The Kinetics of Hydrogen-Deuterium Exchange of Methylisothiazoles (1)

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The rates of hydrogen-deuterium exchange of 3-methyl, 4-methyl, 5-methyl and 3,5-dimethyl-isothiazole were determined and compared with the rate of exchange of 2-methylpyridine. The rates were measured in dimethylsulfoxide-d_6-deuterium oxide (90:10), using sodium deuteroxide as catalyst. The relative rates for exchange of both ring protons and methyl protons were $5 > 3 > 4$. For exchange of methyl hydrogens, the approximate ratio of rate constants is $100:1: < 10^{-4}$ for positions 5,3, and 4, respectively. Activation parameters are reported for 5-methylisothiazole.

The rates of base-catalyzed hydrogen-deuterium exchange reactions of alkylbenzenes (3) have been extensively investigated. Similar extensive studies on aromatic alkyl heterocyclic systems are lacking. A few reports (4) of relative rates of exchange in a variety of solvent systems have appeared, but no extensive quantitative studies have been reported.

The present study reports results of sodium deuteroxide catalyzed isotopic exchange of methylisothiazoles (Ia-d) in dimethylsulfoxide-d_6-deuterium oxide. Pseudo-first-order rate constants were obtained for exchange of methyl hydrogens, and semiquantitative estimates of the rates of exchange of nuclear hydrogens were made.

I
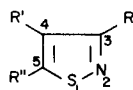
	R	R'	R''
a	CH₃	H	H
b	H	CH₃	H
c	H	H	CH₃
d	CH₃	H	CH₃

METHODS AND RESULTS

Isotopic Analyses.

Hydrogen-deuterium analyses were carried out using an nmr peak integration method in which the signal of the exchangeable protons was compared to that of tertiary

butyl alcohol-O-d (4% by volume), which was used as an internal standard.

Kinetic Data.

All of the kinetic experiments were performed in sealed nmr sample tubes using a medium containing dimethyl-sulfoxide-d_6-deuterium oxide (90:10 by volume) which was 0.35 M in sodium deuteroxide. All runs were made under conditions such that the concentration of exchangeable deuterium in the solvent (considering that dimethyl-sulfoxide-d_6 was part of the deuterium pool) was at least 20 times greater than the concentration of exchangeable hydrogen. Table I records the pseudo-first-order rate constants for isotopic exchange of methyl hydrogens of 3-methyl, 4-methyl, 5-methyl and 3,5-dimethylisothiazole, and 2-methylpyridine. The rate constants were calculated from linear pseudo-first-order plots consisting of a minimum of ten points taken over one to three half-lives, using a linear least squares method.

At 80° rate constants could be determined for isotopic exchange of hydrogen from the methyl groups of the methylisothiazoles, with the exception of the 4-methyl group, which did not undergo exchange to any appreciable extent after 13 days at 80°. The pseudo-first-order rate constant for the methyl group of 2-methylpyridine was also determined under the same conditions. The rate of isotopic exchange of hydrogen on methyl groups decreased in the sequence: 5-isothiazolyl > 2-pyridyl > 3-isothiazolyl >> 4-isothiazolyl. Significant effects on the rate of exchange occurred when a second methyl group was introduced into the isothiazole nucleus, as was shown by the decrease in the rate constant for exchange at the

TABLE I

Pseudo-First-Order Rate Constants for Isotopic Exchange of Methyl Hydrogens

Compound	Temp., °C.	k_1 (Sec.$^{-1}$ x 10^4) (a)
2-Methylpyridine	80	4.32 ± 0.28
3-Methylisothiazole	80	0.616 ± 0.054
4-Methylisothiazole	80	< 0.000026 (b,c)
5-Methylisothiazole	80	31.4 ± 2.2
3,5-Dimethylisothiazole-3-Methyl rate	80	0.320 ± 0.011
3,5-Dimethylisothiazole-5-Methyl rate	80	32.0 ± 4.3
5-Methylisothiazole	60	13.2 ± 1.0
5-Methylisothiazole	50	6.71 ± 0.64
5-Methylisothiazole	40	2.66 ± 0.21

(a) Rates were measured in 0.35 M NaOD in dimethyl sulfoxide-d_6-D_2O, 90:10. (b) Limiting rate constant assuming < 5% exchange after 13 days. (c) Exchange was not observed after 50 hours at 100°.

TABLE II

Approximate Pseudo-First-Order Rate Constants for Ring Hydrogen
Exchange of 4-Methyl and 5-Methylisothiazoles

	Proton	Temp., °C.	k_1 (Sec. $^{-1}$)
4-Methylisothiazole	5	25	1.2 x 10^{-2}
	3	80	3.2 x 10^{-5}
5-Methylisothiazole	3	80	<4.8 x 10^{-7} (a)
	4	80	(b)

(a) Limiting rate constant, assuming a 5% reaction completion at 40 hours. (b) No exchange was observed for this proton under any condition.

3-methyl group of 3,5-dimethylisothiazole compared with 3-methylisothiazole.

Approximate rate constants for isotopic exchange of the ring protons of 4-methyl and 5-methylisothiazole are listed in Table II. Exchange at position 5 was so rapid that precise data could not be obtained, and exchange at position 4 was too slow to be measured. The rate of exchange at position 3 was intermediate, and was markedly influenced by the position occupied by the methyl substituent.

DISCUSSION

The rates of isotopic exchange of methylisothiazoles correlate with LCAO-MO π-electron density calculations (5a) and nmr chemical shift data (5b), at least to the extent that the correct order for variation of rate with position of attachment to the nucleus is concerned. This applies both to exchange of ring hydrogens and hydrogens on attached methyl groups. The magnitude of the differences between rate constants in the series was greater

than expected, however, which seems to indicate that considerations other than electron density are also important. Previous studies (6) on the rate of exchange of the ring hydrogens of isothiazoles and related compounds have indicated that d-σ overlap and possibly other effects may contribute substantially to enhancement of acidity of protons on carbon next to sulfur (7). Our results with sodium deuteroxide in dimethylsulfoxide-d_6 -deuterium oxide follow the same pattern as those of Olofson, et al., (6) for exchange of ring hydrogens of isothiazoles in hydroxylic solvents, except that exchange occurred more rapidly in our medium. We were able to determine approximate rate constants for exchange of hydrogen at position 3 in 4-methyl and 5-methylisothiazole, whereas in hydroxylic solvents (6) the exchange was too slow to be observed. The ratio of approximate rate constants for exchange at position 3 and 5 (k_{H_5}/k_{H_3}) is > 400:1.

The relative rates of exchange of hydrogen on methyl substituents were in the approximate ratio 100:1:$<10^{-4}$ for positions 5, 3, and 4, respectively. The substantially greater rate of exchange for 5-methylisothiazoles compared with 3-methylisothiazoles seems to argue for an extraordinary effect on rate enhancement for removal of a proton from the 5-methyl group. Superficially, it appears that stabilization of the transition state for this process involving participation by the d-orbitals of sulfur would be less favorable than for the case where a ring proton is being lost, because the incipient carbanion is developing farther away from sulfur in the case of loss of a proton from a 5-methyl group. This factor may be partially compensated for, however, because the orbital containing the incipient non-bonding pair of electrons in the transition state for loss of a proton from a 5-methyl group should have significantly more p-character than would be the case for loss of a ring proton. This effect might still permit substantial rate enhancement via d-orbital participation.

The activation parameters calculated from the rate data for 5-methylisothiazole are E_{act} = 13.4 ± 1.3 kcal/mole and $\Delta S^{\ddagger}$ = -33.6 ± 3.8 e.u. at 95% confidence. These data differ substantially from the parameters reported (8) (E_{act} = 18.2 ± 0.4, $\Delta S^{\ddagger}$ = -16.6 ± 0.9) for isotopic exchange of hydrogens on the methyl group of toluene in dimethylsulfoxide-d_6 using potassium tertiary butoxide as catalyst.

The lower E_{act} for 5-methylisothiazole is explicable in terms of the enhanced electron-withdrawing character of the 5-isothiazolyl group compared with the phenyl group. The much more negative value of $\Delta S^{\ddagger}$ for 5-methylisothiazole is puzzling, but can be rationalized in terms of increased solvation of the carbanionoid transition state relative to solvated reactant for 5-methylisothiazole compared to toluene, and differences in solvent composition.

The medium, dimethylsulfoxide-d_6 -deuterium oxide (90:10) using sodium deuteroxide as a basic catalyst and tertiary butyl alcohol-O-d as an internal standard, appears to be generally useful for determination of rates of base-catalyzed hydrogen-deuterium exchange of alkyl heterocycles. Experiments are being carried out to test this hypothesis.

EXPERIMENTAL

3-Methyl, 4-methyl and 5-methylisothiazoles were obtained as gifts (9). 3,5-Dimethylisothiazole was synthesized by a known procedure (10). These substances were purified by fractional distillation prior to use. The deuterated reagents (isotopic purity 99+ %) were purchased from Merck, Sharp, and Dohme, Ltd. They were used without further purification and were stored under dry nitrogen after being opened.

The kinetics were measured using a Varian A-60 nmr spectrometer equipped with a V-6040 temperature regulator and a variable temperature probe. An insulated, thermostated (Precision controller No. 66590) mineral oil bath (five gallon capacity) was used to maintain samples at the desired temperature. Each run was carried out in an nmr tube in which dilute hydrochloric acid had been heated at reflux. The tube was then rinsed several times with distilled water, and dried at 110° for several hours.

Hydrogen-deuterium analyses were carried out at appropriate intervals using an nmr peak integration method in which the signal corresponding to the exchangeable protons in the substrate was compared to that of the methyl protons of tertiary butyl alcohol-O-d, which was present as an internal standard. The hydrogen peak area data (expressed as concentration of exchangeable hydrogen) were then plotted against time to give linear pseudo-first-order plots. The correlation coefficients for these plots were typically greater than 0.99, and in only one run of a total of 49 runs was a value (0.972) less than 0.98 obtained. The error range shown for rate constants in the tables is one standard deviation. Rate constants were generally reproducible to within ± 10% of their mean value. The activation parameters were calculated by regression analysis of the individual rate constants. The error ranges cited correspond to 95% confidence intervals. The correlation coefficient for the Arrhenius line was -0.985.

A Typical Sample Run.

A clean, dry nmr tube was flushed with dry nitrogen to displace the air. A solution (0.25 ml.) containing dimethylsulfoxide-d_6 (0.225 ml.), deuterium oxide (0.023 ml.), tert-butyl alcohol-O-d (0.01 ml.) and sodium deuteroxide in deuterium oxide (40%, 0.01 ml.) was mixed with 3-methylisothiazole (0.023 ml.) and the resulting solution was placed in the sample tube. The tube was sealed and the nmr spectrum was recorded. The sample was placed in the constant temperature bath at the appropriate temperature and its nmr spectrum was recorded at appropriate intervals.

The rate of isotopic exchange for 5-methylisothiazole was sufficiently fast that significant errors could occur due to temperature variation during transfer from bath to probe and vice versa, so the sample tubes were left in the thermostatted nmr probe during the course of the measurements on this compound. The temperature of the probe was determined by use of a plot of temperature versus chemical shift for a standard ethylene glycol sample (11).

REFERENCES

(1) Supported by a research grant (GM 14079) from the National Institutes of Health.

(2a) N.D.E.A. Predoctoral Fellow; (b) Present address: Research and Technical Department, Texaco, Inc., Port Arthur, Texas.

(3a) A. I. Shatenstein in "Advances in Physical Organic Chemistry", V. Gold, Ed., Academic Press, New York, 1963, pp. 155-201; (b) A. Schriesheim, J. E. Hoffman, and C. A. Rowe, *J. Am. Chem. Soc.*, 83, 3731 (1961); (c) W. D. Kollmeyer and D. J. Cram, *ibid.*, 90, 1784 (1968).

(4a) A. I. Shatenstein and E. N. Zvyagentsiva, *Dokl. Akad. Nauk SSSR*, 117, 852 (1967); (b) T. I. Abramovitch, I. R. Gragero, and V. Perekalin, *J. Gen. Chem.*, 31, 1962 (1961); (c) Y. Kawazoe,

M. Ohnishi, and Y. Yashioka, *Chem. Pharm. Bull.* (Tokyo), 15, 1225 (1967); (d) *ibid.*, 15, 2000 (1967).

(5a) A. Adams and R. Slack, *J. Chem. Soc.*, 3061 (1959); (b) R. C. Anderson, *J. Heterocyclic Chem.*, 1, 279 (1964).

(6) R. A. Olofson, J. M. Landesberg, K. N. Houk, and J. S. Michelman, *J. Am. Chem. Soc.*, 88, 4265 (1966).

(7) A suggestion that the extraordinary acidity of the 2 hydrogen of thiamine might be due in some measure to d-σ overlap has been made by R. Breslow [*ibid.*, 80, 3719 (1958)].

(8) J. E. Hoffman, R. J. Muller, and A. Schrieshein, *ibid.*, 85, 3000 (1963).

(9) 3-Methylisothiazole and 4-methylisothiazole were obtained from Vickers-Zimmer A. G., 6-Frankfurt (Main), No. 14, Borsigaller 1, Germany. 5-Methylisothiazole was obtained from Raylo Chemicals, Ltd., 8045 Argyll Road, Edmonton, Alberta, Canada.

(10) M. P. L. Caton, D. H. Jones, R. Slack, and K. R. H. Wolldridge, *J. Chem. Soc.*, 446 (1964).

(11) Varian Publication Number 87-202-006 A567, Figure 4-4, p. 4-9.