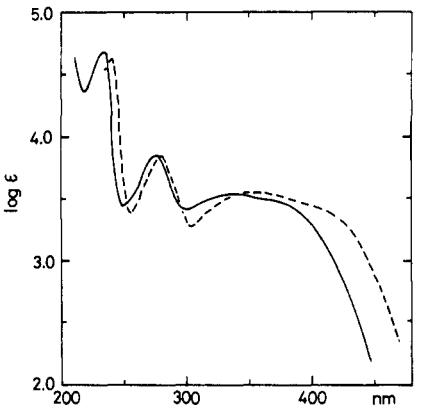

Figure 1. Electronic spectrum of **1** in CH_3CN (—) and CH_2Cl_2 (- - -).

However, the electronic spectrum of **1** (Figure 1) exhibited a broad long wavelength absorption at 300–450 nm (log ϵ >3.0),[15] not found in the spectra of either tropylium tetrafluoroborate[16] or 1,2-dimethyltropylium tetrafluoroborate,[17] clearly indicating a charge-transfer interaction between the tropylium ion and remote benzene rings in **1**. The substantial blue shift accompanying the change from methylene chloride to acetonitrile as solvent (Figure 1) is in accord with the solvent sensitivity of the charge-transfer band.[18]

An important aspect of the significance of the charge transfer interaction in **1** is the fact that donor and acceptor are not in parallel planes. In view of the fact that most charge-transfer interactions both intra- and intermolecular usually place the donor and acceptor in near parallel geometric orientation, we think it worthy to note that in this molecule the interaction is strong despite the minimized overlap of the orbital systems of both donor and acceptor. This of course raises the question of how much through bond interaction is responsible for charge-transfer in this system.[19] Experimental and theoretical study on **1** with molecules containing much stronger donor moieties, e.g., naphthalene and methyl substituted benzene frameworks, which will offer further evidence on the charge-transfer interaction, is in progress.

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(11) All new compounds described in this paper gave acceptable C and H analyses (±0.3%).

(12) We thank San-Abbott Ltd. for the generous gift of DBU.

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(15) The cation **1** showed, in addition to the long wavelength absorption, ultraviolet maxima at 240 nm (log ϵ 4.62), 279 (3.84) in CH_2Cl_2 and at 235 (4.69), 276 (3.86) in CH_3CN.

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(19) We thank a referee for drawing our attention on this point.

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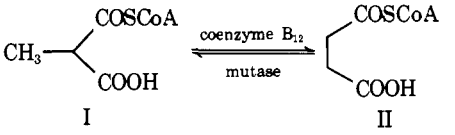
The Mechanism of Action of Coenzyme B_{12}. The Role of Thioester in a Nonenzyme Model Reaction for Coenzyme B_{12} Dependent Isomerization of Methylmalonyl Coenzyme A to Succinyl Coenzyme A

Sir:

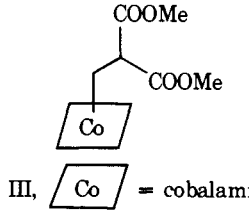
Although much interest has been focused on the search for a mechanistic rationale for the biological reactions of adenosylcobalamin,[1] little parallel exists in organic chemistry for many of the processes involved. The evolution of working, nonenzymic models to uncover the requisite analogies has already led to some suggestive experiments.[2] In the case of the methylmalonyl CoA ⇄ succinyl CoA (I ⇄ II) conversion, such a model in its most sophisticated form would be required to simulate the following salient features of the enzyme catalyzed



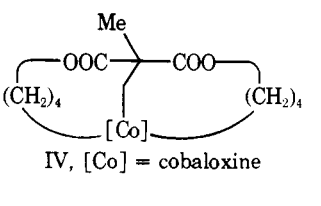
I II

process. (1) The thioester (COSCoA) group migrates[3] in an intramolecular 1,2 shift.[4] (2) Intermolecular hydrogen atom transfer from the CH_3 group via the 5′-methylene of deoxyadenosine and return to substrate is observed.[5] (3) Configuration at both termini of the rearranging species is retained,[6] a process which does not necessarily involve a σ-bonded organocobalt derivative of the substrate.

Recent nonenzymic studies of this reaction have uncovered (a) the conversion of the metastable alkyl cobalamin dimethyl ester III to succinic acid[7] and (b) the rearrangement of the *capped* cobaloxime complex of dimethylmalonic acid (IV) to methyl succinic acid in an intramolecular process.[8] It has also

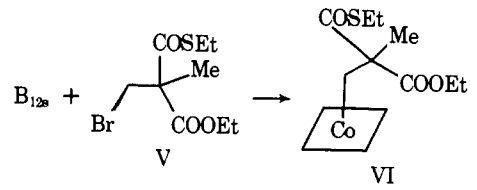


III, Co = cobalamin

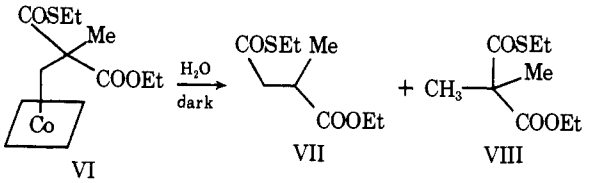


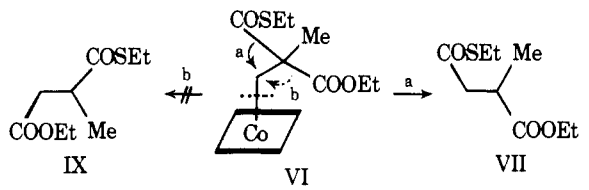
IV, [Co] = cobaloxine

been suggested[8] that the low yield in reaction a is due to loss of contact of the radical (or ionic) substrate species with the central cobalt of reduced coenzyme or cobaloxime. As far as we are aware, the role of the thioester has not yet been evaluated in terms of stabilization of radical (or ionic) intermediates, reaction yield, or migratory aptitude. To this end we have



prepared the dimethylmalonate complex VI[9,10] in which both thio and oxygen ester functions are present. Decomposition[11,12,13] of this unstable species in aqueous solution (pH 8–9) in the dark (24 h) affords as the sole isolable *rearranged* product, the thioester of methyl succinic acid VII[14] in 50–70% yield, together with unused starting bromomethylmalonate V,[15] and the dimethylmalonate VIII.[16] The thioester isomer





IX[17] from migration via path b is not observed, the use of methyl as an intact marker of carbon-2 serving well to differentiate between the two possible paths. Thus, not only is the yield consistently enhanced by use of thioester, but the first condition of the coenzyme model has been met, viz., exclusive thioester migration.[18] Further studies on the development of *catalytic* models to satisfy conditions 2 and 3 above, as well as the question concerning the role[2,8,19,20] of the cobalt atom of B_{12} are in progress.

Acknowledgments. We wish to thank Professor P. Dowd and J. Rétey for informing us of their results in this area prior to publication. We are indebted to Dr. S. Hosozawa for mass spectral data. We are grateful to Dr. L. Penasse, Roussel Uclaf for a gift of vitamin B_{12}. This investigation was supported by National Institutes of Health Grant AM 17014 and NSF Grant CHE76-18975.

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(9) Prepared by treatment of thioester of bromomethylmethylmalonate V with vitamin B_{12s}.[10] Vitamin B_{12s} was prepared by sodium borohydride reduction of hydroxocobalamin.

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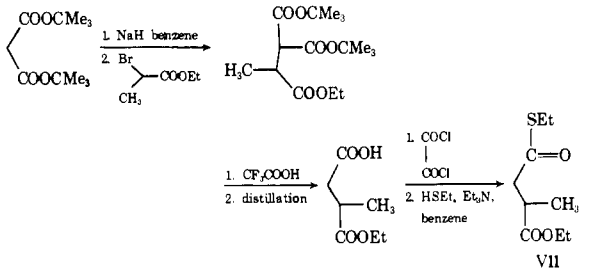
(11) In a typical reaction 600 mg (0.45 mmol) of hydroxocobalamin in 100 mL of water was reduced under an atmosphere of argon with 400 mg (10.57 mmol) of sodium borohydride to the gray-green vitamin B_{12s}. This solution was treated in the dark with 400 mg (1.41 mmol) of bromothioester V in 10 mL of ethanol. After 30 min the electronic spectrum showed the complete formation of the carbon–cobalt bond.[12] The mixture was then allowed to stand in the dark at room temperature with occasional stirring. After 1 day the mixture was extracted with ether (5 × 50 mL) and concentration of the organic layer gave 302 mg of a yellow oil. The oil was separated by preparative layer chromatography (2 mm silica gel) eluting three times with benzene–hexane (8:2). The first band above the origin gave 63.8 mg (70.3%) of an oil identified as rearranged product VII (R_f 0.3). The next band gave 15.2 mg (16.7%) of an oil identified as thioester of dimethylmalonate VIII (R_f 0.4). A third band gave 63 mg of oil identified as unreacted starting bromide IV (R_f 0.5). The yields calculated are based on the limiting reagent (hydroxocobalamin) used. The spectral properties (IR, NMR, and MS) of the three isolated oils were in excellent agreement with those of authentic, synthetic samples.[14,15]

(12) The electronic spectrum of the complex VI was similar to the characteristic absorption of coenzyme B_{12}. The γ (360 mμ) to α (535 mμ) abosrption ratio was 1.65. The ratio was changed rapidly (γ/α = 2.15) upon exposure of the sample to light (→ hydroxocobalamin).

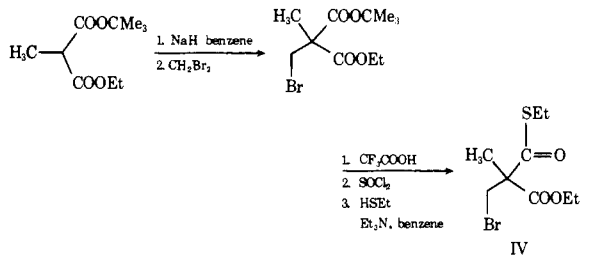
(13) Two control reactions: (1) cobalt(II) chloride was substituted for hydroxocobalamin; (2) in the absence of any added cobalt compound, no rearranged product VII was detected using identical reaction and workup conditions as those described above.

(14) Prepared as follows:



VII: bp 55 °C (0.1 mm); IR (neat) 1690, 1750 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.20 (d, J = 7.7 Hz, 3 H, $-CH_3$), 1.25 (t, J = 7.7 Hz, 6 H, $COOCH_2CH_3$, $COSCH_2CH_3$), 2.62 (m, 1 H), 2.88 (q, J = 7.7 Hz, 2 H, $-SCH_2CH_3$), 2.98 (m, 2 H), 4.17 (q, J = 7.7 Hz, 2 H, $COOCH_2CH_3$); mass spectrum *m/e* 204 (M^+, not observed), 159 (P^+, $M^+ - 45$, OEt), 143 (base, $M^+ - 61$, SEt), 115 ($M^+ - 99$, COSEt; 143 − 28, CO), 87 (115 − 28, CO), 92 (M^*, 92 × 143 = 115^2). Anal. Calcd for $C_9H_{16}O_3S$: C, 52.91; H, 7.89; S, 15.69. Found: C, 52.84; H, 7.83; S, 15.48.

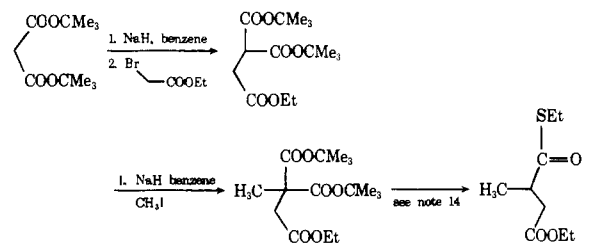
(15) Prepared as follows:



IV: bp 75 °C (0.1 mm); IR (neat) 1740, 1680 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.25 (t, J = 6.8 Hz, 3 H), 1.26 (t, J = 6.8, 3 H), 1.62 (s, 3 H), 2.95 (q, J = 6.8 Hz, 2 H, $-SCH_2CH_3$), 3.70 (d, J = 10 Hz, 1 H, $-CH_2Br$), 3.88 (d, J = 10 Hz, 1 H, $-CH_2Br$), 4.22 (q, J = 6.8 Hz, 2 H, $-COOCH_2CH_3$); mass spectrum *m/e* 284 (M^+, ^{81}Br), 282 (M^+, ^{79}Br), 223 ($M^+ - 61$, SEt, ^{81}Br), 221 ($M^+ - 61$, SEt, ^{79}Br), 203 (M^+ − Br), 195 (223 − 28, CO; 284 − 89, COSEt), 193 (221 − 28, CO; 282 − 89, COSEt), 123 (195 − CO_2, C_2H_2), 121 (193 − CO, C_2H_2). Anal. Calcd for $C_9H_{15}BrO_3S$: C, 38.17; H, 5.34; Br, 28.13; S, 11.32. Found: C, 38.38; H, 5.32; Br, 27.80; S, 10.88.

(16) Prepared by treatment of monoethyldimethylmalonic acid with thionyl chloride and followed by ethanthiol and triethylamine in benzene solution. VIII: IR (neat) 1740, 1680 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.18 (t, J = 6.8 Hz, 6 H, $COOCH_2CH_3$, $COSCH_2CH_3$), 1.4 (s, 6 H, $2CH_3$), 2.86 (q, J = 6.8 Hz, 2 H, $COSCH_2CH_3$), 4.1 (q, J = 6.8 Hz, $COOCH_2CH_3$); mass spectrum *m/e* 204 (M^+) 159 ($M^+ - 45$, OEt), 143 (base, $M^+ - 61$, SEt), 115 (143 − 28, CO), 92 (M^*, 92 × 143 = 115^2).

(17) Prepared as follows:



IX: bp 54 °C (0.07 mm); IR (neat) 1690, 1750 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.25 (t, J = 6.8 Hz, 6 H, $COOCH_2CH_3$, $COSCH_2CH_3$), 1.24 (d, J = 6.8 Hz, 3 H, CH_3), 2.36 (dd, J = 15.8 and 7.9 Hz, Ha) 2.80 (dd, J = 15.8 and 7.9 Hz, Hb), 2.88 (q, J = 6.8 Hz, 2 H, $COSCH_2CH_3$), 3.13 (heptet, J = 6.8 Hz, Hx), 4.15 (q, J = 6.8 Hz, 2 H, $COOCH_2CH_3$); mass spectrum m/e 204 (M^+, not observed), 159 (P^+, $M^+ - 45$, OEt), 143 ($M^+ - 61$, SEt), 115 (143 − 28, CO), 87 (115 − 28, CO), 92 (M^*, 92 × 143 = 115[2]). Anal. Calcd for $C_9H_{16}O_3S$: C, 52.91; H, 7.89; S, 15.69. Found: C, 52.95; H, 7.83; S, 15.55.

(18) P. Dowd, B. K. Trivedi, M. Shapiro, and L. K. Marwaha, *J. Am. Chem. Soc.*, **98**, 7875 (1976), have found that the acrylate group migrates in a nonenzymic model reaction of methylitaconate ⇄ α-methyleneglutarate isomerization. We thank Professor Dowd for a copy of this preprint.

(19) The role of the Co atom of B_{12} in the rearrangement after initial cleavage of the cobalt-carbon bond is still obscure.[20]

(20) B. T. Golding and L. Radom, *J. Am. Chem. Soc.*, **98**, 6331 (1976); R. B. Silverman and D. Dolphin, *ibid.*, **98**, 4626 (1976); K. L. Brown and L. L. Ingraham, *ibid.*, **96**, 7681 (1974).

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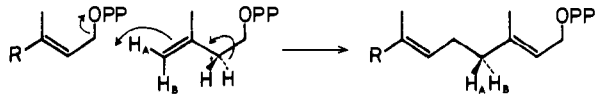
Construction of a Chiral Center by Use of the Stereospecificity of Prenyltransferase

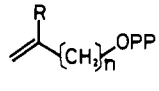
Sir:

The substrate specificity of prenyltransferase (farnesyl PP[1] synthetase EC 2.5.1.1) is not very stringent with respect to the structure of the allylic PP, and about 30 homologues of farnesyl PP have been synthesized by the action of farnesyl PP synthetase.[2] However, the specificity for the non-allylic PP is relatively high and only 3-ethylbut-3-enyl PP (**1b**) and 4-methylpent-4-enyl PP (**1c**) have been shown to be reactive as substrates in place of the natural substrate, isopentenyl PP (**1a**).[3] The stereochemistry of prenyltransferase is well established as shown in Scheme I by elegant works of Cornforth,

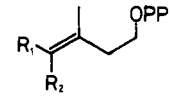
Scheme I



Popjak, and their collaborators.[4] Therefore, the examination of *E*- (**2a**) and *Z*-3-methylpent-3-enyl PP (**2b**) seems attractive



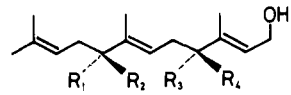
1a: n=2, R=CH_3
b: n=2, R=C_2H_5
c: n=3, R=CH_3



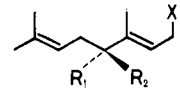
2a: R_1=CH_3, R_2=H
b: R_1=H, R_2=CH_3

and worth doing, because they are expected, if accepted as substrates in place of **1a**, to give chiral molecules which are enantiomeric with each other, and because such an anticipation, however, is dangerous since some modifications of a substrate may cause an abnormal reaction as exemplified by the case of **1b** and **1c** in the reaction catalyzed by isopentenyl PP isomerase[5] and prenyltransferase,[6] respectively. In this paper we now report that both **2a** and **2b** react stereospecifically to give new farnesyl PP homologues having chiral centers at which the new C-C bond is constructed during the enzymatic condensation.

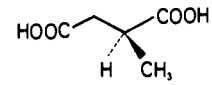
Compounds **2a** and **2b** were prepared from the corresponding alcohols[5] by the phosphorylation as usual. The incubation mixture for the enzymatic reaction contained, in a final volume of 5 mL, 100 μmol of Tris-HCl buffer, pH 7.7, 25 μmol of $MgCl_2$, 500 nmol of dimethylallyl PP or geranyl PP (**4d**), 500 nmol of **2a** or **2b**, and 0.5 mg of farnesyl PP synthetase (specific activity: 68.0 nmol of **1a** incorporated min^{-1} mg^{-1}) purified from pig liver.[2a] The mixture was incubated at 37 °C for 60 min and was then treated with alkaline phosphatase for more than 10 h. The hydrolysates were extracted with light petroleum and subjected to GLC-mass spectrometric analysis.[7] The products derived from dimethylallyl PP with **2a** showed two peaks. The major one emerged at 18.4 min (retention volume relative to that for *E,E*-farnesol (**3a**), 1.04; yield based on **2a**, 12.6%) and the mass spectrum for this material exhibited a parent ion at m/e 250 ($C_{17}H_{30}O$) with an intensity of 0.9% relative to the base peak at 69 (C_5H_9). Peaks were also observed at 232 (M − 18), 219 (M − 31), 189 (M − 18 − 43), 181 (M − 69), 163 (M − 18 − 69), which were reasonable for 4,8-dimethylfarnesol (**3d** or **3e**). The other minor component had a retention time of 7.3 min (1.05 relative to that for geraniol (**4a**), 3.9% yield) and the mass spectrum showed peaks at m/e 168 (M, $C_{11}H_{20}O$), 150 (M − 18), 137 (M − 31), 125 (M − 43), 81 (M − 18 − 69), and 69 (C_5H_9), indicating that the product was 4-methylgeraniol (**4b** or **4c**). The material derived from **4d** and **2a** showed a single peak at a retention volume of 1.02 relative to that for **3a** (19.2% yield) and the mass spectrum exhibited peaks at m/e 236 (M, $C_{16}H_{28}O$), 218 (M − 18), 205 (M − 31), 175 (M − 18 − 43), and 69 (C_5H_9) which was the base peak. These results indicate that the product was 4-methylfarnesol (**3b** or **3c**). The geometry of the newly formed double bond was proved to have *E* configuration by the NMR spectrum as shown later.[8] The *Z*-isomer **2b** was also enzymatically reactive and the products of condensation with dimethylallyl PP or **4d** were not distinguishable in GLC-mass spectrometric analysis from those obtained by the condensation of **2a** with dimethylallyl PP or **4d**.[9] The rates of condensation with **4d** of **2a** and **2b** relative to that of **1a** were 0.39 and 0.15, respectively.



3a: R_1=R_2=R_3=R_4=H
b: R_1=R_2=R_3=H, R_4=CH_3
c: R_1=R_2=R_4=H, R_3=CH_3
d: R_1=R_3=H, R_2=R_4=CH_3
e: R_1=R_3=CH_3, R_2=R_4=H



4a: R_1=R_2=H, X=OH
b: R_1=H, R_2=CH_3, X=OH
c: R_1=CH_3, R_2=H, X=OH
d: R_1=R_2=H, X=OPP
e: R_1=H, R_2=CH_3, X=OPP
f: R_1=CH_3, R_2=H, X=OPP



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Then, incubations of preparative scale (ca. 80-fold of the usual) were made to determine the configuration of the products and the free alcohols liberated by the treatment with alkaline phosphatase were purified by TLC.[10] The 4-methylfarnesol[11] formed by the condensation of **4d** and **2a** gave a negative ORD curve ($[\alpha]_D$ −10.7 ± 2.1°),[12] and conversely, the alcohol derived from **4d** and **2b** was found to be dextrotatory as expected ($[\alpha]_D$ +10.0 ± 8.3°). When these alcohols were converted to the corresponding aldehydes with active MnO_2, the signs of the ORD curves were both reversed. These results indicate that they were enantiomeric with each other. The 4,8-dimethylfarnesol[13] derived from dimethylallyl PP and **2a** also showed a negative ORD curve ($[\alpha]_D$ −11.4 ± 5.1°). The 4-methylfarnesal and the 4,8-dimethylfarnesol both of which were derived from **2a** were degraded by ozonolysis followed by hypoiodite oxidation to methylsuccinic acid.[4] Both samples of methylsuccinic acid were found to be levorotatory, indicating that the methylsuccinic acid was the *S* isomer (**5**).[14] Consequently the 4-methylfarnesyl PP from **2a** and **4d** and 4,8-dimethylfarnesyl PP from **2a** and dimethylallyl PP were both assigned to have *S* configuration, **3b**-PP and **3d**-PP, respectively. It is apparent that the products obtained by the