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Amine Base-catalyzed H-D Exchange Reaction of 2,3,4-Trimethylthiazolium Iodide in Methanol-d_4

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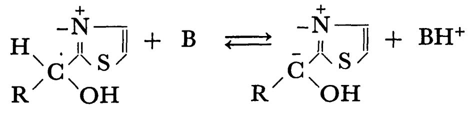
Synopsis. The rates of amine base-catalyzed H-D exchange of 2-methyl hydrogens of 2,3,4-trimethylthiazolium iodide were measured in deuterated methanol by using following amines: α-picoline, imidazole, 2- and 4-aminopyridine. The results indicated that the reaction was subject to a general base catalysis. The solvent effect is also described.

The acyloin condensation catalyzed by thiazolium salts are known to involve multistep reaction pathways.[1] One crucial step of them is the ionization of initially formed 2-(α-hydroxyalkyl)thiazolium salt (**1**) to form so called "active aldehyde (**2**)" (Eq. 1).


(1)

1 **2**

Until recently, the mechanism of this step has been left uncertain whether it is subject to specific base or general base catalysis. Recently, the deprotonation from 2,3,4-trimethylthiazolium and 2-(α-hydroxyethyl)-thiazolium ions has been reported to occur by general base catalysis in aqueous buffer solution.[2,3] In contrast, we were unable to detect general base catalysis by an internal dimethylamino group of thiazolium salt in the benzoin condensation in methanol.[4] Therefore it was desired to examine base catalysis of externally added amines, also in methanol. In this paper, we describe the H-D exchange reaction of 2,3,4-trimethylthiazolium iodide (**3**) in deuterated methanol, catalyzed by several amines.

TABLE 1. THE RATE CONSTANTS OF H-D EXCHANGE REACTION OF 2,3,4-TRIMETHYLTHIAZOLIUM IODIDE[a)] IN METHANOL-d_4 AT 38 °C

Base	pK_a (in MeOH)	10^2[Base] / M	$10^4\,k_{obsd}$ / s^{-1}	$10^3\,k_{app}$ / $M^{-1}\,s^{-1}$[b)]
α-Picoline	6.11[c)]	40	0.967	0.242
2-Amino-pyridine	7.9[d)]	10	4.03	4.03
Imidazole	8.10[e)]	3.3	2.77	
		6.8	4.44	
		13.6	8.41	
		27.2	16.5	6.10
4-Amino-pyridine	9.9[d)]	5.0	146	292

a) [Thiazolium salt] = 0.1 M. b) Apparent second-order rate constants, $k_{app}=\frac{k_{obsd}}{[Base]}$. c) C.H. Rochster, *J. Chem. Soc.*, *B*, **1967**, 33. d) Estimated values. e) M. Tanaka, "Acid and Base," Shoka-bo, Tokyo (1975), p. 46.

TABLE 2. THE RATE CONSTANTS[a)] IN CD_3OD–D_2O AT 38 °C

CD_3OD (%)	D[b)]	$10^4k_{obsd}/s^{-1}$	Rel rate
100	32.6	146	128
50	58.5	21.1	18
10	75.0	1.60	1.4
0	78.5	1.14[c)]	1

a) 4-Aminopyridine (0.05 M) was used as a base.
b) Dielectric constants in CH_3OH–H_2O system.[7)]
c) This is the extrapolated value.

Results and Discussion

The amines employed were α-picoline, imidazole, 2- and 4-aminopyridine. The rate constants of H-D exchange were determined by following the relative peak area of 2-methyl protons and that of non-exchangeable 3- or 4-methyl protons by NMR. No decomposition products were detected under the present reaction conditions. The results are shown in Table 1. The base concentration was changed for imidazole. The rate constants are linearly dependent on the concentration of imidazole. From the slope, the apparent second-order rate constant for imidazole is calculated to be $6.10\times10^{-3}\,M^{-1}\,s^{-1}$. Since p$K_a$ values of the bases in CD_3OD are not available, the estimated pK_a values in CH_3OH were employed. The estimation is based on the fact that the plots of pK_a values of ammonia and substituted anilines in H_2O against those in CH_3OH give a single straight line. Thus, the pK_a of desired amine in CH_3OH can be estimated from the pK_a in H_2O, as indicated in Table 1 for 2- and 4-aminopyridine. Plots of log k_{app} against the pK_a's of the bases gave a straight line [slope=0.81(γ=0.995)].[5)] This may indicate that a general base catalysis is also important for the present H-D exchange reaction in addition to the lyate ion catalysis.

In model reactions of thiamine catalysis, it has been shown that all kinetically significant steps proceed faster in ethanol than in water.[6)] This suggests that in many thiamine pyrophosphate dependent enzymatic reactions, the catalysis is in large part to occur through the binding of the thiazolium portion of the coenzyme in a hydrophobic region of the protein. Therefore, more detailed solvent effects were also examined for the present exchange reaction, by changing the composition of D_2O in CD_3OD as shown in Table 2.

Regarding this solvent effect, it may be of interest to see a relationship between the dielectric constants and the composition of CH_3OH–H_2O mixture. Albright *et al.* reported that the dielectric constant increases linearly with the increase of water content.[7)] As shown in Table 2, log k_{obsd} decreases linearly with the increase of the apparent dielectric constants. Thus, less polar solvent is more favorable for the present H-D exchange reaction. This may be accounted for by an accepted view that the ionic structure of the reactant state is stabilized more in a polar solvent and the neutral zwitter ionic carbanion is stabilized more in a less polar solvent. This suggests that the enzyme-mediated reaction of thiamine occurs in a relatively nonpolar environment. The results of the above model reaction also support the occurrence of a general base catalysis for the carbanion formation at the α-carbon of 2-(α-hydroxyethyl)thiazolium ion, especially under hydrophobic conditions. Thus, it is tempting to speculate that aminopyrimidine moiety of thiamine would act as an internal base in step of the carbanion formation from 2-(α-hydroxyethyl)thiazolium ion. However, it should also be kept in mind that previous failure to observe internal base catalysis in benzoin condensation has been still left unanswered.

Experimental

NMR spectra were recorded on a Varian A-60 spectrometer.

Materials. Deuterium oxide (99.75%, Merck) and methanol-d_4 (99%, Merck) were used. 2- and 4-Aminopyridines were purified by recrystallization from diethyl ether–hexane, mp 58 °C (lit,[8] mp 58 °C) and mp 156—158 °C (lit,[9] mp 157 °C). Imidazole (Wako Pure Chemical Co.) was used without further purification. Imidazole hydrochloride was prepared from imidazole and HCl in EtOH. Purification was performed by recrystallization (MeOH–diethyl ether). α-Picoline was purified by distillation.

2,3,4-Trimethylthiazolium Iodide was prepared from 2,4-dimethylthiazole and methyl iodide. Mp 250 °C (EtOH), NMR (CD_3OD), δ 2.58 (3H, s), 2.98 (3H, s), 3.96 (3H, s), and 7.60 (1H, s). Found: C, 28.30; H, 3.97; N, 5.46%. Calcd for $C_6H_{10}INS$: C, 28.25; H, 3.95%; N, 5.48%.

Exchange Kinetics. The salt (5×10^{-2} mmol) was weighed accurately in NMR tube and 0.45 ml of CD_3OD was added. This was placed in the probe of the NMR spectrometer for 10 min. The reaction was initiated by adding 0.05 ml of the base solution by a microsyringe. 2-Methyl protons (2.98 ppm) were followed by integration as a function of time, relative to the 3- or 4-methyl protons, which was found not to be exchangeable under the present reaction conditions. The rate constants were calculated as described in the previous paper.[10]

References

1) R. Breslow, *J. Am. Chem. Soc.*, **80**, 3719 (1958); *Ann. N. Y. Acad. Sci.*, **98**, 445 (1962).

2) a) A. A. Gallo and H. Z. Sable, *J. Biol. Chem.*, **251**, 2564 (1976); b) J. A. Zoltewicz and S. Sridharan, *J. Org. Chem.*, **43**, 3785 (1978).

3) Y. Yano, Y. Tamura, Y. Hoshino, and W. Tagaki, *Bull. Chem. Soc. Jpn.*, **53**, 2340 (1980).

4) Y. Yano, Y. Tamura, and W. Tagaki, *Bull. Chem. Soc. Jpn.*, **53**, 740 (1980).

5) This is not the Brönsted β value. In separate experiments, the buffer concentration (imidazole–imidazole hydrochloride) was changed with a constant buffer ratio. The rate constants were linearly dependent on the concentration of free imidazole.

6) J. Crosby, R. Stone, and G. E. Lienhard, *J. Am. Chem. Soc.*, **92**, 2891 (1970); J. Crosby and G. E. Lienhard, *ibid.*, **92**, 5707 (1970).

7) L. J. Gosting and P. S. Albright, *J. Am. Chem. Soc.*, **68**, 1061 (1946).

8) "The Merck Index," ed by P. G. Stecher, Merck and Co., N. J. (1968), p. 485.

9) T. Ishii, *J. Pharm. Soc. Jpn.*, **72**, 1315 (1952).

10) Y. Yano, T. Okonogi, and W. Tagaki, *J. Org. Chem.*, **38**, 3919 (1973).