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Acyl Transfer from *S*-Monoacyldihydrolipoamide to Benzylamine in the Presence of Oxidizing Agents

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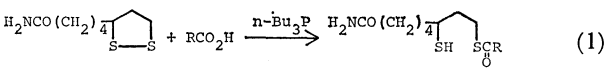
Acyl transfer reaction from *N*-benzyl-8-*S*-(*p*-nitrobenzoyl)dihydrolipoamide to benzylamine was enhanced with oxidizing agents such as cobalt(II) ion or a soluble flavin under an oxygen atmosphere or with di-4-pyridyl disulfide, accompanied by the formation of *N*-benzyllipoamide.

Lipoic acid is known to work as an acyl carrier in the oxidative decarboxylation of α-keto acids in living systems through formation of active acyl intermediates, 6-*S*-acyldihydrolipoic acids which in turn acylate coenzyme A, and subsequent oxidation of the resultant dihydrolipoic acid to lipoic acid, enzymatically.

We have already reported that 8-*S*-monoacyldihydrolipoamides were synthesized by the reductive acylation of lipoamide with tributylphosphine in high yields (Eq. 1).[1)]



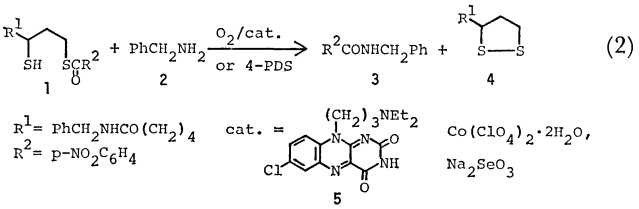
(1)

Further, we have found that acyl transfer from *S*-monoacyldihydrolipoamides to amine was accelerated by silver ion more effectively than that from *S,S'*-diacyl derivatives, caused by the activation of acyl group by silver ion bound to the neighboring mercapto group.

On the other hand, the acyl transfer from hydroquinone monobenzoates to alcohols has been reported to proceed oxidatively by use of oxidizing agents such as Ce^{4+}, Tl^{3+}, NBS, or Br_2,[3)] and by electrochemical oxidation.[4)]

These results suggested us to investigate the acyl transfer from *S*-monoacyldihydrolipoamide to amines in the presence of oxidizing agents for thiols, expecting that the activation of acyl group through two-electron oxidation of neighboring mercapto group to form amide and lipoamide. Various kinds of oxidizing agents are considered to be applied to the present case. However, by using some oxidizing agents which form S radicals rather than S cations from thiols, the dimerization of *S*-monoacylated dithiols might precede the activation of acyl groups, as reported in the iodine oxidation of 8-*S*-acetyldihydrolipoic acid in methanol[5)] (Scheme 1).

We now report the acyl transfer from *N*-benzyl-8-*S*-(*p*-nitrobenzoyl)dihydrolipoamide (**1**) to benzylamine (**2**) in the presence of oxidizing agents such as an active flavin (**5**),[6)] metal salts,[7)] and di-4-pyridyl disulfide (4-PDS),[8)] which are known to oxidize thiols to disulfides *via* the formation of complexes or adducts between oxidizing agents and thiols (Eq. 2).



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Experimental

^{1}H-NMR spectra were recorded on a JEOL-PMX 60 NMR spectrometer using tetramethylsilane as an internal reference.

N-Benzyl-8-*S*-(*p*-nitrobenzoyl)dihydrolipoamide (**1**) and *N*-benzyl-*S,S'*-bis(*p*-nitrobenzoyl)dihydrolipoamide were prepared by the methods reported previously.[2b)] An active flavin (**5**) was also prepared according to the procedure of King *et al.*[9)] GLC analyses were carried out on a JEOL-1100 gas chromatograph (10% SE-30, stainless-steel column, 220 °C, N_2 carrier gas).

Acyl Transfer Reaction from Monoacyl Derivative ***1*** *to Benzylamine (****2****) in the Presence of Cobalt(II) Perchlorate as Catalyst.* To a THF solution (3 ml) of **1** (20 mg, 0.045 mmol) and amine **2** (0.1 ml, 0.9 mmol) was added cobalt(II) perchlorate (1.2 mg, 0.004 mmol) under an oxygen atmosphere and stirred for 15 h at room temperature. The reaction mixture was poured into ethyl acetate (50 ml), and the solution was washed with 0.1 M† HCl and saturated aqueous NaCl, then dried over $MgSO_4$. The solvent was removed under reduced pressure to obtain a solid residue. ^{1}H-NMR spectrum of the residue in $CDCl_3$ was measured to show a quantitative formation of *N*-benzyl-*p*-nitrobenzamide (**3**) and *N*-benzyllipoamide (**4**) compared with the authentic samples. The yield of amide **3** was calculated from the ratio of the ^{1}H-NMR signal of benzyl proton in **3** (δ=4.6) to the sum of benzyl protons in **1** and **4** (δ=4.4) to be 100% (Fig. 1). The residue obtained in the scale up experiment (two times of the above procedure) was chromatographed on silica gel with ethyl acetate to obtain amide **3** (18 mg, 78%) and **4** (19 mg, 71%). Authentic sample of **3** was prepared from *p*-nitrobenzoyl chloride and benzylamine mp 142.5—143.5 °C (from ethanol) (lit,[10)] 141—142.5 °C); NMR ($CDCl_3$): δ 4.6 (2H, d, J=5.8 Hz, $PhCH_2$), 5.9 (1H, s, NHCO), 7.4 (5H, s, C_6H_5), 8.1 (4H, q, J=9.2 Hz, *p*-$NO_2C_6H_4$). Amide **4** was prepared by the method reported previously.[2c)] NMR ($CDCl_3$): δ 1.5—2.0 (8H, m, $>CH_2$), 3.2 (2H, t, 5-membered CH_2–SS), 3.6 (1H, m, CH–SS), 4.4 (2H, d, J=5.7 Hz,

† 1 M = 1 mol dm^{-3}.

$PhCH_2$), 5.9 (1H, s, NHCO), 7.3 (5H, s, C_6H_5).

In case of other catalysts or 4-PDS, the reaction was carried out in the same procedure as described above.

Kinetic measurements were carried out by GLC analyses of the reaction solutions operated in the same way described above at 30 °C in the presence of *N*-cyclohexyl-*p*-nitrobenzamide as an internal standard for GLC analyses.

Acyl Transfer Reaction from Monoacyl Derivative ***1*** *to Methanol in the Presence of Oxidizing Agents.* The reaction was carried out in the same way as described above. Methanol (1 ml, 24 mmol) and triethylamine (0.13 ml, 0.9 mmol) were added instead of amine **2** and allowed to react for 15 h at room temperature. The residue was chromatographed on silica gel with ethyl acetate as eluent to afford methyl *p*-nitrobenzoate (**8**) identical with the authentic sample prepared from *p*-nitrobenzoyl chloride and methanol. The yield of ester **8** was calculated from the ratio of ^{1}H-NMR signal of methyl proton in **8** (δ=4.0) to that of benzyl protons in **1** and **4** (δ=4.4).

Results and Discussion

The acyl transfer reaction was carried out by treating monoacyl derivative **1** with excess benzylamine (**2**) in tetrahydrofuran (THF) in the presence of some oxidizing catalysts under an oxygen atmosphere, or in the presence of 4-PDS under a nitrogen atmosphere at 30 °C. The progress of the reaction was followed by GLC analyses of the acyl transfer product, *N*-benzyl-*p*-nitrobenzamide (**3**), in the reaction solution (Fig. 1). In every case, the formation of **3** followed first-order kinetics, and pseudo first-order rate constants, *k*, were obtained from the slopes of the first-order plots (Table 1). The yields of **3** were determined by ^{1}H-NMR method by carrying out the acyl transfer reaction at room temperature for 15 h, and the results were summarized in Table 1 together with those obtained by treating a diacyl derivative, *N*-benzyl-*S,S'*-bis(*p*-nitrobenzoyl)dihydrolipoamide, with amine **2**.

In the presence of excess amine **2**, amide **3** was obtained in 55% yield without oxidizing agents. No or slight enhancement was observed by bubbling oxygen gas into the reaction mixture or by adding a catalytic amount of Co(II) ion under a nitrogen atmosphere. On the other hand, the acyl transfer reaction was promoted by adding catalytic amounts of flavin (**5**), Co(II), or Se(IV) ion to the reaction mixture of monoacyl derivative **1** and amine **2** under an oxygen atmosphere, as observed both in the rate enhancements and the increase of yields in Table 1. Co(II)

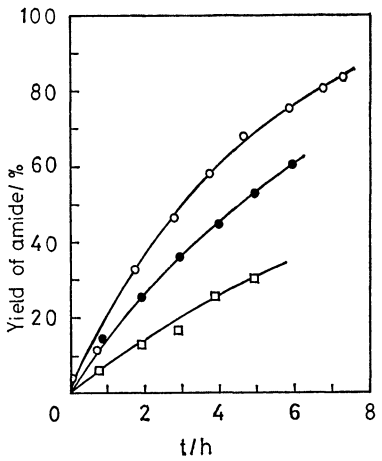


Fig. 1. Effects of oxidizing agents on the acyl transfer reaction from monoacyl derivative **1** to benzylamine (**2**) in THF (3 ml) at 30 °C; **1** 0.045 mmol, **2** 0.9 mmol,
○: 4-PDS (0.045 mmol), ●: Co(II) (0.004 mmol)/O_2, □: no catalyst/N_2.

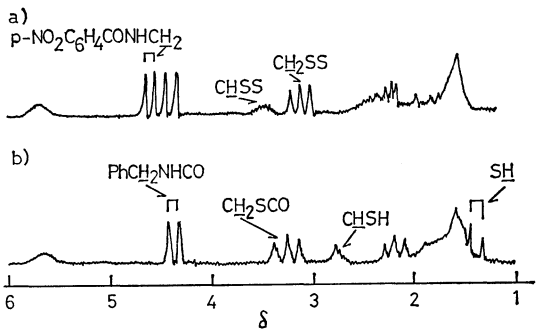


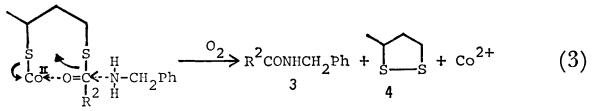
Fig. 2. ^{1}H-NMR spectra obtained by Co(II) catalyzed acyl transfer from monoacyl derivative **1** to benzylamine (**2**).
a): Reaction products, b): **1**.

Table 1. Acyl transfer reaction from *S*-acyl derivatives to benzylamine (**2**)[a]

Acyl derivative	Oxidizing agent	Yield of **3**/%[b]	$k\times10^3$/min^{-1} [c]
Monoacyl deriv. **1**	None (N_2)	55	0.91
	O_2	53	1.03
	N_2/$Co(ClO_4)_2\cdot2H_2O$	59	1.20
	O_2/$Co(ClO_4)_2\cdot2H_2O$	100	2.00
	O_2/**5**	80	1.67
	O_2/Na_2SeO_3	64	
	4-PDS	100	2.37
Diacyl deriv.[d]	None (N_2)	50	
	O_2	53	
	O_2/$Co(ClO_4)_2\cdot2H_2O$	63	

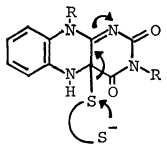
a) Conditions; monoacyl deriv. **1** 0.045 mmol (diacyl deriv. 0.023 mmol), amine **2** 0.9 mmol, cat. 0.004 mmol (4-PDS 0.045 mmol), THF 3 ml, room temperature, 15 h. b) Yields were determined by ^{1}H-NMR method as mentioned in experimental section. c) Kinetic measurements were carried out at 30 °C. d) *N*-Benzyl-*S,S'*-bis(*p*-nitrobenzoyl)dihydrolipoamide.

ion was the most effective catalyst to lead to the quantitative formation of amide **3** in the present reaction conditions. The ^{1}H-NMR spectrum of the products in the presence of Co(II) ion was shown in Fig. 2. Proton signal of mercapto group in **1** at δ=1.4 (1H, d) disappeared completely by the reaction and new signals at δ=3.2 (2H, d, $PhCH_2N$) appeared which suggested the quantitative formation of *N*-benzyllipoamide (**4**) accompanying the acyl transfer. However, only slight enhancement was observed by Co(II) ion catalyst in case of the acyl transfer reaction from diacyl derivative. Co(II) ion is known to catalyze the oxidation of dithiols to cyclic disulfides by oxygen effectively by way of complex formation.[7] It is presumed therefore that Co(II) ion catalyzed the acyl transfer oxidatively through the activation of acyl group by way of the complex formation with monoacyl derivative **1** as shown in Eq. 3.



(3)

In the oxidation of dithiols by flavins, Loechler *et al.*[9] proposed the formation of a thiol-*C*(4a)-flavin adduct (**6**). Also in the present flavin catalyzed reaction, flavin (**5**) presumably enhanced the acyl transfer reaction oxidatively by the formation of adduct intermediate (**7**), and the reduced flavin formed might be reoxidized by oxygen to work catalytically.



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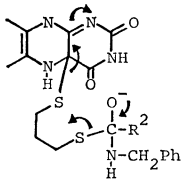

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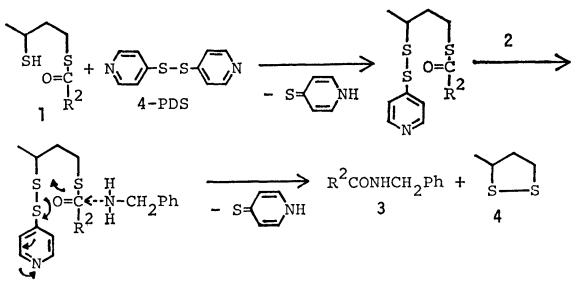
In he presence of 4-PDS as an oxidizing agent, acyl transfer reaction was enhanced most effectively to result in the quantitative formation of amide **3** and lipoamide **4**. The formation of 4(1*H*)-pyridinethione was ascertained from the UV spectrum of the reaction mixture (λ_{max}, 350 nm). Further 4-PDS is known to form reactive mixed disulfides with thiols very easily.[8] Therefore, the mechanism shown in Scheme 2 is proposed for the 4-PDS promoted acyl transfer reaction.



Scheme 2.

Table 2. Acyl transfer reaction from monoacyl derivative **1** to methanol[a]

Oxidizing agent	Yield of **8**/%[b]
None (N_2)	24
O_2/$Co(ClO_4)_2 \cdot 2H_2O$	26
4-PDS	22
I_2	21

a) Conditions; monoacyl derivative **1** 0.045 mmol, methanol 24 mmol, Et_3N 0.9 mmol, cat. 0.004 mmol (4-PDS 0.045 mmol, I_2 0.05 mmol), room temperature, 15 h. b) Yields were determined by ^{1}H-NMR method as mentioned in experimental section.

The effect of oxidizing agents was further examined in case of the acyl transfer reaction from monoacyl derivative **1** to methanol. The reaction was carried out in the presence of various kinds of oxidizing agents and triethylamine (Et_3N). The results are shown in Table 2. No enhancement was observed for the formation of methyl *p*-nitrobenzoate (**8**) by adding oxidizing agents in the present reaction conditions, contrary to the reported results[5] where methanol was used as a solvent. The SH proton signal disappeared completely in ^{1}H-NMR spectrum of the reaction products. These results suggested that the dimerization of monoacyl derivative **1** preceded the enhancement of acyl transfer reaction in case of acyl transfer to weak nucleophiles such as alcohols.

The results in this study suggest that lipoamide might work as an acyl carrier in the synthesis of amides from carboxylic acids and amines by combining both the reductive acylation (Eq. 1) and the oxidative acyl transfer reaction (Eq. 2). We are planning to apply these reactions to a lipoamide immobilized on polystyrene beads to get a polymeric acyl carrier which is capable of recycle uses.

References

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