The Effect of Cobalt(II) Complex on the Reactivity of Thioester in Radical Process

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The 1,2-rearrangement of an (alkylthio)carbonyl group and the radical substitution on sulfur are stimulated by the coexisting cobalt(II) complex, generated intermolecularly or intramolecularly.

The enzymatic rearrangement of methylmalonyl-coA to succinyl-coA is triggered by the homolysis of adenosyl-coenzyme-B_{12} into a cobalamin(II) and adenosyl radical. The latter radical abstracts hydrogen from a substrate (H-Sub) to produce a radical pair of cobalamin(II), $\{Co^{II}\}$, and substrate radical (**a** in Scheme 1).[1] The radical pair in this enzymatic process has been proved by a magnetic field effect.[2]

Homolysis of triphenyltincobaloxime,[3] $Ph_3Sn[Co]L$, in the presence of a halide (X-Sub') generates a radical pair of a cobalt(II) complex radical, $[Co^{II}]$, and an organo radical (Sub'•) (**b** in Scheme 1). The most conventional radical generation from an alkyl halide by tributyltin radical, on the contrary, produces a lone radical (Sub"•) (**c** in Scheme 1). These backgrounds prompted us to explore the reaction of 2-(ethylthio)carbonyl-2-phenylpropyl bromide (**1**) with triphenyltincobaloxime, hexaphenylditin, and tributyltinhydride. The tincobaloxime produces the cobaloxime(II) radical which is expected to interact with the thioester and to affect the reactivity of the thioester.[4]

$$\text{Ad-\{Co\}} + \text{H-Sub} \xrightarrow{enzyme} \text{Ad-H} + \{Co^{II}\}\bullet + \text{Sub}\bullet \qquad (a)$$

$$Ph_3Sn\text{-}[Co] + \text{X-Sub'} \xrightarrow{h\nu} Ph_3Sn\text{-}X + [Co^{II}]\bullet + \text{Sub'}\bullet \qquad (b)$$

$$Bu_3Sn\bullet + \text{X-Sub"} \longrightarrow Bu_3SnX + \text{Sub"}\bullet \qquad (c)$$

Scheme 1.

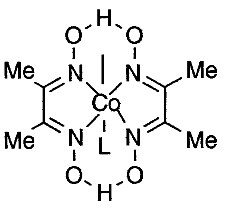
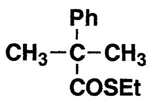


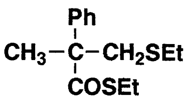
Figure 1. Cobaloxime, [Co]L.

The thioester **1** was chosen as a substrate since the resulting radical **2** gives phenyl-migrated products (**4a** and **4b**) and thioester-migrated products (**5a** and **5b**) by competitive radical migrations (Scheme 2).[5] The phenyl migration (**a** in Scheme 2) should not be affected by the coexisting cobalt(II) complex and can be used as an internal radical clock.[6] Radical **2** results in the formations of a reduction product **6**,[5] a hydrogen abstraction product **4a**[5,7] and a hydrogen-elimination product **4b**[5] from the phenyl-migrated radical (**A** in Scheme 2), a hydrogen-abstraction product **5a**[5,8] and a hydrogen-elimination product **5b**[5] from the thioester-migrated radical (**B** in Scheme 2), and an intermolecular radical substitution product **7**[5] on sulfur.



$$CH_3\text{-}\underset{\textstyle COSEt}{\overset{\textstyle Ph}{C}}\text{-}CH_3$$

6

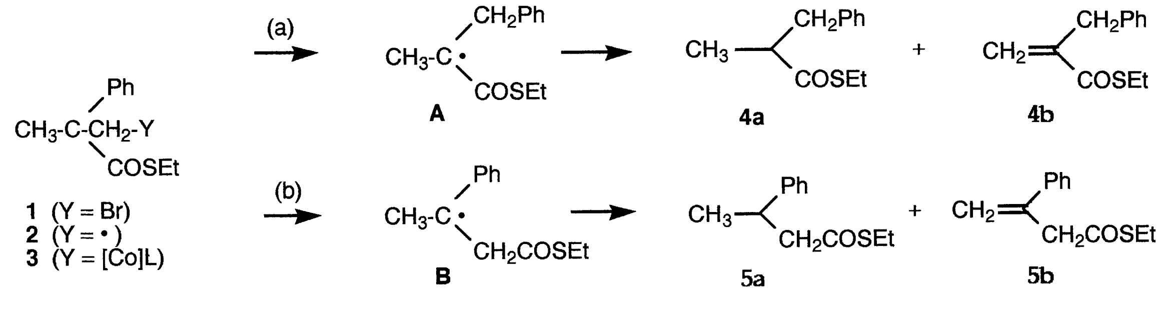


$$CH_3\text{-}\underset{\textstyle COSEt}{\overset{\textstyle Ph}{C}}\text{-}CH_2SEt$$

7

All the products were identified with the reported or independently synthesized authentic samples and the yields were determined by gaschromatography using internal standards.

As seen in the table 1, the radical **2** generated by tin radicals (run 1 and 2) rearranges its phenyl group in preference to the thioester group judged from the product ratio **5**/**4**. On the contrary, thioester migration (**b** in Scheme 2) prevails over phenyl migration (**a** in Scheme 2) when the radical **2** coexists with the cobaloxime(II) complex (run 3 and 4).



Scheme 2.

Table 1. Radical reactions of 2-(ethylthio)carbonyl-2-phenylpropyl bromide (**1**) and cobaloxime **3**

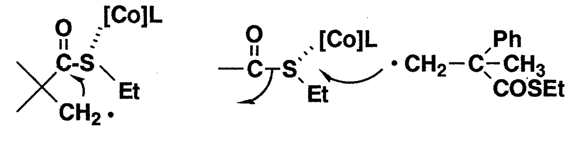
Run	Substrate and reagent ^{a}	Concentration $/10^{-3}$ mol/dm^{3}	Activation method	Reaction time /h	Yield/% **4**	**5**	**6**	**7**	Total yield/%	Ratio **5/4**	**7/4**
1	**1** + Bu_3SnH^{b}	1.0	reflux in benzene	4	42	5.4	32	0	79.4^{5}	0.13^{5}	0
2	**1** + $(Ph_3Sn)_2$	1.6	hν in benzene^{c}	48	14	2.5	9.7	0	26.2^{d}	0.18	0
3	**1** + $Ph_3Sn[Co]L^{e}$	1.6	hν in benzene^{c}	62	3.0	8.7	0.5	13	25.2^{d}	2.9	4.3
4	**3**	5.4	hν in benzene	48	7.2	12	0	26	45.0^{5}	1.7^{5}	3.6

[a] [Reagent] / [**1**] = 1.0. [b] Catalytic amount of AIBN was added. [c] Rayonett 350 nm lamps were used.
[d] Large amount of the starting materials were recovered. [e] L = 4-t-Butylpyridine.

Furthermore, it is notable that the radical **2** gave an intermolecular radical substitution product **7**[9] as a major product in the presence of cobaloxime(II) species (run 3 and 4), whereas no intermolecular substitution on sulfur takes place in the absence of the cobalt(II) complex (run 1 and 2). Thus the radical substitution on sulfur is also stimulated by the coexisting cobaloxime(II) species as evidenced by the product ratio **7/4**. The rate of the phenyl rearrangement is considered to be constant throughout runs 1- 4 since no special interaction is envisaged between the phenyl group and the cobaloxime(II). The relative rates of thioester-migration and the substitution on sulfur are reasonably estimated from the values of **5/4** and **7/4** respectively. All the isolated products were stable under the reaction conditions. These results convince us the involvement of the cobalt(II) species in the radical reactions, rearrangement and substitution, of thioester group.

In the case of run 4, the migration of thioester group may take place in the bound state to cobalt or in the solvent caged radical pair immediately after the homolysis. The coexisting cobalt(II) complex stimulates both intramolecular and intermolecular processes, and the above mentioned mechanisms are excluded from the result of run 3 in which the organo radical and cobalt(II) radical generate independently from the different sources. This stimulation effect seen in runs 3 and 4 must originate from the same mode of action by the cobalt(II) complex.

Murakami *et al*[10] have proved that a similar 1,2-rearrangement of a thioester group is stimulated by confining an organo radical and a cobalamin(II) derivative in a rigid bimolecular membrane. Though they did not specify, there are two explanations for this effect. One is the elongation of the life time of the radical species and another is the stimulation by the interaction between the radical pair. In the present reaction systems the radical pair diffuse fast, and the effect of the cobalt(II) complex is modest in comparison with Murakami's system.



a) 1,2-Rearrangement b) Radical substitution on sulfur

Figure 2. Possible mechanism of the involvement of cobaloxime(II) in the radical processes.

We cannot define the origin of the cobaloxime(II) complex effect from present observations, but the cobalt(II)-sulphur interaction shown by ESR[4] suggests these reactions being stimulated by this kind of coordinative interaction (Figure 2). This concept is supported by the effect of a trans ligand (L) of cobaloxime(II) to the reactivity of radical substitution on the sulfur of thioester by methyl radical.[11]

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References and Notes

1 *B12,* ed. D. Dolphin, John-Wiley and Sons, New York (1982).

2 C. B. Grisson, *Chem. Rev.*, **95**, 3 (1995).

3 $Ph_3Sn[Co](4\text{-}^{t}Bu\text{-}Py)$: mp 180 - 182 °C (dec); δ_H (90 M Hz, $CDCl_3$) 1.24 (9H, s), 1.71 (12H, s), 7.03-7.83 (17H, m), 8.40 (2H, d, J=5.1), 18.43-18.52 (2H, br s). Elemental analysis (C, H, N), $C_{35}H_{42}CoN_5O_4Sn$.

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5 M. Tada, K. Inoue, K. Sugawara, M. Hiratsuka, and M. Okabe, *Chem. Lett.*, **1985**, 1821; **1986**, 703.

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7 Bp 115 °C/2.5 mmHg; δ_H (90 MHz, $CDCl_3$) 1.15 (3H, d, J=7.3), 1.19 (3H, t, J =7.6), 2.83 (2H, q, J =7.6), 2.59-3.17 (3H, m), 7.05-7.34 (5H, m); ν_{max}/cm^{-1} (neat) 1686; *m/z* 208 (M^+, 12.5%), 91 (100%). Elemental analysis (C, H, N), $C_{12}H_{16}OS$.

8 Bp 108 °C/1.8 mmHg; δ_H (90 MHz, $CDCl_3$) 1.19 (3H, t, J=7.3), 1.29 (3H, d, J=6.9), 2.79 (2H, d, J =5.9), 2.83(2H, q, J =7.3), 3.29 (1H, t, J=7.3), 7.08 - 7.38 (5H, m); ν_{max}/cm^{-1} (neat) 1686; *m/z* 208 (M^+, 13%), 105 (100%). Elemental analysis (C, H, N), $C_{12}H_{16}OS$.

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10 Y. Murakami, Y. Hisaeda, and T. Ohno, *J. Chem. Soc., Perkin Trans. 2*, **1991**, 405.

11 M. Tada, T. Yoshihara, and K. Sugano, *J. Chem. Soc., Perkin Trans. 1,* in press.