the twisted-boat structure has a barrier of ca. 9 kcal mol^{-1}.[8]

If we assume that the hybridization for the cycloheptyl radical is somewhere between sp^2 and sp^3 at the radical center, then the center should, by comparison with cycloheptanone,[5] be at the 1, 2, or 7 positions, cf. Figure 3. We therefore presume that the motion which interconverts the magnetically inequivalent β-hydrogens is a pseudorotation just as in the parent hydrocarbon. As in the case of the cyclohexyl radical, such a molecular motion should be made easier by the inversion at the radical center. The barrier for inversion of the radical is greater than that of the parent hydrocarbon. However, the difference is relatively small and is difficult to associate with any molecular motion.

Summary

Analysis of the inversion barriers of cyclopentyl, cyclohexyl, and cycloheptyl radicals suggest that they are closely related to those of their parent hydrocarbons. In the five- and seven-membered rings the β-hydrogens are magnetically inequivalent in pairs but can be "exchanged" by a mechanism which probably involves pseudorotation. Like its parent hydrocarbon, the six-membered ring can only achieve such an exchange by a true inversion of the ring.

Registry No. Cycloheptyl radical, 4566-80-7.

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Reduction of Cyclic Compounds Having an N-O Linkage by Dihydrolipoamide-Iron(II)

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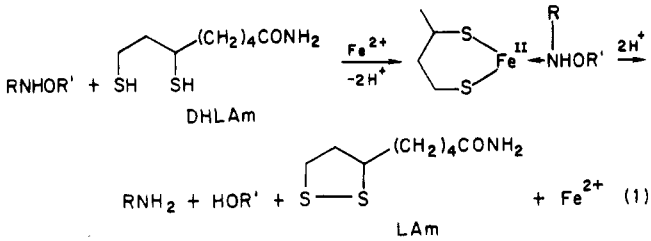
Lipoamide (LAm) is a coenzyme in acyl transfer and redox reactions in living systems, undergoing the redox reaction LAm $\rightleftharpoons$ dihydrolipoamide (DHLAm).

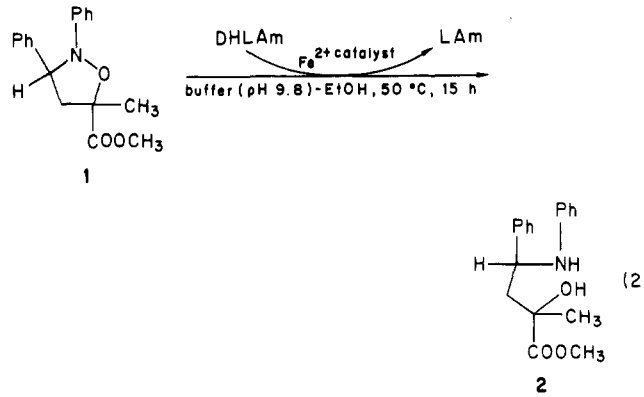
In the study of application of this redox function for organic synthesis, we have recently reported[1] that hydroxylamine derivatives were reduced by DHLAm-Fe(II) through coordination of substrates to a complex of DHLAm-Fe(II) under weakly basic conditions as shown in eq 1. We have also reported the reduction of azo- and azoxybenzene,[2] and selective reduction of monosubstituted nitrobenzenes with ester, ketone, nitrile, or other functional groups to corresponding anilines.[3] Further, we have found[4] that LAm and hydrophilic polymers having lipoamide structure in the presence of a catalytic amount of ferrous ammonium sulfate worked catalytically in the reduction of *O*-benzylhydroxylamine with sodium borohydride.



In this paper, we describe the reductive ring-opening reaction of isoxazolidines and isoxazoles by DHLAm-Fe(II).

Results and Discussion

Reduction of Isoxazolidines. The reduction of methyl 5-methyl-2,3-diphenylisoxazolidine-5-carboxylate (**1**) was carried out by DHLAm in the presence of a catalytic amount of ferrous ion under a slightly basic condition to give amino alcohol **2** in 81% yield (eq 2). Additionally, isoxazolidine **1** was not reduced by DHLAm or ferrous ion alone.



The reduction of isoxazolidines was widely studied by catalytic hydrogenation,[5] Zn-acetic acid,[6] $LiAlH_4$.[7] However, it was reported[8] that **1** was reduced by H_2/Ni and cyclized to give hydroxy lactam **3** and reduced by H_2/Pd to give **4** by the elimination of aniline (eq 3). In contrast, Amino alcohol **2** was obtained in the case of reduction by DHLAm-Fe(II), which proceeded under mild conditions to obtain **2** without elimination, cyclization, or

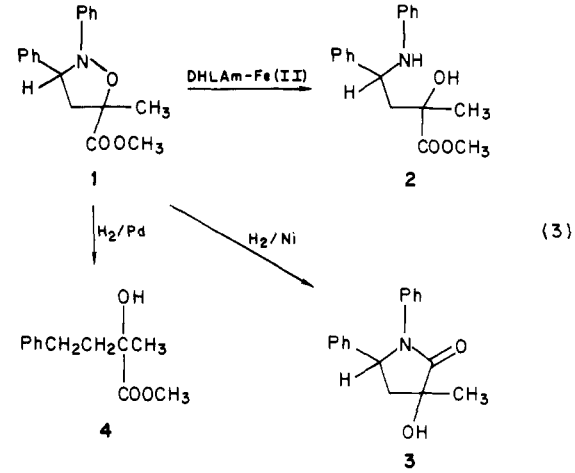


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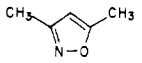
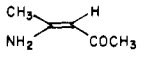
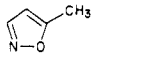
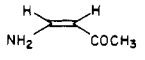
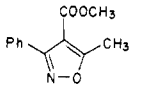
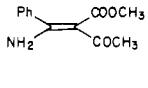
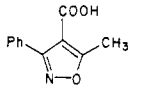
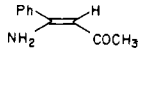
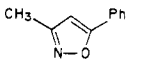
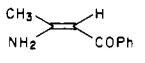
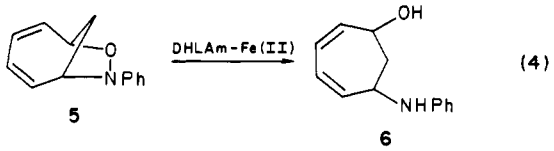
Table I. Reduction of Isoxazoles by DHLAm-Fe(II)[a]

substrate	product	reactn time, h	yield, %	mp, °C	ref
 8	 9	1	89	40–43	24
 12	 13	3	67	100–110[b] (5 mmHg)	25
 14	 15	1	95	94–95	
 16	 17	15	90	86–87	
 18	 19	15	67	141–142	24

[a] Condition: [isoxazole] = 200 mM, [DHLAm] = 250 mM, [Fe^{2+}] = 4 mM, 0.1 M carbonate buffer(pH 9.8)–EtOH (1:3), 50 °C, Ar. [b] boiling point.

hydrolysis of the ester group.

Further, 9-phenyl-8-oxa-9-azabicyclo[4.2.1]nona-2,4-diene (**5**) was reduced by DHLAm–Fe(II) to afford 3-anilinocyclohepta-4,6-dienol (**6**) in 83% yield (eq 4).



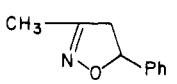
5 6 (4)

In the reduction of **5**, DHLAm–Fe(II) reduced the N–O bond selectively to give **6** without the reduction of C=C double bond or addition of DHLAm to the C=C double bond.

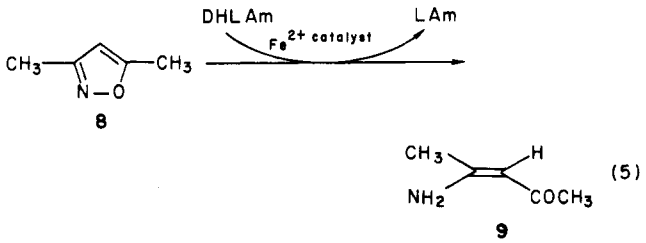
The pK_a values of isoxazolidines are ca. 5,[9] and the basicity of isoxazolidines are presumably similar to acyclic hydroxylamines. Therefore, the reduction of the isoxazolidine **1** is thought to proceed in the same way as the acyclic hydroxylamines[1] shown in eq 1.

Isoxazolidines are prepared easily and stereoselectively from intermolecular cycloaddition between nitrones and olefins. Isoxazolidines are cleaved reductively to give 3-amino alcohols, which are starting materials for 1,3-oxazines[10] or alkaloids.[11]

DHLAm–Fe(II) showed good selectivity for the cleavage of N–O linkage in the reduction of **1** and **5**. We previously reported[3] that DHLAm–Fe(II) did not reduce ketone, aldehyde, ester, and nitrile functional groups. Thus, DHLAm–Fe(II) represents an effective reagent for the selective reduction of isoxazolidines in the presence of other functional groups. However, isoxazoline **7** was not reduced by DHLAm–Fe(II) and **7** was recovered.


7

Reduction of Isoxazoles. The reduction of 3,5-dimethylisoxazole (**8**) by DHLAm–Fe(II) was carried out in buffer(pH 9.8)–EtOH at 50 °C for 1 h under N_2 to give β-amino enone **9** in 89% yield (eq 5). No reduction occurred when an equimolar amount of either DHLAm or ferrous ion was used. These results suggest that in the reduction of isoxazole **8** DHLAm–Fe(II) complex is an active species in analogy with the reduction of hydroxylamine derivatives.[1]



8 9 (5)

It is reported that isoxazoles form complexes with various transition metals and behave as monodentate or bidentate ligands,[12] in spite of its low basisity.[13]

In the reduction of isoxazole by $Mo(CO)_5$, isoxazole forms a complex with $Mo(CO)_5$.[14] A similar intermediate with **10** was suggested in the reductive cleavage of isoxazole by samarium ion.[15] Therefore, the reduction of isoxazoles by DHLAm–Fe(II) might proceed as in eq 6. Isoxazole makes a complex with DHLAm–Fe(II) through nitrogen and is subjected to one-electron reduction by DHLAm–Fe(II) to produce intermediate **10** which is transformed simultaneously to **11** by isomerization. One-electron reduction of **11** by DHLAm–Fe(II) then gives β-amino enone, LAm, and ferrous ion.

The reduction of some isoxazoles by DHLAm–Fe(II) are summarized in Table I. In every case, isoxazoles were cleaved reductively under mild conditions to give the β-amino enones in good yields. Isoxazoles **8**, **12**, and, **14** were reduced effectively. Isoxazole **16** was reduced to give **17** with successive decarboxylation. Isoxazole **18** was less reactive than others. 3,5-Diphenylisoxazole was not reduced because of its poor solubility.

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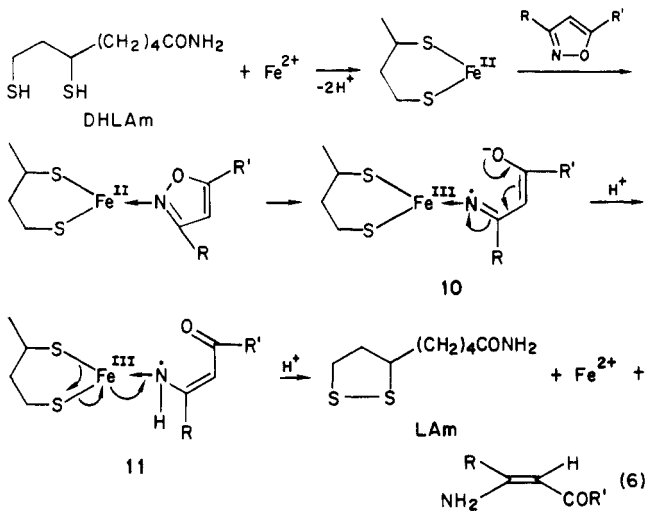

β-Amino enones produced by the reductive cleavage of isoxazoles are major tools for the syntheses of homo- and heterocyclic compounds. There have been many reports on the reduction of isoxazoles and their synthetic applications,[16] but reduction by DHLAm–Fe(II) proceeds under mild conditions and has superior functional group selectivity.[3] DHLAm–Fe(II) has much to recommend it for reduction of isoxazoles.

Experimental Section

General Procedures. ^{1}H NMR spectra were measured with a Varian EM-360 NMR spectrometer in deuteriochloroform with tetramethylsilane as an internal standard.

Materials. Dihydrolipoamide (DHLAm) was prepared by the reduction of lipoamide (LAm) with sodium borohydride according to the procedure of Reed et al.[17] and recrystallized from carbon tetrachloride; mp 62–64 °C (lit.[17] mp 64–66 °C). α,*N*-Diphenyl nitrone was prepared by the method of Berry et al.[18] (60%) and recrystallized from *n*-hexane; mp 106–110 °C (lit.[18] mp 112 °C). Methyl 5-methyl-2,3-diphenylisoxazolidine-5-carboxylate (**1**) was prepared according to the procedure of Huisgen et al.[8] and recrystallized from methanol (67%); mp 70–71 °C (lit.[8] mp 75.5–78 °C). The NMR data of the methyl ester (3.43 ppm, CCl_4) showed that one isomer was prepared. 9-Phenyl-8-oxa-9-azabicyclo-[4.2.1]nona-2,4-diene (**5**) was prepared according to the procedure of Ito et al.[19] 3-Methyl-5-phenylisoxazoline (**7**) was prepared from phenyl isocyanate, nitroethane, and styrene by the method of Mukaiyama et al.[20] (65%); bp 132–134 °C (6 mmHg) (lit.[20] bp 133–134 °C (6 mmHg)). 3-Methyl-5-phenylisoxazole (**18**) and 3,5-diphenylisoxazole were prepared by the condensation reaction of the corresponding 1,3-diketone with hydroxylamine according to the method reported[21] and recrystallized from *n*-hexane. **18**, mp 62–63 °C (lit.[21] mp 64–65 °C); 3,5-diphenylisoxazole, mp 141–142 °C (lit.[22] mp 140–141 °C). Methyl 5-methyl-3-phenylisoxazole-4-carboxylate (**14**) was prepared by the following procedure. 5-Methyl-3-phenylisoxazole-4-carboxylic acid (**16**) (1.015 g, 5 mmol) was dissolved in 10 mmol of tetrahydrofuran (THF) and 1 mL of methanol, and dicyclohexylcarbodiimide (0.88 g, 5 mmol) was added to the solution. The mixture was stirred for 24 h at room temperature. THF was evaporated and ethyl ether was added, and the dicyclohexyl urea produced was removed by filtration. The ethereal solution was evaporated and the solid residue was recrystallized from *n*-hexane (85%); mp 77–78 °C (lit.[23] mp 79–80 °C).

Other chemicals used in this study were reagent grade. Solvents were purified by the usual method.

Reduction of Isoxazolidines by DHLAm–Fe(II). Methyl 5-methyl-2,3-diphenylisoxazolidine-5-carboxylate (**1**) (0.297 g, 1 mmol) and DHLAm (0.259 g, 1.25 mmol) were put into a Schlenk tube, which was degassed and filled with argon. To the Schlenk tube were added 1 mL of 0.1 M Menzel carbonate buffer (pH 9.8), 3.75 mL of ethanol, and 0.25 mL of 20 mM ferrous ammonium sulfate aqueous solution, which were previously bubbled with argon. The solution was stirred at 50 °C for 15 h. The reaction solution was extracted with dichloromethane, and the organic layer was dried over anhydrous magnesium sulfate and evaporated to give an oily residue. The residue was purified by column chromatography on silica gel (benzene–ether (4:1)) to give methyl 3-anilino-1-methyl-1-hydroxybutyrate (**2**) in 80% yield: NMR ($CDCl_3$) δ 1.48 (s, 3 H, CH_3), 2.24–2.40 (m, 2 H, CH_2), 3.64 (s, 3 H, CH_3OCO), 4.32–4.60 (m, 3 H, PhCH-, PhNH-, OH), 6.48–7.40 (m, 10 H, C_6H_5-, C_6H_5NH-). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.30; H, 7.10; N, 4.68.

The reduction of 9-phenyl-8-oxa-9-azabicyclo[4.2.1]nona-2,4-diene (**5**) was carried out with the same procedure as the reduction of **1** except for the concentration of substrate and reducing agent, [DHLAm] = 125 mM, [**5**] = 100 mM. **6**: NMR ($CDCl_3$) δ 2.20–2.60 (m, 2 H, CH_2), 3.00–3.50 (br s, H, OH, NH), 4.36–4.56 (m, 1 H, C*H*NHPh), 4.64–4.88 (m, 1 H, C*H*OH), 5.64–6.04 (m, 4 H, >C=CH)—), 6.56–6.92, 7.08–7.42 (m, 5 H, C_6H_5NH). Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 76.60; H, 7.55; N, 6.73.

Reduction of Isoxazoles by DHLAm–Fe(II). The reductions of isoxazoles were carried out with the same procedure as the reduction of **1** except for the concentration of ferrous ion, [Fe^{2+}] = 4 mM. 4-Amino-3-penten-2-one (**9**) and 4-amino-3-buten-2-one (**13**) were isolated by Kugelrohr distillation and confirmed by NMR. **9**: mp 40–43 °C (lit.[24] mp 42–43 °C). **13**: bp 100–110 °C (5 mmHg) (lit.[25] bp 70–71 °C (2 mmHg)). 4-Amino-4-phenyl-3-(methoxycarbonyl)-3-buten-2-one (**15**), 4-amino-4-phenyl-3-buten-2-one (**17**), and 4-amino-1-phenyl-3-buten-2-one (**19**) were purified by column chromatography on silica gel (benzene–ether (4:1)) and these compounds were confirmed by NMR. **15**: mp 94–95 °C; NMR ($CDCl_3$) δ 2.30 (s, 3 H, CH_3CO-), 3.27 (s, 3 H, $COOCH_3$), 7.33 (m, 5 H, C_6H_5-). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.63; H, 5.88; N, 6.30.

17: mp 86–87 °C; NMR ($CDCl_3$) δ 2.16 (s, 3 H, CH_3CO-), 5.47 (s, 1 H, PhCOCH=), 7.30–7.80 (m, 5 H, C_6H_5-). Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.56; H, 6.91; N, 8.67. **14**: mp 141–142 °C (lit.[24] mp 143 °C).

Registry No. **1**, 19345-05-2; **2**, 95192-67-9; **5**, 13554-75-1; **6**, 95192-68-0; **8**, 300-87-8; **9**, 870-74-6; **12**, 5765-44-6; **13**, 2976-86-5; **14**, 2065-28-3; **15**, 95192-69-1; **16**, 1136-45-4; **17**, 14088-41-6; **18**, 1008-75-9; **19**, 1128-85-4; DHLAm, 3884-47-7; ferrous ammonium sulfate, 10045-89-3.

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