J=7.2 Hz, 1H), 7.46-7.28 (m, 3H), 8.04 (dd, J=7.6, 1.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.5, 38.4, 125.4, 125.6, 126.2, 127.4, 130.5, 137.3, 165.2; MS (EI) m/z (relative intensity) 147 (M^+, 61), 128 (10), 118 (100), 90 (56), 77 (4).

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Unexpected Carbon-Nitrogen Bond Hydrolysis of Terminal Amides Catalyzed by Porcine Liver Esterase

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Enzymatic resolution of ester derivatives with esterase are the most commonly used approaches for the synthesis of optically active acids or esters. The esterases are very popular in the biotransformations.[1] Most of the esterases catalyze the hydrolysis or the formation of ester bond. In some cases, the carboxyl groups have been protected as amides which are very stable in the mild alkaline hydrolysis. The general deprotecting reagents of amide are butyl nitrite,[2] nitrosyl chloride,[3] and nitrosonium tetrafluoroborate.[4] The hydrolysis of amide into carboxylic acid usually requires severe condition, for example, heating in the presence of a strongly basic or acidic catalyst. However, the advantages of enzymatic hydrolysis require a neutral pH, room temperature, very few side product and atmospheric pressure. Esterases are generally unable to cleave amide bonds because of the greater stability of an amide bond as compared to that of an ester. The report of the hydrolysis of a highly strained β-lactam derivative by pig liver esterase is an exception.[5] Enzymatic resolution of amino acid amides by amino acid amidases (aminopeptidases) are generally used to obtain the L-amino acid[6] and (S)-naproxen.[7] We screened the enzymes for the hydrolysis of terminal amide. Accidently, the porcine liver esterase showed the activity of hydrolysis of the amide bond of lipoamide. Here we wish to report the deamination of the carboxy amide group by the porcine liver esterase.

A typical hydrolysis procedure was carried out under the following condition; lipoamide (50 mg, 0.24 mmol), porcine liver esterase (750 unit) suspended in 3.2 M $(NH_4)_2SO_4$ solution (pH=8) from sigma, 0.1 N potassium phosphate buffer (pH=7, 25 mL). The reaction was carried out at 36 °C and 250 rpm. After 2 days of reaction period, the mixture was filtered and washed with 10 mL of methanol. The combined solution was evaporated under reduced pressure to obtain lipoic acid. For the isolation with silicagel column chromatography, the crude lipoic acid in MeOH (4 mL) was treated with diazomethane[8] to give methyl lipoate in 71% yield. The yield of enzymatic reaction was based on the isolated methyl lipoate.

Comparative hydrolysis of lipoamide in mixture of phosphate buffer and various organic solvents were carried out with porcine liver esterase. The conversion yield of lipoamide into lipoic acid decreased from nonpolar solvent to polar solvent. Because of the good solubility of substrate, it was expected that the reaction would proceed very fast in polar solvents, but no product was obtained in these solvents. One of the possible speculations is that the enzyme is deactivated in polar solvents.[9] When isooctane was used as a cosolvent, the best conversion yield was obtained as shown in Table 1.

The pH-dependence of the hydrolysis reaction was studied over a pH range of 5-9. The best conversion yield was obtained at pH=7 as shown in Table 2. At pH 8 and 9, the reaction progressed faster than that of pH 5 and 6. At the higher pH, the reaction rate and yield of the product are

Table 1. Hydrolysis of lipoamide in various phosphate buffer-organic solvents with porcine liver esterase at 36 °C

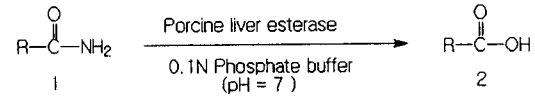
solvent[a]	reaction time (hr)	yield[b] (%)
isooctane	70	71
n-hexane	87	54
toluene	90	33
methanol	115	8
acetone	120	none
acetonitrile	129	none

[a] The ratio of buffer: organic solvent was 80 : 20. [b] The yield was based on methyl lipoate.

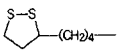
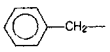
Table 2. Effects of pH on the hydrolysis of lipoamide with the porcine liver esterase

pH	reaction time (hr)	yield (%)
5	136	21
6	136	42
7	45	71
8	13	63
9	13	54

Table 3. Porcine liver esterase catalyzed hydrolysis of terminal amide



1 2

R=	Time(h)	Yield(%)
	40	71[a]
$CH_3(CH_2)_6$-	20	43[b]
$CH_3(CH_2)_8$-	160	20[b]
	90	95
	140	81

[a] The yield was based on methyl lipoate. [b] The unreacted starting material [octanoic amide (50%), decanoic amide (70%)] was recovered.

better than that of the lower pH. The reaction rate at pH 5 and 6 was very slow and the yield was 20-40%.

We expanded the utility of terminal amide hydrolysis by porcine liver esterase to the other amide derivatives in biphasic system. The broad substrate specificity of porcine liver esterase for the hydrolysis of terminal amide bond is shown in Table 3. The deamination of the carboxyamide group in aromatic amides was performed with facility giving the corresponding carboxylic acid. However, the hydrolyses of octanoic amide and decanoic amide were so slow and gave low yields of octanoic and decanoic acid. It is suggested the binding site of this catalyst may have strong affinity to an aromatic ring. These results indicated that the porcine liver esterase will be conveniently employed as a mild deprotecting method of terminal amide.

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Coordination Mode *vs.* Anticancer Activity of the Platinum(II) Complexes Involving Sulfur-Containing Ylidenemalonate Ligands

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Cisplatin, *cis*-diamminedichloroplatinum(II), is one of the most effective agents[1-3] against cancers of testis, ovary, bladder, and head and neck. However, its usefulness is limited due to its severe toxicities[4-6] such as nephrotoxicity, nausea, vomitting and myelosuppression along with development of resistance.[7,8] Therefore, there is a strong demand for the development of more efficient platinum anticancer drugs with lower toxicity and no cross-resistance. (Diamine)-platinum(II) complexes of sulfur-containing ylidenemalonate ligands were synthesized in our laboratory to display a variety of coordination modes depending on the anionic ligand structures, for example, (O,O)-chelation[9,10] for the 1,3-dithiol-2-ylidenemalonate (DTOYM) and 1,3-dithiolan-2-ylidenemalonate (DANYM) ligands, (O,S)-chelation[11,12] for the 1,3-dithian-2-ylidenemalonate (DTAYM) ligand and (S, S)-chelation[11-13] for the 1,3-dithiepane-2-ylidenemalonate (DTEYM), bismethylthiomethylenepropanedioate (BMTMP) and bisethylthiomethylenepropanedioate(BETMP) ligands.