 g, 20.8 mmol) were stirred in 4.5 mL of THF under N_2. Several drops of 2-bromopropene were added, and when the mixture became warm, the rest of 1.33 mL (15.0 mmol) of 2-bromopropene in 5 mL of THF was added over 20 min. After an additional 20 min, most of the Mg was decomposed, and the solution was cooled to 0 °C with vigorous stirring. CuI–PBu_3 (17 mg) was added followed by ethyl crotonate (1.86 mL, 15.0 mmol) in 5 mL of THF over 25 min. Another 10 mg of copper complex was added during this time. After the solution was stirred overnight and refluxed 0.5 h, the solution was poured into 1.2 N HCl and ether. Workup and distillation (15 mmHg, 50–70 °C) gave the product, which was further purified by preparative GC. ^{1}H NMR: δ 1.07 (d, J = 6.9 Hz, 3 H), 1.24 (t, J = 7.1 Hz, 3 H), 1.72 (s, 3 H), 2.26 (dd, J = 14.7, 8.0 Hz, 1 H), 2.43 (dd, J = 14.7, 7.0 Hz, 1 H), 2.65 (m, 1 H), 4.11 (q, J = 7.1 Hz, 2 H), 4.70 (s), 4.72 (s), total 2 H. Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.16; H, 10.21.

Reduction Products of 10. The direct product **25** was identified by comparison of its NMR spectrum to a literature spectrum. The rearranged products **26**[32] and **27**[33] were prepared and authenticated by comparison with literature NMR spectra.

Reductions with Sodium Naphthalenide. A solution of the radical anion was prepared by vacuum distillation of DME from Na–benzophenone onto naphthalene and 1.3 equiv of sodium metal in a graduated flask (~0.06 M). The mixture was shaken overnight.

A typical reduction was performed as follows: NaNaphth solution (4.2 mL, 0.061 M, 0.26 mmol) was cooled to −78 °C. The alkyl bromide (0.12 mmol) was injected, and after 1–10 min, propionic acid (0.16 mmol) was added to quench the reaction. Dodecane was added as a GC standard, and after it was warmed to room temperature, the resultant supernatant liquid was analyzed, yielding the results reported in Table VI.

Reduction with Zn–Cu Couple. A total of 5 mL of a solution of 5–7% NH_4I (w/v) in MeOH was purged with N_2 and added to Zn–Cu couple (3–4 mmol) under N_2. The bromide (0.6–1.0 mmol) was added, and the suspension was stirred overnight. The solvent was removed, and the residue was extracted with pentane. Examination of the concentrated extracts by GC and/or NMR showed complete reduction to yield the products reported in Table VI.

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Supplementary Material Available: Table VIII containing representative material balances for the reaction of various bromides with $(n\text{-Bu})_3SnH$ (1 page). Ordering information is given on any current masthead page.

Thermal Decomposition and Cobalt–Carbon Bond Dissociation Energies of Organocobalamins: Neopentyl-, (Cyclopentylmethyl)-, (Cyclohexylmethyl)-, (Tetrahydrofurfuryl)- and ((Tetrahydro-2*H*-pyryl)methyl)cobalamin

Sook-Hui Kim, Hui Lan Chen, Natalie Feilchenfeld, and Jack Halpern*

Contribution from the Department of Chemistry, The University of Chicago, Chicago, Illinois 60637. *Received September 18, 1987*

Abstract: The title compounds were prepared and characterized and their thermal decomposition reactions were studied in aqueous solutions of varying pH and containing varying concentrations of cob(II)alamin (B_{12r}) and of bis(dimethylglyoximato)cobalt(II), [Co(DH)$_2$]. Homolytic cobalt–carbon bond dissociation pathways were identified through competitive trapping of the resulting free radicals according to the following scheme: R-B_{12} $\rightleftharpoons$ R$^\bullet$ + B_{12r}; R$^\bullet$ + Co(DH)$_2$ $\rightarrow$ R-Co(DH)$_2$. Determination of the kinetics of these reactions yielded (after correction for the base on–base off equilibria) the following values of the activation parameters: R = neopentyl, $\Delta H^\ddagger$ = 26.7 ± 1.2 kcal/mol, $\Delta S^\ddagger$ = 15 ± 5 cal/(mol K); R = cyclopentylmethyl, $\Delta H^\ddagger$ = 26.8 ± 2 kcal/mol; $\Delta S^\ddagger$ = 3 ± 6 cal/(mol K). From these measurements the Co–C bond dissociation energies of the base-on forms of neopentyl-B_{12} and cyclopentylmethyl-B_{12} were deduced to be ca. 24 kcal/mol. In ethylene glycol $\Delta H^\ddagger$ for homolytic dissociation of the Co–C bond of neopentyl-B_{12} was found to be about 4 kcal/mol higher than in aqueous solution.

It is now widely accepted that coenzyme B_{12} dependent rearrangements are initiated by enzyme-induced homolytic dissociation of the coenzyme cobalt–carbon bond to generate a 5′-deoxyadenosyl radical.[1-5]

Accordingly, a knowledge of the Co–C bond dissociation energy of this and related organocobalt compounds, and of the factors that influence such bond dissociation energies and that may contribute to enzyme-induced bond weakening and dissociation, is important to an understanding of the coenzyme's role. In this context we have previously determined the Co–C bond dissociation energies of a variety of organocobalt complexes (coenzyme B_{12} models!) in which the nature of the equatorial ligand (porphyrin, Schiff base, etc.), the cobalt-bonded alkyl group, and the trans-axial ligand (amine, phosphine, etc.) were varied.[6-9] Such prior studies have included determination of the Co–C bond dissociation energy of coenzyme B_{12} itself ((5′-deoxyadenosyl)cobalamin), for which values ranging from 26 to 30 kcal/mol have been reported.[10,11] Attention also is directed to several other earlier studies on the thermal decomposition of cobalamins.[12]

In this paper we report studies on the thermal decomposition of several other cobalamins (R-B_{12}) and, in some cases, determination of their Co–C bond dissociation energies. A particular objective was to attempt to identify distinctive features that might be associated with the 5′-deoxyadenosyl moiety as compared with other organic substituents. These studies also bear on the validity of one of the procedures that has previously been employed to determine the Co–C bond dissociation energy of coenzyme B_{12}.[10]

Results and Discussion

General. The general approach used in these studies parallels that employed in several earlier investigations.[7,8,10,11,12a,13] Co–R bond dissociation energies were deduced from measurements of the kinetics of the homolytic bond dissociation reactions in the presence of a radical trap (in the present study bis(dimethyl-

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