The Hydrogen-Deuterium Exchange of 3,5-Dimethylisoxazoles

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By the hydrogen-deuterium exchange reaction in methanol-d_4, 3,5-dimethylisoxazole (**1**) was found to react regioselectively at the C-5 methyl group. This methyl group was, however, less reactive than the methyl groups of 2-picoline or quinaldine. This reaction was shown to be retarded by the electron-donating substituents, and to be accelerated by the electron-withdrawing substituents, at the C-4 position of **1**.

The isoxazole derivatives frequently show some pharmaceutical activities, and they are also employed as intermediates for the syntheses of peptides[1] and natural products.[2] Previously, we reported that 3,5-dimethylisoxazole (**1**) reacted with various kinds of electrophiles in the presence of bases to give 5-substituted 3-methylisoxazoles.[3-5] For example, 3-methyl-5-ethylisoxazole was obtained by the treatment of **1** with methyl iodide in the presence of sodium amide in liquid ammonia.[3] For the development of these reactions, it is necessary to investigate the application and the limitation of these reactions. However, no quantitative study has yet been reported.

The reaction of active methyl and methylene groups on the heteroaromatic compounds, such as 2-picoline[6] and quinaldine,[7] has been extensively investigated. White and Anderson[8] reported that the hydrogen on the methyl group of 5-methylisothiazole was exchanged with the activation energy of 5.61×10^4 J/mol in deuterium oxide. Also, Zatspina *et al.*[9] reported that the activation energies of the hydrogen exchange of 2-picoline and quinaldine are 1.03×10^5 and 8.70×10^4 J/mol respectively in deuterium oxide. In these papers, the rate-determining step of these reactions is supposed to be the formation of the corresponding carbanions by proton abstraction from active methyl and methylene groups.

The rate-determining step of the reaction of **1** with the electrophiles should be the formation of the carbanion of **1**. Therefore, the stability of an intermediate carbanion was calculated by means of the MINDO/2 method. Also, the present study will report the results of the sodium methoxide-d_3 catalyzed isotopic exchange of **1** in methanol-d_4 in order to compare the reactivity of **1** with those of the heteroaromatic compounds with a methyl group. Furthermore, the substituent effect of 4-substituted 3,5-dimethylisoxazoles is discussed in terms of the hydrogen-deuterium-exchange reaction rates.

Results and Discussion

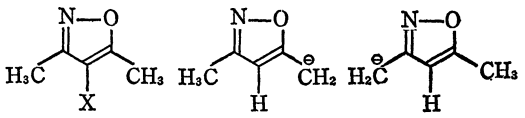
Regioselectivity. Two methyl groups of 3,5-dimethylisoxazole (**1**) are expected to be activated by the isoxazole ring. When the proton abstraction from the active methyl group is considered to be the rate-determining step, the stability of the carbanion should reflect the reactivity of the corresponding methyl groups. The total energies of the (3-methyl-5-isoxazolyl)methyl carbanion (**2**) and the (5-methyl-3-isoxazolyl)methyl carbanion (**3**) were calculated by means of the MINDO/2 calculation method. The calculation showed that **2** is more stable than **3** by 3×10^3 J/mol. These results were roughly supported by the following data. The carbanions introduced from **1** were prepared by the treatment of **1** with butyllithium in ether. After equilibration for 3 h at room temperature, the resulting carbanions were quenched by deuterium oxide. The deuterated products were then analyzed by mass spectrometry; the results are summarized in Table 1. In this table, the relative intensity of *m/e* 98 showed that the monodeutero derivative was formed in a yield of 37%. The peak of *m/e* 82 was assigned to the **4** ion, while the peak of *m/e* 54 was assigned to the **5** ion.[10] In both ions, **4** and **5**, the C-5 methyl group was expelled from the molecule. When the mass spectrum of **1** was compared with that of the deuterated products, the isotopic peaks of **4** and **5**, *m/e* 83 and 55, were observed to have a difference in relative intensity.

TABLE 1. MASS SPECTRAL DATA OF **1** AND THE DEUTERATED DERIVATIVE

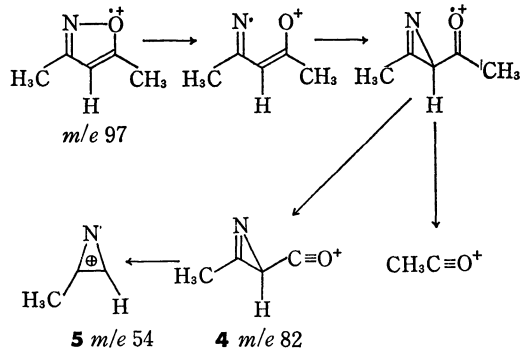
m/e	Relative intensity	
	1	Deuterated derivative
99	0.9	6.1
98	11.9	36.2
97	78.6	49.0
83	5.1	7.1
82	100.0	100.0
56	2.0	5.0
55	30.4	31.7
54	70.3	67.5

The hydrogen-deuterium exchange rates of very weak acids often parallel the acidities of this type of heteroaromatic compound.[11] This parallelism can be expected from the Brønsted catalysis law.[12] The relative reactivity of the methyl group of **1** was studied kinetically by means of a hydrogen-deuterium exchange reaction at 110.6 °C in the presence of sodium methoxide-d_3 in methanol-d_4 (16.5 mg/282 mg). Actually, the hydrogen-deuterium exchange was monitored by the decreases in the NMR peaks of **1** at δ 2.13 and 2.30 ppm, which were identified as C-3 methyl and C-5 methyl groups respectively. The pseudo-first-order rate constants of this reaction were found to be $k=3.3\times10^{-4}$ s^{-1} at the C-5 methyl group and $k=1.2\times10^{-6}$ s^{-1} at the C-3 methyl group. That is, the C-5 methyl group was activated 280 times as much as the C-3 methyl group.

Reactivity. The reaction rates of the hydrogen-deuterium exchange on the C-5 methyl group of **1**



1 X=H **2** **3**
6 X=OCH_3
7 X=CH_3
8 X=Cl
9 X=I
10 X=$COOCH_3$
11 X=NO_2



m/e 97

5 *m/e* 54 **4** *m/e* 82

were also measured at 80.1, 89.0, 100.0, and 121.2 °C in methanol-d_4. The activation parameters for the C-5 methyl group of **1** were calculated to be $E_{act}=(1.200\pm0.008)\times10^5$ J/mol and $\log A=12.76$, while those for the methyl groups of 2-picoline and quinaldine were $E_{act}=1.03\times10^5$ J/mol; $\log A=9.86$ and $E_{act}=8.70\times10^4$ J/mol; $\log A=9.77$, respectively.[9] Apparently the C-5 methyl group of **1** is less reactive than those of 2-picoline and quinaldine.

Effect of Substituents. The hydrogen-deuterium exchange reaction rates for the C-5 methyl group of 4-substituted 3,5-dimethylisoxazoles were measured in order to clarify the effects of the substituents. The 4-methoxy- (**6**), 4-methyl- (**7**), 4-chloro- (**8**), 4-iodo- (**9**), 4-carbomethoxy- (**10**), and 4-nitro- 3,5-dimethylisoxazoles (**11**) were prepared and the exchange rates were measured in methanol-d_4 in the presence of sodium methoxide-d_3 at 34.2, 80.1, and/or 110.6 °C. The results are presented in Table 2. Unfortunately, the reaction of **10** was too fast for us to determine the exchange rate accurately at 34.2 °C. The NMR peak of the C-5 methyl group of **11** could not be observed even 1 min after the **11** and methoxide-d_3 were dissolved in methanol-d_4 at room temperature. Table 2 shows that the hydrogen-deuterium exchange was retarded by the electron-donating groups at the C-4 position of the isoxazole ring.

TABLE 2. HYDROGEN-DEUTERIUM EXCHANGE REACTION RATES OF 4-SUBSTITUTED 3,5-DIMETHYLISOXAZOLES

4-Substituents	Temp (°C)	Reaction rate (s^{-1})	
		C-3 CH_3	C-5 CH_3
OCH_3	110.6	6.4×10^{-7}	1.3×10^{-5}
CH_3	110.6	4.1×10^{-7}	7.8×10^{-5}
H	110.6	1.2×10^{-6}	3.3×10^{-4}
	80.1	—	9.5×10^{-6}
Cl	80.1	—	5.5×10^{-4}
I	110.6	7.7×10^{-5}	8.0×10^{-3}
	80.1	—	9.4×10^{-4}
$COOCH_3$	34.2	—	$>2\times10^{-3}$

Experimental

MINDO/2 Calculations. Using the coordinates shown in Table 3, the total energies of the **2** and **3** carbanions were calculated as −1252.483 and −1252.149 eV respectively by means of the MINDO/2 method.

TABLE 3. THE COORDINATES OF **2** AND **3**

Isoxazole ring			
Bond length		Bond angle	
O-N	1.39 Å	C-5-O-N	107°
N-C-3	1.33 Å	O-N-C-3	110°
C-3-C-4	1.42 Å	N-C-3-C-4	108°
C-4-C-5	1.37 Å	C-3-C-4-C-5	107°
C-5-O	1.39 Å	C-4-C-5-O	108°
C-3-C	1.50 Å	N-C-3-C	126°
C-4-H	1.08 Å	C-3-C-4-H	126.5°
C-5-C	1.50 Å	O-C-5-C	126°
Side chain methyl			
Bond length of C-H		1.08 Å	
Bond angle of H-C-H		109.5°	
Bond angle of C-C-H		109.5°	
Dihedral angle of C-4-C-C-H		0°	
Side chain methylene			
Bond length of C-H		1.08 Å	
Bond angle of H-C-H		120°	
Bond angle of C-C-H		120°	
Dihedral angle of C-4-C-C-H		0°	

Materials. *3,5-Dimethylisoxazole (**1**)* was prepared by the method of Lampe[13] from acetylacetone and hydroxylamine hydrochloride. Yield, 59%; bp 139—141 °C (lit, 140—142 °C[13]).

*3,5-Dimethyl-4-methoxyisoxazole (**6**).* According to the method of Katritzky,[14] **6** was prepared from diazomethane and 3,5-dimethyl-4-hydroxyisoxazole [NMR: δ^{CDCl_3} 2.17 (s, 3H), 2.27 (s, 3H), and 5.5 ppm (broad s, 1H)]; yield (from 4-acetoxy-2,4-pentanedione), 8%; bp 106—115 °C/2 mmHg. NMR: δ^{CD_3CD} 2.19 (s, 3H), 2.53 (s, 3H) and 3.78 ppm (s, 3H).

*3,4,5-Trimethylisoxazole (**7**).* According to the method of Sokolov,[15] **7** was prepared from 3-methyl-2,4-pentanedione, hydroxylamine hydrochloride, and anhydrous potassium carbonate. Yield, 26%; bp 98—99 °C/69 mmHg. NMR: δ^{CD_3OD} 1.89 (s, 3H), 2.16 (s, 3H), and 2.28 ppm (s, 3H).

*3,5-Dimethyl-4-chloroisoxazole (**8**).* According to the method of Sokolov,[15] **8** was prepared from 3-chloro-2,4-pentanedione and hydroxylamine hydrochloride. Yield, 63%; bp 82 °C/25 mmHg. NMR: δ^{CD_3OD} 2.22 (s, 3H), and 2.37 ppm (s, 3H).

*3,5-Dimethyl-4-iodoisoxazole (**9**).* According to the method of Kochetkov,[16] **9** was prepared from **1**, iodine, and a catalytic amount of nitric acid. Yield, 59%; mp 51—53.5 °C (lit, 51.5—53 °C[16]). NMR: δ^{CD_3OD} 2.21 (s, 3H), and 2.42 ppm (s, 3H).

*3,5-Dimethyl-4-carbomethoxyisoxazole (**10**).* According to the method of Stork,[17] **10** was prepared from nitroethane and methyl acetoacetate. Yield, 30%; bp 95—98 °C/3 mmHg. NMR: δ^{CD_3OD} 2.34 (s, 3H), 2.59 (s, 3H), and 3.83 ppm (s, 3H).

*3,5-Dimethyl-4-nitroisoxazole (**11**).* By the method of Morgan,[18] **1** was nitrated by nitric acid and concentrated sulfuric acid. Yield, 60%, mp 62—64 °C (lit, 63.5 °C[18]). NMR: δ^{CD_3OD} 2.50 (s, 3H), and 2.75 ppm (s, 3H).

Hydrogen-Deuterium Exchange Reaction Rate. Isoxazole (0.45 mmol) was treated with sodium methoxide-d_3 (16.5 mg) in methanol-d_4 (282 mg) in sealed tubes at the refluxing temperature of tetrachloroethylene (bp 121.2 °C), toluene (bp 110.6 °C), water (bp 100.0 °C), aqueous *p*-dioxane (bp 89.0 °C), or benzene (bp 80.1 °C), and at appropriate time intervals the NMR spectra were measured at 34.2 °C, using cyclohexane as the internal standard, by means of a JEOL H-100 NMR spectrometer. From the NMR data, the reaction rates were calculated; they are summarized in Table 2.

Mass Spectral Analysis of Deuterated Derivative. To a solution of **1** (1.01 g) in anhydrous ether, a 15% hexane solution of butyllithium (6 ml) was added at −70 °C. The mixture was then stirred for 3 h at room temperature under a nitrogen atmosphere. After the addition of deuterium oxide (1.97 g), the stirring was continued for another 0.5 h at room temperature. The reaction mixture was separated. The organic layer was washed with dilute hydrochloric acid, water, and aqueous sodium chloride, and dried over anhydrous sodium sulfate. After the solvent had been removed, the residue was distilled. Yield, 0.21 g; bp 135—142 °C. NMR: δ^{CDCl_3} 2.21 (s), 2.33 (s), and 5.78 ppm (s); the intensity ratio is 30 : 26 : 11.

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