85736-02-3; **22**, 56986-88-0; **22C**, 85736-03-4; **23**, 18113-81-0; **23C**, 85736-04-5; **24**, 72693-04-0; **24C**, 85736-05-6; **25**, 6343-58-4; **25C**, 85736-06-7.

Supplementary Material Available: Table IV [GEOMO (MINDO/3)-derived ring geometries and total energies for substituted pyridines], Table V [GEOMO (MINDO/3)-derived ring geometries and total energies for substituted *N*-methylpyridinium cations] and Table XII [correlation matrix of nonadditive parts of experimental and GEOMO (MINDO/3)-derived parameters] (5 pages). Ordering information is given on any current masthead page.

Reduction of Azo-, Azoxy-, and Nitrobenzenes by Dihydrolipoamide-Iron(II)

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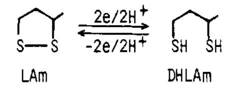
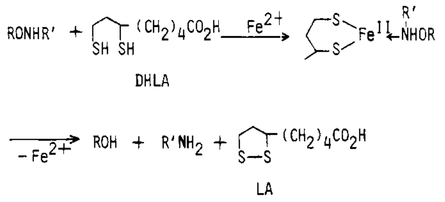
Dihydrolipoamide (DHLAm) was found to be an effective reagent for the reduction of nitrobenzene derivatives in the presence of a catalytic amount of ferrous ion. Azo- and azoxybenzenes were reduced to hydrazobenzene without the formation of aniline, and nitrobenzene, nitrosobenzene, and phenylhydroxylamine were also reduced to aniline in good yields under mild conditions. The reduction was presumed to proceed through the complex formation between DHLAm, ferrous ion, and substrates.

Lipoamide (LAm) works as a coenzyme related to acyl-transfer and redox reactions in living systems based on a redox function of LAm ⇌ dihydrolipoamide (DHLAm) (eq 1). We have studied[1] applications of LAm derivatives for acyl-transfer reactions. We have also reported[2] that hydroxylamines are cleaved reductively to give corresponding amines and alcohols by dihydrolipoic acid (DHLA) through the coordination of substrates to a 1:1 complex of DHLA–Fe(II), as shown in eq 2. The reduction system seems to have mechanistic interest due to the reactivity of the dithiol–iron complex related to non-heme iron proteins such as rubredoxins and ferredoxins in living systems.



(1)



(2)

In this paper, we describe the reduction of azo-, azoxy-, and nitrobenzenes by the DHLA or DHLAm (DHLAs)–Fe(II) system.

Results and Discussion

The reactivity of the DHLAs–Fe(II) system for the reduction of various functional groups was preliminarily investigated by spectrophotometric methods. As described[2] in the reductive cleavage of hydroxylamine derivatives by DHLAs–Fe(II), the progress of the reduction could be monitored by the appearance of UV absorption (λ_{max} 333 nm) due to the 1,2-dithiolane ring of LA or LAm, which were produced during the reduction. The reductions of some compounds by DHLAs were now attempted in the presence of a catalytic amount of ferrous ion, and the change of UV absorption was followed. No UV absorption change at 333 nm was observed in the reduction of activated olefin (cinnamyl alcohol), ketone (cyclohexanone), and aldehyde (benzaldehyde). In the case of the reduction of azo-, azoxy-, and nitrobenzenes by DHLAm–Fe(II), the formation of LAm was observed by UV absorption change, which suggested the progress of the reduction. We investigated in detail the reduction of azo-, azoxy-, nitrobenzene, and related compounds by DHLAm–Fe(II).

Table I. Reduction of Azobenzene by DHLAs-Fe(II)[a]

[reducing agent], M		% yield of hydrazobenzene[b]
DHLAs	Fe^{2+}	
1×10^{-1} (DHLAm)	5×10^{-4}	90 (80)[c]
1×10^{-1} (DHLA)	5×10^{-4}	9
1×10^{-1} (DHLAm)	0	0
0	1×10^{-1}	0

[a] Conditions: [azobenzene] = 5×10^{-2} M, 0.2 M carbonate buffer (pH 9.8)-EtOH (1:3), 30 °C, 24 h. [b] Determined by ^{1}H NMR method. [c] Isolated yield.

Reduction of Azobenzene by DHLAm–Fe(II). The reduction of azobenzene was carried out by DHLAm in the presence of a catalytic amount of ferrous ion in 0.2 M carbonate buffer (pH 9.8)–ethanol (1:3) under an argon atmosphere at 30 °C for 24 h. The results are summarized in Table I together with those for the DHLA–Fe(II) system.

Azobenzene was found to be reduced to hydrazobenzene almost quantitatively by DHLAm–Fe(II) under mild conditions without the formation of aniline (eq 3). On

$$PhN{=}NPh \xrightarrow[\text{pH 9.8 buffer–EtOH}]{\text{DHLAs, Fe}^{2+}\text{, catalyst}} PhNHNHPh \quad (3)$$

the other hand, no reduction occurred when an equimolar amount of either DHLAm or ferrous ion was used. These results suggest that in the reduction of azobenzene the DHLAm–Fe(II) complex is an active species in analogy with the reduction of hydroxylamine derivatives.[2] Azo-

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[1] Nambu, Y.; Endo, T.; Okawara, M. *J. Polym. Sci., Polym. Chem. Ed.* **1980**, *18*, 2793; **1981**, *19*, 1937.

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0022-3263/83/1948-2407$01.50/0

Table II. Reduction of Azoxybenzene by DHLAs-Fe(II)[a]

[reducing agent], M		% yield	
DHLAs	Fe^{2+}	azo-benzene	hydrazo-benzene
2×10^{-1} (DHLAm)	5×10^{-4}	14	82
2×10^{-1} (DHLA)	5×10^{-4}	14	0
2×10^{-1} (DHLAm)	0	0	0
0	0	0	0

[a] Conditions: [azoxybenzene] = 5×10^{-2} M, 0.2 M carbonate buffer (pH 9.8)-EtOH (1:3), 30 °C, 24 h.

benzene is known to coordinate to ferrous complex through π electrons.[3] The reduction might proceed by a coordination of azobenzene to DHLAm-Fe(II) complex through π electrons and by electron migration to give hydrazobenzene.

On the contrary, in the case of the DHLA-Fe(II) system the reactivity was low. The complex, DHLA-Fe(II), was presumably formed by the coordination of two thiolates and a carboxylate ligand to ferrous ion. The steric hindrance or coulombic repulsion in the approach of azobenzene to the complex might be the reason for the low reactivity.

The reduction of azobenzene to hydrazobenzene by $LiAlH_4$-metal halides[4] and to aniline by $Na_2S_2O_4$[5] have been reported, but both lack selectivity and need strict conditions. By use of the present system, the reduction of azobenzene proceeded under mild conditions to give hydrazobenzene selectively in good yield.

Nakamura et al. have reported[6] that the reduction of azobenzene catalyzed by molybdenum-sulfur chelates and iron-sulfur clusters as a nitrogenase model gave hydrazobenzene and aniline. It is interesting that the present dithiol-Fe(II) reagent showed a high reactivity for azobenzene.

Reduction of Azoxybenzene by DHLAm-Fe(II). The reduction of azoxybenzene by DHLAm-Fe(II) was carried out in the same way to give azobenzene and hydrazobenzene (eq 4). The results are summarized in Table II.

$$\mathrm{PhN(\rightarrow O){=}NPh} \xrightarrow[\text{pH 9.8 buffer-EtOH}]{\text{DHLAm/Fe}^{2+}\text{ catalyst}} \mathrm{PhN{=}NPh + PhNHNHPh} \tag{4}$$

Hydrazobenzene was obtained in good yield in the reduction of azoxybenzene by DHLAm-Fe(II) under mild conditions, accompanied by the formation of small amount of azobenzene, whereas the reduction proceeded neither with DHLAm nor ferrous ion. Thus, hydrazobenzene might form via azobenzene through the coordination of azoxybenzene to the active DHLAm-Fe(II) complex. Further, in the reduction of azoxybenzene, DHLA showed low reactivity compared with DHLAm, which might be caused by the same reason as that in the reduction of azobenzene. DHLAm-Fe(II) might be a selective reagent compared to $LiAlH(OCH_3)_3$,[7] which reduces ketones, esters, and amides as well as azoxybenzene.

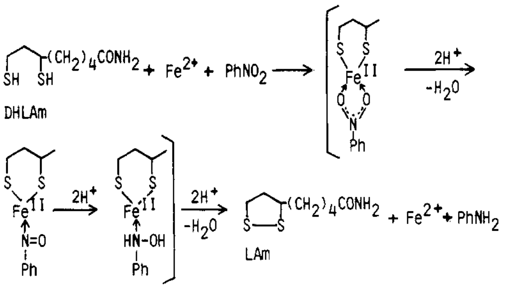
Reduction of Nitrobenzene and Related Compounds by DHLAm-Fe(II). The reductions of nitrobenzene, nitrosobenzene, and phenylhydroxylamine were attempted under similar conditions by use of DHLAm-Fe(II), and the yields of aniline formed were determined by GLC analysis of the trifluoroacetylated derivatives (see Experimental Section). In every case, aniline was obtained in good yield without production of azoxy-, azo-, or hydrazobenzene (Table III). On the other hand, nitrobenzene and phenylhydroxylamine were scarcely reduced by either DHLAm or ferrous ion (1.7-2 equiv) alone, and nitrosobenzene was reduced to azoxybenzene which might be caused by the coupling of nitrosobenzene with phenylhydroxylamine under slightly alkaline conditions.

Table III. Reduction of Nitrobenzene, Nitrosobenzene, and Phenylhydroxylamine by DHLAm-Fe(II)[a]

	[reducing agent], M		% yield	
substrate	DHLAm	Fe^{2+}	azoxy-benzene	ani-line
$PhNO_2$	2×10^{-1}	5×10^{-4}	0	51
	2×10^{-1}	0	0	0
	0	6×10^{-1}	2	1
PhNO	2×10^{-1}	5×10^{-4}	0	71
	2×10^{-1}	0	42	5
	0	4×10^{-1}	66	2
PhNHOH	1×10^{-1}	5×10^{-4}	0	76
	1×10^{-1}	0	2	8
	0	1×10^{-1}	13	23

[a] Conditions: [substrate] = 5×10^{-2} M, 0.2 M carbonate buffer (pH 9.8)-EtOH (1:3), 30 °C, 24 h.

Scheme I



From these results, it is considered that an active DHLAm-Fe(II) complex was formed as described in the reduction of hydroxylamine derivatives[2] and that aniline was obtained without any byproduct through the coordination of substrates (nitrobenzene, nitrosobenzene, and phenylhydroxylamine) to the complex, followed by the stepwise migration of electrons. Since nitrobenzene has been reported to make complexes with ferric ion via oxygen atom[8] and nitrosobenzene does with ferrous phthalocyanine via a nitrogen atom,[9] the reduction is suggested to proceed as shown in Scheme I.

Although the reductions of aromatic nitro compounds to corresponding amines have been carried out with many methods such as Birch reduction,[10] Zn/NaOH,[11] Sn/HCl,[12] Fe/HCl,[13] and $NaBH_2S_3$,[14] the reductions by these reagents mostly need severe conditions or have little selectivity. The reduction of nitrobenzenes under neutral or weak alkaline conditions, e.g., by $NaBH_4$[15] or electrolysis,[16] gives azo-,

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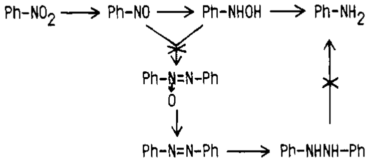
Scheme II



azoxy-, or hydrazobenzenes due to a coupling reaction between intermediates, and a few methods using phthalocyanine cobalt(I),[17] $NaBH_4$/Pd–C,[18] have been reported to give amines. In the present system, aniline was obtained from nitrobenzene in good yield without the formation of azo-, azoxy-, or hydrazobenzene presumably through the coordination of nitrobenzene and its intermediates to the active complex. In addition, as DHLAm–Fe(II) showed no reactivity to some functional groups such as olefin, ketone, and aldehyde, as described previously, it is expected to be a selective reducing agent.

It is known that nitrite reductase in microorganisms and plants reduces nitrite to hyponitrite, which is further reduced to hydroxylamine and ammonia (eq 5). The en-

$$NO_2^- \rightarrow N_2O_2^{2-} \rightarrow NH_2OH \rightarrow NH_3 \tag{5}$$

zymes have been reported[19] to contain Fe and thiols. With respect to the functions of nitrite reductases, it is interesting that DHLAm, which is regarded to be a reduced form of coenzyme LAm, could reduce nitrobenzene, nitrosobenzene, and phenylhydroxylamine to aniline in the presence of a catalytic amount of ferrous ion.

The results obtained in the reduction by DHLAm–Fe(II) are conclusively summarized in Scheme II. Nitrobenzene was reduced to aniline without coupling between the reduction intermediates (nitrosobenzene and phenylhydroxylamine), and azoxy- and azobenzene were reduced to hydrazobenzene without the formation of aniline.

Further studies on the selective reduction of nitro groups in substituted nitrobenzenes by DHLAm–Fe(II) and the DHLAm–Fe(II)-catalyzed reduction of nitrobenzenes with simple reducing agents are in progress.

Experimental Section

General Procedures. ^1H NMR spectra were measured with a Varian EM-360 NMR spectrometer in deuterioacetonitrile with tetramethylsilane as an internal standard. UV absorption spectra were recorded on a Hitachi 200-10 spectrophotometer. GLC analyses were carried out on a JEOL JGC-1100 gas chromatograph (10% SE-30, stainless-steel column, N_2 carrier gas).

Materials. Dihydrolipoic acid (DHLA) was prepared by the reduction of lipoic acid (LA) with $NaBH_4$ according to the procedure of Gunsalus et al.[20] Dihydrolipoamide (DHLAm) was also prepared by the reduction of lipoamide (LAm) with $NaBH_4$ according to the procedure of Reed et al.[21] and recrystallized from carbon tetrachloride; mp 62–64 °C (lit.[21] mp 64–66 °C). Other chemicals used in this study were reagent grade; solvents were purified by the usual procedure.

Preliminary Experiments for the Reduction of Some Substrates. DHLA (10.4 mg, 0.05 mmol) and each substrate (0.04 mmol) were put into a quartz cell by using a three way cock, and the cell was degassed and filled with argon. To the cell were added 0.2 mL of 1 mM ferrous ammonium sulfate aqueous solution (2×10^{-4} mmol) and 3.8 mL of 0.1 M Sørensen borate buffer (pH 9.2) which were previously bubbled with an argon gas. The UV absorption change around 333 nm was examined by UV spectrophotometer. The reactivity of DHLAm was also examined in the same way.

Reduction of Azo- and Azoxybenzenes. Azobenzene (91 mg, 0.5 mmol) and DHLAm (207 mg, 1 mmol) were put into a Schlenk tube, which was degassed and filled with argon. To the Schlenk tube were added 0.5 mL of 10 mM ferrous aqueous solution, 2 mL of 0.2 M Menzel carbonate buffer solution (pH 9.8), and 7.5 mL of ethanol, which were previously bubbled with argon. The solution was stirred at 30 °C for 24 h. After removal of ethanol by evaporation, the reaction solution was extracted with chloroform, and the organic layer was dried over magnesium sulfate and evaporated to yield a solid residue. The residue was chromatographed on a short silica gel column (benzene as the eluent) to remove LAm and DHLAm and gave a solid mixture of azobenzene and hydrazobenzene (89 mg). The yield of hydrazobenzene (90%) was calculated from the ^1H NMR spectra of the residue and was based on the ratio of the area of the phenyl proton signals of azobenzene, δ 7.40–8.10 (m, 10 H), and hydrazobenzene, δ 6.50–7.35 (m, 10 H). The mixture was purified by passage through a silica gel column (hexane and benzene as the eluents) to yield hydrazobenzene: 80%; mp 126–128 °C (lit.[22] mp 128 °C).

Similarly, azoxybenzene (99 mg, 0.5 mmol) and DHLAm (404 mg, 2 mmol) were put into a Schlenk tube, and the reduction was carried out in the same manner as above to give a solid mixture of azobenzene and hydrazobenzene (88 mg). The yield was calculated to be 14% of azobenzene and 82% of hydrazobenzene on the basis of the ratio of the area of the phenyl proton signals of azoxybenzene, δ 8.10–8.50 (m, 4 H), azobenzene, δ 7.65–8.10 (m, 4 H), and hydrazobenzene, δ 6.50–7.00 (t, 6 H).

No other products were detected by TLC and GLC, and the recovery of raw material and products was more than 95% in each case.

Reduction of Nitrobenzene, Nitrosobenzene, and Phenylhydroxylamine. The reduction of nitrobenzene (65 mg, 0.5 mmol) was carried out in the same way as described above by using DHLAm (414 mg, 2 mmol) and ferrous ion (0.005 mmol).

After the reaction, no hydrazobenzene was detected by TLC. Then the reaction solution was acidified with 2 M HCl aqueous solution and evaporated to remove ethanol, and the aqueous solution was washed with chloroform to remove azo- and azoxybenzene, DHLAm, and LAm. The aqueous layer was evaporated to dryness in vacuo to yield a residue which was a mixture of aniline hydrochloride and inorganic salts. To the mixture were added 20 mL of dry THF and 2 mL of trifluoroacetic anhydride, and the mixture was allowed to react for 1 h at 0 °C and for 2 h at room temperature. After the reaction, the excess anhydride was decomposed by adding 10 mL of water, and the solution was evaporated to remove THF and extracted with methylene dichloride. The organic layer was dried over magnesium sulfate, and the yield of aniline was calculated from GLC analysis of trifluoroacetanilide in the solution with dodecane as an internal reference. The anilide was purified by recrystallization from hexane; mp 86–87 °C (lit.[23] mp 88.5–90 °C). The isolated yields agreed with those obtained by GLC within 5%. The yield of azobenzene in the methylene dichloride layer was determined by the same method as described in the reduction of azobenzene. The reductions of nitrosobenzene and phenylhydroxylamine were carried out in the same way.

Registry No. DHLA, 462-20-4; DHLAm, 3884-47-7; iron(II), 15438-31-0; azobenzene, 103-33-3; hydrazobenzene, 122-66-7; azoxybenzene, 495-48-7; nitrobenzene, 98-95-3; nitrosobenzene, 586-96-9; phenylhydroxylamine, 100-65-2; aniline, 62-53-3.

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