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A MIMIC STUDY ON COENZYME-B_{12} USING ORGANOCOBALOXIMES. THE REARRANGEMENT OF 1-SUBSTITUTED-2-OXOCYCLOPENTYLMETHYL RADICAL

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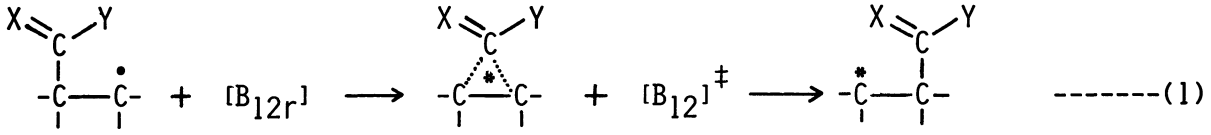
The radical cleavage of the carbon-cobalt bond of 1-phenyl-2-oxocyclopentylmethyl cobaloxime (1) and 1-ethoxycarbonyl-2-oxocyclopentylmethyl cobaloxime (2) gave only 3-phenylcyclohex-2-enone (7) and 3-ethoxycarbonylcyclohex-2-enone (8), respectively, by acyl migration. This rearrangement may be a reasonable mimicry of the ester migration mediated by coenzyme-B_{12}.

Enzymatic isomerizations such as glycol to aldehyde and methylmalonyl-CoA to succinyl-CoA involve coenzyme-B_{12} in the deep site of the rearrangement.[1] Cation mechanism,[2] radical-cation mechanism,[3] radical mechanism,[1] and carbene mechanism[4] have been proposed for the rearrangement of a hydroxy group or an amino group. Cation,[5] radical,[6] and anion[7] mechanisms have been claimed for the isomerization of methylmalonyl-CoA or α-methyleneglutaric acid. The real entity of the rearrangement step depicted by Eq. 1, however, is still in a black box. It has been shown that coenzyme-B_{12} splits into paramagnetic cobalamin ($[B_{12r}]$) and 5'-deoxyadenosyl radical and the latter radical abstracts a hydrogen atom from a substrate to give a substrate radical.[8] The $[B_{12r}]$ and the substrate radical may collapse into a radical pair (* = •; ‡ = •) or an ion pair (* = + or −; ‡ = − or +). The ionic path must involve an electron transfer process between the radicals. The soft nature and the electronic diversity[9] of coenzyme-B_{12} make all the three mechanisms possible.



(X = CH_2, Y = COOH) or (X = O, Y = SCoA)

It has been shown by our study[10] and others[11] that the photolysis of the Co-C bond of organocobaloxime gives a organo-radical and cobaloxime(II). A pair of radical thus formed must be a reasonable mimicry of the substrate radical and the $[B_{12r}]$. Now we like to report model reactions of coenzyme-B_{12} using bis-dimethylglyoximato(pyridine)cobalt, cobaloxime, as the mimicry of cobalamin.

1-Phenyl-2-oxocyclopentylmethyl cobaloxime (1)[12] and 1-ethoxycarbonylcyclopentylmethyl cobaloxime (2)[7,12] were prepared from the corresponding bromides and cobaloxime anion, $(Co^{I})^{-}$.[13] Conservation of the carbon skeleton in the organic moiety of the organocobaloximes (1 and 2) is shown by the AB-type signals due to the methylene group next to cobalt (δ=1.05 and 2.91 for 1; 1.50 and 2.15 for 2).

The photolysis[14] of 1-phenyl-2-oxocyclopentylmethyl cobaloxime (1) gave 3-phenylcyclohex-2-enone (7) as an only isolable product from the organic moiety. Similarly 1-ethoxycarbonyl-2-oxocyclopentylmethyl cobaloxime (2) gave only 3-ethoxycarbonylcyclohex-2-enone (8). The product (7)[15] and (8)[16] were identical with the authentic samples prepared by the reported methods. The isolated yield of the products on the photolyses are listed in the table below. The photolyses under the present condition left the starting organocobaloximes in varying amount, especially in the case of 2, but the yields listed in the table were based on the amount of organocobaloxime (1) or (2). The photoreactivity of the organocobaloximes seems not to relate with the polarity or the ability of hydrogen atom donation of solvents. This fact indicates that the rearrangement takes a radical process to give a radical (5 or 6) and the loss of hydrogen atom from the radical intermediate is followed.

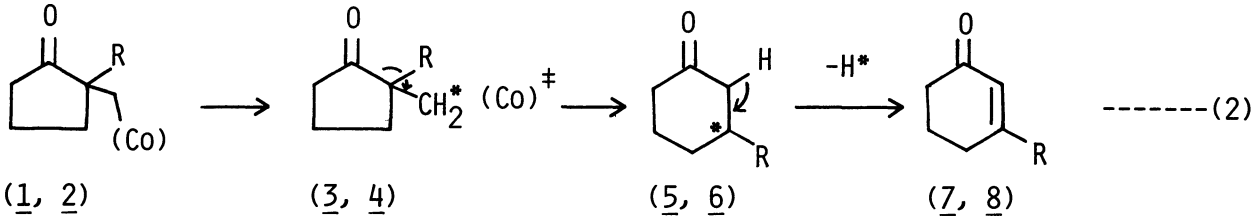
Table. The yield of 7 and 8 on the photolyses of 1 and 2

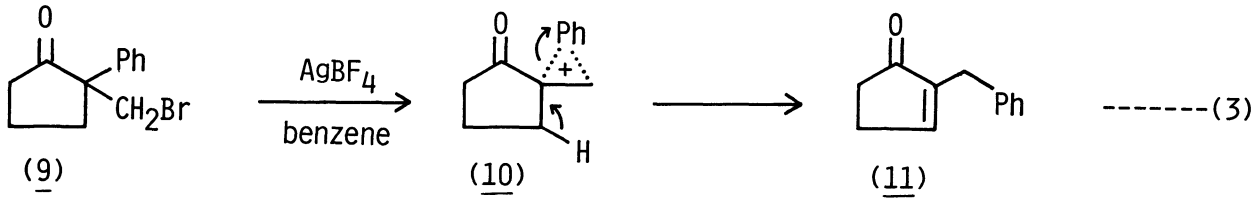
Product %	Solvent			
	Benzene	Chloroform	Acetonitrile	Acetonitrile-water (3:1)
7	85	72	80	92
8	31	36	44	40

The carbonium ion formed by the action of Ag^{+} on 1-phenyl-2-oxocyclopentylmethyl bromide (9) gave only 2-benzylcyclopent-2-enone (11)[17] possibly through a phenonium ion (10). This result excludes the cationic nature (* = +), of the intermediate (3) in the photolysis of organocobaloxime (1) which gave only 7.

If the intermediates (3 and 4) have anionic nature (* = -), the photolyses in the protic medium (CH_3CN-H_2O) must give saturated ketones, 3-substituted cyclohexanones, instead of the enones (7 and 8). For the formation of the enones (7 and 8), a hydride must be lost from the adjacent position to carbonyl group at the intermediates (5 and 6). Lowe and Ingraham[7] reported that 3-ethoxycarbonylcyclohexanone was formed in only 0.3 % yield by the action of 1,4-butanedithiol on organocobaloxime (2), and they claimed an anion mechanism for this process. 1,4-Butanedithiol, however, is a good hydrogen donor and the radical species (6) (* = •) can collapse into 3-ethoxycarbonylcyclohexanone in the presence of the dithiol. This possibility was ascertained by the reaction of 1-phenyl-2-oxocyclopentylmethyl bromide (9) with tributyltin hydride, which produces the radical intermediate (3) (* = •) effectively. 3-Phenylcyclohexanone, an acyl-migrated product, was obtained as a major product (89%) and 2-methyl-2-phenylcyclopentanone, a non-rearranged product, was obtained as a minor product (3%).[18]

As we described here, the migration of acyl group in preference to alkyl, phenyl, and ethoxycarbonyl groups takes a radical process. Though the radical in





solution may differ in its chemical nature from the radical generated in an enzyme system, the present finding indicates the less validity of ion mechanisms for the coenzyme-B_{12} mediated isomerization of methylmalonyl-CoA, α-methyleneglutaric acid, and the related transformation of substrates.

Rétey et al.[1] proposed the catalytic action of cobalt for the migration of ester group. As model they used the organocobaloxime which was strapped by the chain containing dimethylmalonyl ester group. The steric strain on the medium ring in this "strapped cobaloxime" should be a driving force to enlarge the strapped ring by the migration of the ester group, and this model system may not be good enough to imitate the coeyzyme-B_{12} mediated rearrangement of ester groups. The present study shows that the radical rearrangement of an acyl group is a favored process even without the catalysis of cobalt. It may be inferred therefore that the migration of COSCoA (a group similar to COR, though not identical) in the enzyme system, methylmalonyl-CoA mutase, may proceed via a protein-bound radical ($\cdot CH_2CH(COOH)COSCoA$) and not require the assistance of cobalt.

The biomimetic systems in the present study are chosen for experimental convenience and differ from the biochemical system of the nature. Also the radical generated by photolysis may differ in its property from the radical in the enzyme system. These problems shoud be solved by seeking the better biomimetic system and studies are currently under way in our laboratory.

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12) The organocobaloximes (1 and 2) gave reasonable values in elemental analyses and spectral data. 1, mp 150-155°C(dec.); ir(KBr), 1724, 1601, 1560, 1495, 1445, and 1226 cm^{-1}; nmr($CDCl_3$), (δ), 1.05(1H, d, J=10 Hz), 1.80(6H, s), 1.89(6H, s), 1.84-2.30(6H, m), 2.91(1H, d, J=10 Hz), 6.93-7.55(7H, m), 7.71(1H, t, J=8 Hz), and 8.49(2H, d, J=8 Hz).
2, mp 165-168°C(dec.); ir(KBr), 1735, 1705, 1601, 1560, 1495, 1450, 1240, and 1090 cm^{-1}; nmr($CDCl_3$) (δ), 1.19(3H, t, J=7 Hz), 1.32-2.36(6H, m), 1.50(1H, d, J=10 Hz), 2.02(12H, s), 2.15(1H, d, J=10 Hz), 3.91 and 3.96(2H, q, J=7 Hz), 7.00(2H, t, J=8 Hz), 7.44(1H, t, J=8 Hz), and 8.21(2H, d, J=8 Hz).

13) Cobaloxime anion, $(Co^{I})^{-}$, was prepared in methanol or ethanol from $CoCl_2$, dimethylglyoxime, pyridine, and $NaBH_4$ under basic condition. See ref. 10.

14) A solution of one of the organocobaloximes (1 or 2, $2.0X10^{-4}$ mol) in 20 ml of solvent was placed in a soft glass tube and dissolved oxygen was purged by bubbling argon. The photolysis was carried out under water cooling for 18 h by a 40w fluorescent lamp, and the product was isolated by chromatography on Florosil using hexane-chloroform as eluent.

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18) The mixture of Bu_3SnH (0.1 $mol.dm^{-3}$), bromide (9) (0.05 mol. dm^{-3}, and AIBN (trace) in benzene was refluxed for 3 h.

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