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BIOMIMETIC RADICAL REARRANGEMENT OF A THIOESTER GROUP MEDIATED BY A COBALT COMPLEX, COBALOXIME

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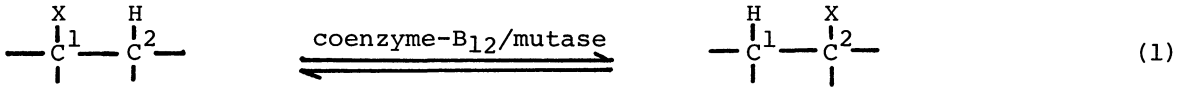
The possible involvement of cobalt in the radical rearrangement of a thioester group was tested by using cobaloxime as a mimic of cobalamin. The coexistence of cobaloxime(II) species stimulates the rearrangement of the thioester group. A coordinative interaction between sulfur and cobalt is proposed for the assistance of this rearrangement.

In biological system, coeyzyme-B_{12} catalyzes the rearrangement of variety of functional groups as shown in Eq. 1 (X=OH, NH_2, $C(CH_2)COOH$, $CH(NH_2)COOH$, COSCoA).[1)]



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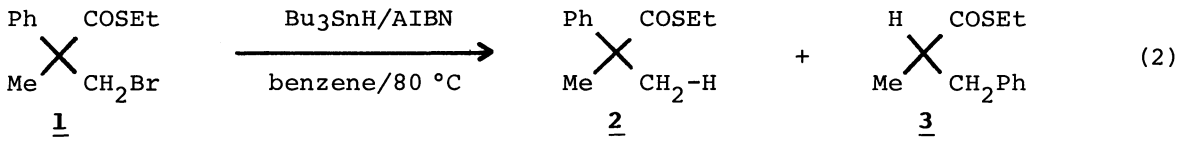


(2)

1 **2** **3**

We have been concerned with model studies on the conversion of methylmalonyl-CoA into succinyl-CoA (X=COSCoA in Eq. 1) using organo-dimethylglyoximato-(pyridine)cobalt(III), organo-cobaloxime, and showed the following migratory order of the groups in radical mechanism: ArCO-, RCO- > Aryl- ≫ ROCO-.[2)]

The chemical property of a thioester group is more like a ketone than an ester due to the poor n-π conjugation.[3)] We assume therefore that the migration tendency of a thioester group is in between a ketone and an ester, and we tested the competitive radical rearrangement of a thioester group and a phenyl group.

Treatment of 2-(ethylthio)carbonyl-2-methylphenetyl bromide (**1**) with tributylstannane in benzene gave a reduction product **2** and a phenyl-migrated product **3** in quantitative yield: **2**/**3** = 100/0 (Bu_3SnH, 10^{-1} M), 72/28 (10^{-2} M), and 21/79 (10^{-3} M) (Eq. 2).[4)] This result suggests that a phenyl group rearranges more easily than a thioester group and is in accord with the kinetic studies by Ingold et al., and Wollowitz and Halpern.[5,6)] Photolyses of 2-(ethylthio)carbonyl-2-methylphenethylcobaloxime (**4**) gave somewhat contrasting results (Eq. 3 and Table 1).[7,8)] The photolyses gave the products formed by the rearrangement of both phenyl and thioester groups (total yield: 45% in benzene - ca. 100% in THF).

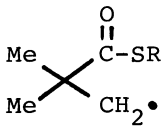
It has been established that the photolysis of alkylcobaloxime generates a pair of alkyl and cobaloxime radicals.[2, 9)] The formation of **5** and **6** in protic medium can not be rationalyzed by an anion mechanism. The formation of unexpected

product **7** can be explained by the attack of radical intermediate on the thioester group and that is another competing process to the radical rearrangement of the thioester group.[10] Contrary to the radical reaction initiated by tributylstannane (Eq. 2), the (ethylthio)carbonyl group rearranges even more efficiently than the phenyl group on the photolysis of cobaloxime **4**. In chloroforn the reduction product **2** is the only product due to the strongly hydrogen donating ability of this solvent. These findings suggest that the rearrangement of the thioester group can be explained by a radical mechanism under the influence of the cobatl complex.[11,12]

Photolyses of 2-(alkylthio)carbonyl-2-methylpropylcobaloxime (**8**) gave the rearranged products **10** and **11** in addition to the reduction product **9** (total yield: 30 - 40% based on the consumed **8**)(Eq. 4 and Table 2).[8, 13, 14] In these photolyses 2-(alkylthio)carbonyl-2-methylpropyl radical (**12**) takes competitive process of hydrogen abstraction and thioester migration. The hydrogen abstraction to give **9** surpasses the thioester migration in chloroform, and the migrated products **10** and **11** become more important in poor hydrogen donating solvents. Treatment of 2-(alkylthio)carbonyl-2-methylpropyl bromide with tributylstannane in benzene gave only the reduction product **9**.

It is notable that ethyl-thioester group rearranges with more ease than t-butyl-thioester group in the same solvent. Two explanations are possible for this difference in the rearrangement tendency. One is the steric inhibition of cobalt-sulfur interaction which facilitates the radical rearrangement by the reduction of n-π conjugation. Another is the conformational effect in which the t-butyl group destabilyzes the geometry of a transition state of the radical rearrangement. We prefer the first explanation since the cobalt-assisted migration of the thioester group in the photolysis of **4** can not be explained by the second factor. The coordinative interaction between sulfur and cobaloxime in the intermediate radical **13** must suffer a severe steric inhibition when the alkyl group (R) is a bulky t-butyl group.

The present findings, (a) the reversal of the rearrangement tendencies of phenyl and thioester group in the absence and presence of cobaloxime and (b) the difference in the migration tendency of ethyl- and t-butyl-thioester groups, indicate the involvement of cobalt(II) species in the migration of thioester group.



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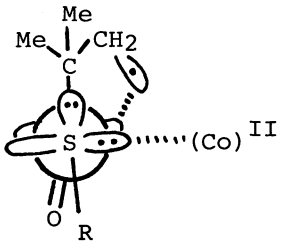

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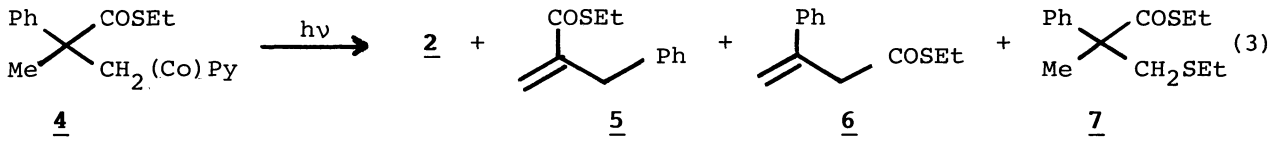

Table 1. Photolyses of **4**

Solvent	Product composition/% 2	5	6	7
benzene	0	16	27	57
methanol	25	7	18	50
THF	60	8	11	21
chloroform	100	0	0	0

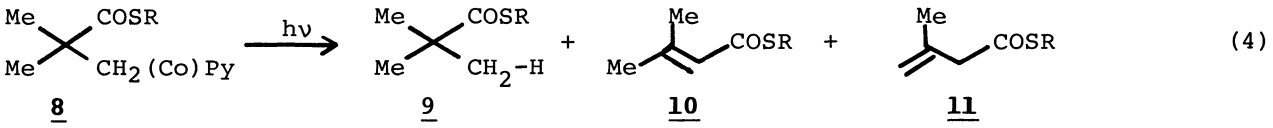

Table 2. Photolyses of **8**

R	Solvent	Product composition/% 9	10	11	R	Solvent	Product composition/% 9	10	11
Et	benzene	30	0	70	t-Bu	benzene	50	0	50
Et	dichloromethane	50	50	0	t-Bu	dichloromethane	88	12	0
Et	methanol	76	24	0	t-Bu	methanol	100	0	0
Et	chloroform	100	0	0	t-Bu	chloroform	100	0	0

References

1) Review: "B_{12}," ed by D. Dolphin, John-Wiley and Sons, New York (1982); "Comprehensive Organic Chemistry," ed by E. Haslam, Pergamon Press, Oxford (1979), Vol. 5, pp. 563-584.

2) M. Tada, K. Miura, M. Okabe, S. Seki, and H. Mizukami, Chem. Lett., 1981, 33; M. Okabe, T. Osawa, and M. Tada, Tetrahedron Lett., 22, 1899 (1981); M. Tada, S. Akinaga, and M. Okabe, Bull. Chem. Soc. Jpn., 55, 3939 (1982); M. Tada, K. Inoue, and M. Okabe, Bull. Chem. Soc. Jpn., 56, 1420 (1983).

3) "The Chemistry of Enzyme Action," ed by M. I. Page, Elsevier, Amsterdam (1984), pp. 253.

4) A benzene solution of **1** (1.0×10^{-4} mol), tributylstannane (4×10^{-4} mol), and small amount of AIBN was refluxed for 4 h. The concentration of the reaction mixture was varied by changing the volume of benzene.

5) D. A. Lindsay, J. Lusztyk, and K. U. Ingold, J. Am. Chem. Soc., 106, 7080 (1984).

6) S. Wollowitz and J. Halpern, J. Am. Chem. Soc., 106, 8319 (1984).

7) Cobaloxime **4** and **8** were prepared from bromide **1** and 2-(alkylthio)carbonyl-2-methylpropyl bromide, respectively, by the reaction with cobaloxime(I) prepared in situ from cobaloxime(III) by $NaBH_4$-reduction. The organo-cobaloximes thus obtained were purified by chromatography (Florisil/chloroform) and recrystallization from benzene-hexane. **4**, IR($CHCl_3$): 2970, 1662, 1558 cm^{-1}; NMR($CDCl_3$): δ (J) 1.11(3H, t, J=6.5), 1.73(1H, d, J=9), 1.74(3H, s), 1.92(6H, s), 1.97(6H, s), 2.67(2H, q, J=6.5), 2.89(1H, d, J=9), 7.10-7.45(7H, m), 7.70(1H, t, J=8), 8.49(2H, d, J=9). **8**(R=Et), IR($CHCl_3$): 2970, 1665, 1555 cm^{-1}; NMR($CDCl_3$): 1.15 (6H, s), 1.19(3H, t, J=6.5), 1.88(2H, s), 2.03(12H, s), 2.74(2H, q, J=6.5), 7.25(2H, t, J=8), 7.60(1H, t, J=8), 8.46(2H, t, J=8). **8**(R=t-Bu), IR($CHCl_3$): 2970, 1665, 1560 cm^{-1}; NMR($CDCl_3$): 1.12(6H, s), 1.42(9H, s), 1.87(2H, s), 2.15 (12H, s), 7.38(2H, t, J=8), 7.80(1H, t, J=8), 8.68(2H, d, J=8).

8) A solution of **4** (50 mg) in one of the solvent (16 ml) was irradiated by a high pressure mercury lamp through a soft glass filter. Products **2** and **5** were identified with the authentic samples. The structures of **6** and **7** were deduced from spectral data. **6**, IR(CCl_4): 1689, 1630, 701 cm^{-1}; NMR($CDCl_3$): 1.21(3H, t, J=7.5), 2.83(2H, q, J=7.5), 3.68(2H, s), 5.32(1H, s), 5.64(1H, s), 7.17-7.58(5H, m). **7**, IR(CCl_4): 1675, 958, 699 cm^{-1}; NMR($CDCl_3$): 1.11(3H, t, J=7.5), 1.21(3H, t, J=7.5), 1.75(3H, s), 2.29(2H, q, J=7.5), 2.86(2H, q, J=7.5), 3.12(1H, d, J=13), 3.18(1H, d, J=13), 7.35(5H, diffused s).

9) D. N. Ramokrisna Rao and M. C. R. Symons, J. Chem. Soc., Faraday Trans. 1, 80, 423 (1984); B. T. Golding, T. J. Kemp, and H. H. Sheena, J. Chem. Res. S, 1981, 34 and M, 1981, 0334-0361.

10) In the related study a similar sulfide was obtained when 2-ethoxycarbonyl-2-(ethylthio)carbonyl-propyl bromide was treated with tributylstannane in the presence of ethyl-thioester of 3-methylbutanoic acid.

11) Other types of cobalt participation have been also proposed. H. Flohr, W. Pannhorst, and J. Rétey, Helv. Chim. Acta, 61, 1565 (1978); L. Salem, O. Eisenstein, N, Anh, H. B. Burgi, A. Devaquest, G. Segal, and A. Veillard, Nouv. J. Chim., 1, 335 (1977).

12) We do not deny the anion mechanism under reductive conditions but we believe that the non-reductive conditions are more alike to biological conditions. J. H. Grate, J. W. Grate, and G. N. Schrauzer, J. Am. Chem. Soc., 104, 1588 (1982). It has been also reported that an organo-cobaloxime gives alkyl radical even under reductive conditions. D. J. Pasto, D. A. Timmers, and N. J. Huang, Inorg. Chem., 23, 4117 (1984).

13) A solution of **8** (40 mg) was irradiated in the same manner as in the photolyses of **4** and the products were identified with authentic samples using glc-mass. The yields and relative ratio of the products were determined by glc analyses.

14) Product **11** must be a primary one even in dichloromethane and methanol, and **11** is expected to isomerize to **10** under the photolysis conditions. This feature is supported by the photolysis of **4** in this work to give the terminal olefins and the similar results in the earlier studies.[2)]

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