related organocobalt compounds to steric influences, a likely mechanism for such bond weakening is a steric interaction with the 5′-deoxyadenosyl group resulting from an enzyme-induced "upward" conformational distortion of the corrin ring in the enzyme-bound coenzyme.

Acknowledgment. Support of this research through grants from the National Institutes of Health (AM-13339) and the National Science Foundation (CHE82-17950) is gratefully acknowledged. The NMR facilities were supported in part through the University of Chicago Cancer Center Grant NIH CA-14599.

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(18) **Note Added in Proof**: Subsequent to submission of this communication, Finke and Hay[19] reported a related study of the thermolysis of coenzyme B_{12} in *ethylene glycol* with 2,2,6,6-tetramethylpiperidinyl-1-oxy (Tempo) as a radical trap. Although the full kinetics for trapping of the 5′-deoxyadenosyl radical, in competition with its recombination with B_{12r}, were not observed, the limiting kinetics yielded a significantly higher values (34.5 kcal/mol) for $(\Delta H^{\ddagger})_{corr}$ and a correspondingly higher value of 32 kcal/mol for the Co–C bond dissociation energy. The reason for this ca. 6 kcal/mol discrepancy, which may be solvent related, is unclear. We thank Prof. Finke for informing us of these results and for helpful comments.

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Free Radical Rearrangement Involving the 1,2-Migration of a Thioester Group. Model for the Coenzyme B_{12} Dependent Methylmalonyl-CoA Mutase Reaction

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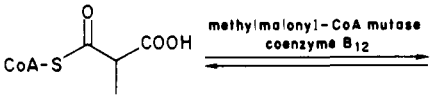
Notwithstanding extensive investigation and discussion, the mechanisms of the remarkable reactions promoted by coenzyme B_{12}, exemplified by the methylmalonyl-CoA (**1**) to succinyl-CoA (**2**) rearrangement (eq 1), continue to be unresolved and controversial.[1]



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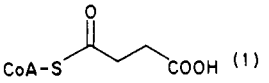
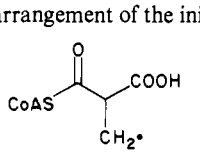


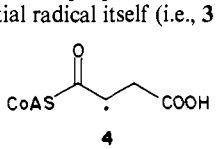
(1)

2

It is widely accepted[1,2] that the rearrangement is *initiated* by the enzyme-induced homolytic dissociation of the cobalt–carbon bond of coenzyme B_{12} to form a 5′-deoxyadenosyl radical, which abstracts an H atom from the substrate to generate a substrate free radical, i.e., **3**. However, there is little evidence or agreement concerning the nature of the rearrangement step itself. Possible mechansims that have been proposed include, in addition to rearrangement of the initial radical itself (i.e., **3** → **4**), rearrangement of the corresponding carbanion or carbonium ion, formed by reduction or oxidation of the initial radical, or of an organocobalt derivative (**5**) formed by combination of the initial radical with the coenzyme-derived vitamin B_{12r}.[1]



3



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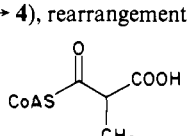

5

Several attempts have been reported[3–8] to probe the mechanisms of coenzyme B_{12} promoted rearrangements by preparing model substrate–cobalt adducts analogous to **5** [where (Co) = cobalamin or a related cobalt complex] and decomposing these under various conditions (thermal, photolytic, reductive, etc.). In some cases workup of the decomposed solutions yielded some rearranged products (e.g., analogous of **2**).[5,6] However, it was not possible to draw convincing conclusions about the rearrangement mechanisms which were variously interpreted as proceeding through free radicals, carbanions, or organometallic intermediates.[3–8] Direct studies on various functionalized free radicals have revealed a few examples of $\beta \rightarrow \alpha$ migrations of acyl groups[8] but not, hitherto, of an ester or thio ester group.[3c,8c,9,10] We now report unequivocal evidence of such a 1,2-migration of a thio ester group in a model free radical related to **3** and measurements of the kinetics of this rearrangement.

Our procedure parallels that previously used by Walling[12] to study the rearrangement of the 5-hexenyl radical. The model radical **7**, which also has been invoked in several earlier attempts to model the methylmalonyl-CoA rearrangement,[5,6] was generated from the corresponding bromide **6**[13] by reduction with *n*-Bu_3SnH,[14] and the competition between direct trapping with *n*-Bu_3SnH (k_t) to yield **8** and rearrangement (k_r), followed by trapping to yield **10** in accord with eq 1, was monitored as a function of the initial *n*-Bu_3SnH concentration. Only the direct trapping product **8** and that resulting from 1,2-migration of the thioester group (**10**) were obtained, together in essentially quantiative yield (GC, based on reacted **6**). No other products, notably that resulting from migration of the ester group (**11**), were detected.

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(10) Prior attempts to observe 1,2-migration of a thio ester group include studies by Aeberhard et al.[11] on the photolysis and thermolysis of the perester $(CH_3)_3CO_3CCH_2CH(COOEt)(COSEt)$, a potential precursor of the $\cdot CH_2CH(COOEt)(COSEt)$ radical. No rearranged product resulting from thio ester 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, $EtS(CO)CH_2CH_2COOEt$.

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(13) Starting materials and products prepared as in ref 5a.

(14) Typical conditions: 0.001–0.005 M *n*-Bu_3SnH;[15] 10–50% excess **6**; benzene;[16] 60–113 °C.

(15) The initial *n*-Bu_3SnH concentration range was limited by the low yields of rearranged product **10** at higher *n*-Bu_3SnH concentrations and by the difficulty of product isolation at lower concentrations. For the concentration range used the results were consistent and reproducible.

(16) Toluene proved unacceptable as a solvent since H abstraction from the solvent ($7 + C_6H_5CH_3 \rightarrow 8 + C_6H_5CH_2\cdot$) turned out to be a significant side reaction compared with the relatively slow rearrangement **7** → **9**.

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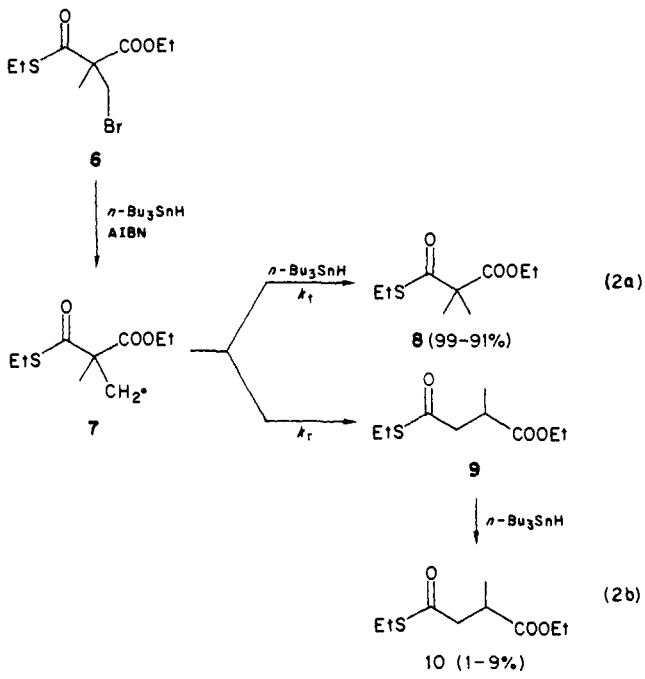


(2a)

(2b)

According to the scheme of eq 2,

$$\frac{d[\mathbf{10}]}{d[\mathbf{8}] + d[\mathbf{10}]} = \frac{-d[\mathbf{10}]}{d[n\text{-}Bu_3SnH]} = \frac{k_r}{k_t[n\text{-}Bu_3SnH] + k_r} \quad (3)$$

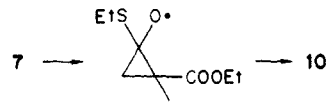
Integration under the applicable limiting conditions, i.e., $[\mathbf{6}]_i > [n\text{-}Bu_3SnH]_i$, yields

$$[\mathbf{10}]_f = \frac{k_r}{k_t} \ln\left[\frac{k_t[n\text{-}Bu_3SnH]_i}{k_r} + 1\right] \quad (4)$$

where the subscripts i and f refer to initial and final concentrations.

Values of k_r/kt were deduced by optimal fitting (using an iterative procedure) of the observed dependence of $[\mathbf{10}]_f$ on $[n\text{-}Bu_3SnH]_i$ to the functional form of eq 4; typical such fits are depicted by the plots in Figure 1. The sensitivity of such fits to the value of k_r/k_t was found to be severe. Values of k_t could be reliably deduced from earlier measurements on the kinetics of reactions of various free radicals with n-Bu_3SnH, which yielded $\log k_t = (9.06 - 3.65)/(2.3RT)$.[17,18] The resulting determinations of k_r (s^{-1}) at various temperatures (°C) are 23.5 ± 2.2 (60.5), 43.2 ± 2.7 (70), 74.9 ± 6.8 (79.5), 209 ± 20 (96.5), and 473 ± 130 (113.5). The corresponding activation parameters are $\Delta H_r^* = 13.8 \pm 0.5$ kcal/mol and $\Delta S_r^* = -11 \pm 1$ cal/(mol K).

Other methods of radical generation, notably reduction of **6** with Zn in MeOH, gave qualitatively similar rearrangement patterns, e.g., ca. 10% **10** and no **11**. A plausible mechanism for migration of the thio ester group involves intramolecular rearrangement via an intermediate cyclopropyloxy radical (**12**, eq 5),



(5)

analogous to that invoked for the corresponding radical migrations of vinyl and acyl groups.[9,11,19,20]

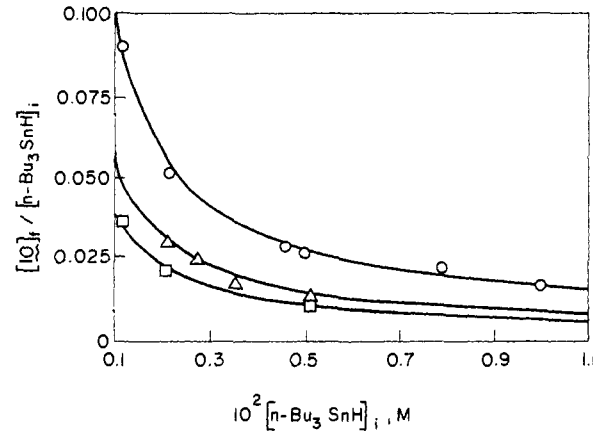
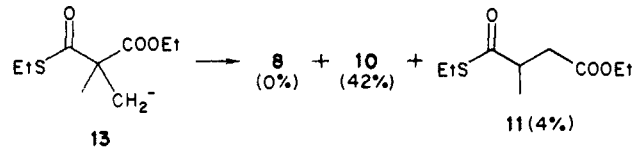


Figure 1. Plots of $[\mathbf{10}]_f/[n\text{-}Bu_3SnH]_i$ vs. $[n\text{-}Bu_3SnH]_i$ at 96.5 (○), 79.5 (△), and 60.5 °C (□). The points denote experimental values. The curves are calculated by using eq 4 and the "optimal fit" values of k_r/k_t, i.e., 2.69×10^{-5}, 1.20×10^{-5}, and 5.15×10^{-6} M, respectively.

At 30 °C, the uncatalyzed rearrangement rate of **7** (k_r) is 2.5 s^{-1}. k_{cat} for the enzymatic methylmalonyl-CoA reaction under these conditions has been estimated to be ca. 10^2 s^{-1}.[22] This relatively modest 40-fold rate difference could well be accommodated by the chemical and structural differences between **7** and **3** (although the additional CH_3 group in **7** is expected to enhance the migration rate),[23] as well as by the effects (e.g., hydrogen bonding to the sulfur atom, or conformational influences) of interaction of the (enzyme-bound) substrate radical with the enzyme.

To explore the alternative possibility of a carbanionic rearrangement, we also generated the corresponding anion **13** by reduction of **6** with sodium naphthenide in DME at −78 °C (eq 6).[24] Reduction and rearrangement under these conditions were



(6)

rapid but less selective since, upon quenching with propionic acid after 2 min, no **8** was found but only a reproducible ca. 10:1 mixture of the thio ester and ester migration products **10** and **11**, together with unidentified decomposition products.

While anionic rearrangement clearly is sufficiently rapid to accommodate the enzymatic process, we consider the formation of such a substrate carbanion (presumably by electron transfer between the initially formed vitamin B_{12r} and substrate radical) to be highly unfavorable and, on balance, much less likely than the alternative free radical rearrangement that we now have demonstrated to be a chemically viable pathway. Thus, we conclude that, while contributions from pathways involving carbanion, carbonium ions, or organocobalt intermediates cannot be definitively excluded, there is no plausible rationale at this stage for invoking such additional intermediates.

Related studies on the rearrangements of other model radicals and on the influence of radical structure on the rearrangement kinetics are continuing.

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(18) The value of k_t was found to be relatively insensitive to the nature of the radical. Thus, at 27 °C, $10^6 k_t$ = 2.0, 2.34, 1.35, 2.47, and 1.84 for ethyl, butyl, isopropyl, cyclohexyl, and *tert*-butyl radicals, respectively.[17]

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(20) An alternative dissociative mechanism, analogous to that proposed[21] for related radical rearrangement involving acyl migration, i.e., $EtSC(C{=}O)(CH_3)(CH_2{\cdot})COOEt \rightarrow EtS(C{=}O){\cdot} + CH_2{=}C(CH_3)COOEt \rightarrow EtSC(=O)CH_2C(CH_3)COOEt$, was tested by adding an equivalent of $CH_2{=}C(CH_3)COOMe$. No (<0.3%) crossover product analogous to **10**, i.e., $EtS(C{=}O)CH_2CH(CH_3)COOMe$, could be detected.

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Reductive Coupling of H-H, H-C, and C-C Bonds from Pd Complexes

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Reductive coupling to form H-H, C-H, and C-C bonds from transition-metal complexes is of fundamental importance in many catalytic processes. However, despite numerous experimental[1] and theoretical[2] studies, there remain a number of puzzles concerning these processes. For example, reductive elimination of methane from $Pt(H)(CH_3)(PPh_3)_2$ is quite facile at −25 °C,[1d] while $Pt(CH_3)_2(PPh_3)_2$ is quite stable (it decomposes at 237 °C!).[1t] This puzzle is exacerbated by the theoretical results of Siegbahn and co-workers[2e,f] whose calculations lead to essentially the same barriers for C-H and C-C reductive elimination.

In this work we show that the activation barrier for reductive elimination is sensitive to the nature of the bond being formed. Hydrogen has a spherically symmetric 1s valence orbital allowing it to simultaneously form H-H bonds while breaking M-H bonds, leading to small (1.55 kcal) intrinsic barriers. The directionality of the methyl sp^3 hybrid orbital makes it more difficult to convert from M-C to form C-C or C-H bonds during reductive elimination. Thus the CH_3 group needs to have a different orientation for the M-C and C-C bonds, and in the transition state a compromise must be reached that is not optimal for either bond. The result is an intrinsic barrier of 10.4 kcal for C-H coupling and 22.0 kcal for C-C coupling.

Studies on a prototypical oxidative addition/reductive elimination process[3]

$$Pt(PH_3)_2 + H_2 \leftrightarrow Pt(H)_2(PH_3)_2 \qquad (1)$$

showed that oxidative involves promotion of the d^{10} configuration for $Pt(PH_3)_2$ to an s^1d^9 configuration involving two *covalent* bonds to the hydrogens. In order to clarify the nature of H-H, H-C, and C-C processes without the complication of steric interactions with phosphorus or other metal ligands, we have examined

$$Pd(H)_2 \leftrightarrow Pd + H_2 \qquad (2)$$

$$Pd(H)(CH_3) \leftrightarrow Pd + CH_4 \qquad (3)$$

$$Pd(CH_3)_2 \leftrightarrow Pd + C_2H_6 \qquad (4)$$

Since the Pd atom has a low-spin d^{10} ground-state configuration and an s^1d^9 configuration when it forms two convalent bonds, it can serve as a model for reductive elimination from Pt(II), Pd(II), Ni(II), and Au(III) complexes.

The calculated energetics for reductive elimination from PdH_2, $PdH(CH_3)$, and $Pd(CH_3)_2$ are shown in Figure 1. The overall bonding energies correspond to an average Pd-H bond energy (D_e)

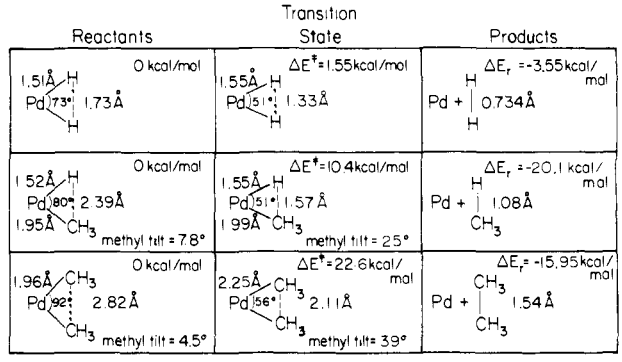

Figure 1. Geometries and energetics for the reactions $PdH_2 \rightarrow Pd + H_2$, $PdH(CH_3) \rightarrow Pd + CH_4$, and $Pd(CH_3)_2 \rightarrow Pd + C_2H_6$. The angle between the Pd-C bond and the vector from the C atom to the center of mass of the methyl hydrogen atoms is defined to be the methyl tilt.

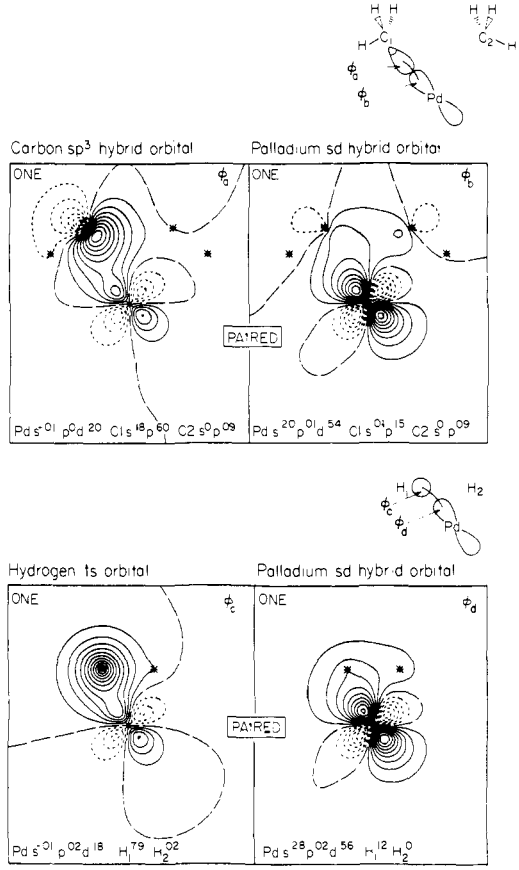

Figure 2. GVB orbitals for the Pd-C bonds at the transition state for the reaction $Pd(CH_3)_2 \rightarrow Pd + C_2H_6$ and the GVB orbitals for the Pd-H bonds for the reaction $PdH_2 \rightarrow Pd + H_2$. The Mulliken populations are listed with each orbital to show the hybridization of each orbital.

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