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Proton Ionization of N′-Methyl-2-aminoethylisothiuronium Salt Prior to Its Transguanylation

Akira Hanaki

National Institute of Radiological Sciences[1]

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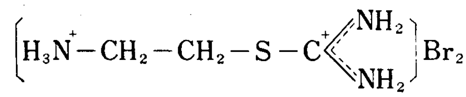
The determination of the proton ionization constant of N′-methyl-2-aminoethylisothiuronium (N′-methyl-AET) was attempted. This compound was also transguanylated, as in AET, during the potentiometric titration. The first conjugate base of N′-methyl-AET is relatively stable and subsequently ionized to the second base with its rapid transguanylation to the sulfhydryl compound. The first ionization is due to amino group, pK 8.05 and ΔH 12 kcal/mole, and the second is due to isothiuronium group, pK 9.88 and ΔH 18 kcal/mole. The reactivity of two conjugate bases of N′-methyl-AET was discussed.

Recent studies have revealed that 2-aminoethylisothiuronium (AET) salt undergoes the proton ionization prior to its transguanylation.[2] AET, having two ionizable groups, *i.e.*, ammonium and isothiuronium group, is considered to be a dibasic acid. However, because of the extreme lability of the conjugate base, probably $H_2N-CH_2-CH_2-S-C(NH_2)_2^+$, which was subsequently transguanylated, the isothiuronium group did not undergo the second ionization.[3] The modification of this compound is expected to affect the rate of the transguanylation. The rate is retarded by the substitution at the nitrogen atom of isothiuronium group, abbreviated as the N′-substitution.[4] This fact indicates that the conjugate base in the N′-substituted AET is rather unlabile and is apt to undergo the further ionization. The present paper was concerned with the ionization, especially in the second step, of N′-methyl-AET.



$$\left[H_3\overset{+}{N}-CH_2-CH_2-S-\overset{+}{C}\begin{smallmatrix}NH_2\\ NH_2\end{smallmatrix}\right]Br_2$$

AET (2—Aminoethylisothiuronium bromide hydrobromide)

Chart 1

Experimental

Material——N′-Methyl-AET was prepared by the procedure reported previously.[5] Other chemicals were of analytical grade and were used without further purification.

Instrument——A Radiometer TTTlc titrator and SBR2c titrigraph equipped with the glass electrode 202C and the calomel electrode K401 was used for the potentiometric titration. For the measurement above 20°, the glass electrode 202B was employed. The instrument was standardized with phthalate and phosphate buffers before and after the measurement.

Potentiometric Titration——The N′-methyl-AET solution in a 30 ml double-walled beaker was titrated with decarbonated 0.1N KOH at a constant temperature. At the start of the titration, the concentration of N′-methyl-AET was approximately 5.00×10^{-3}M. When 1 equivalent KOH, corresponding to 1.0 ml, had been added, the concentration of the compound became exactly 5.00×10^{-3}M. During the titration, the nitro-

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[1] Location: *Anagawa-4, Chiba.*

[2] A. Hanaki, *Chem. Pharm. Bull.* (Tokyo), **17**, 1146 (1969).

[3] A. Hanaki, *Chem. Pharm. Bull.* (Tokyo), **18**, 766 (1970).

[4] A. Hanaki, P. Xumsaeng, T. Hino and S. Akaboshi, *Chem. Pharm. Bull.* (Tokyo), **17**, 677 (1969).

[5] T. Hino, K. Tana-ami, K. Yamada and S. Akaboshi, *Chem. Pharm. Bull.* (Tokyo), **14**, 1139 (1966).

gen gas presaturated with 0.1N KNO_3 was bubbled into the titration solution. In order to avoid the transguanylation of the compound during the measurement, the solution was prepared just prior to use and the titration was done rapidly as possible.

The Rate of the Transguanylaion——The rate of the transguanylation, expressed by the half life of the reactive species, was measured potentiometrically at 15° as described previously.[6] The reaction was initiated by adding alkali, the amounts of which were varied from 0.5 to 1.5 equivalents.

Result and Discussion

The transguanylation of AET derivatives is generally begun spontaneously after adding alkali and the pH value of the solution is dropped progressively thereafter. The pH drop is considered as a reflection of the transguanylation, because the range of pH drop is related to the extent of the reaction as shown in Eq. (1);

$$\mathrm{p}(1-T)=\Delta\mathrm{pH} \qquad (1)$$

where T and ΔpH represent the extents of the transguanylation and of the pH drop, respectively. In N′-methyl-AET, the pH drop was observed significantly in the region where more than one equivalent alkali was added. This fact indicates the possibility that this isothiuronium salt is likely to be transformed in this region and that the conjugate base produced in the first-step ionization, which is presumably unlabile, undergoes the second ionization. On the contrary, the pH drop in AET was measured even in the region of less than one equivalent alkali, which indicates the extreme lability of this compound. The calculation of the reliable ionization constant of N′-methyl-AET was attempted from the titration curve measured under the condition where the pH drop was minimized as possible. The ionization constant, along with that of AET, was summarized in Table I. The values in Table I are all practival ionization constants K'.[7] The calculated titration curve using pK_1 and pK_2 in Table I was coincided satisfactorily with the experimental curve, indicating the validity that this compound is undoubtedly a dibasic acid. The pK_1 may be due to amino group, and the second constant may be due to either isothiuronium group of this isothiouronium salt or sulfhydryl group of the transguanylation product as observed in AET.

The proton ionization reaction in N′-methyl-AET may be compared with that of ethylenediamine or propane-1,3-diamine from the electrostatic viewpoint. The pK values of amino group in methylamine and of isothiuronium group in S-methylamidinum ion were reported to be 10.64[8] and 9.8,[9] respectively. If those

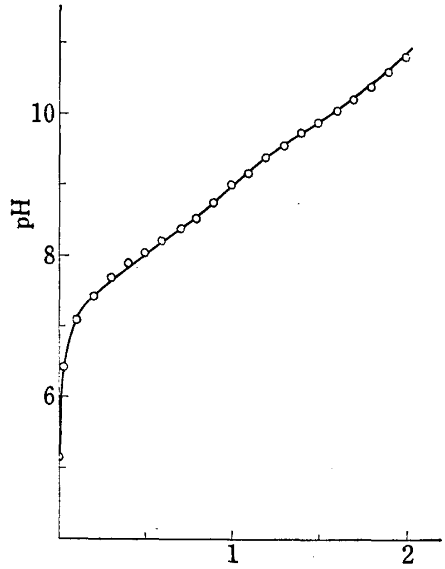

Fig. 1. Potentiometric Titration of N′-Methyl-AET at 15° (ionic strength 0.1)

The circle indicates the experimental value and the solid line is the calculated titration curve.

Table I. Proton Ionization Constant of N′-Methyl-AET and AET at 15°

Compound	pK_1	pK_2
N′-Methyl-AET	8.05	9.88
AET	7.97	8.94

ionic strength; 0.1 with KNO_3

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[6] A. Hanaki, *Chem. Pharm. Bull.* (Tokyo), **16**, 2023 (1968), **18**, 1653 (1970).

[7] $K'=\alpha_{H^+}[A]/[AH^+]$

[8] H.S. Harned and B.B. Owen, *J. Am. Chem. Soc.*, **52**, 5079 (1930).

[9] A. Albert, R. Goldacre and J. Phillips, *J. Chem. Soc.*, **1948**, 2240.

two moieties are linked with a chemical bond, two ionizable group will electrostatically interact each other and their ionization constants will be varied significantly from the original values. In a dibasic acid like alkylenediamine, the ionization in the first step will be facilitated according to the electrostatic interaction with another positively charged group, while the second ionization, in which the weak inductive effect from the terminal group will be expected, is less affected. For instance, the pK_1 in ethylenediamine is 7.13 and the pK_2 is 9.91.[10] In propane-1,3-diamine, the pK values are 8.49 and 10.47, respectively.[11]

The enthalphy for the proton ionization of amino group in alkylenediamine are dispersed from 11 to 14 kcal/mole. For the proton ionization, in which the intense electrostatic interaction is expected, the enthalpy is relatively low; *e.g.*, 11 kcal/mole in ethylenediamine[10] and 12.4 kcal/mole in propane-1,3-diamine.[12] The enthalpy for the second ionization gives a little higher value. The enthalpy due to amino group in alkylamine shows higher value, approximately 14 kcal/mole. Thus, the enthalpy for the ionization of amino group is generally less than 14 kcal/mole. The enthalpy for the ionization of sulfhydryl group of aminothiol or mercaptoethylamine, in which sulfhydryl group is dissociated prior to the ionization of amino group, is relatively low, approximately 7 kcal/mole.[2,13] On the other hand, the enthalpy of isothiuronium group, though has not hiterto been determined, would be endothermic and be higher than that of amino group. The isothiuronium group, in which the positive charge would be symmetrically located along the –N–C–N– bond, is thermodynamically stable. Therefore, in order to remove one proton from this group to form the conjugate base, probably electrostatically unsymmetric, the work consuming large amounts of heat would be needed. If one nitrogen atom of the isothiuronium group is fused in a ring, as in 2-amino-2-thiazoline, the location of the positive charge would be limited and the heat of the ionization be reduced. Certainly, in 2-amino-2-thiazoline or 2-amino-2-penthiazoline, the enthalpy for the ionization of amidinum group was reduced to approximately 11 to 12 kcal/mole.[2] The second ionization of N′-methyl-AET, consuming large amount of heat, may be attributed to its isothiuronium group.

TABLE II. Enthalpy for the Proton Ionization

Compound	pK	ΔH kcal/mole	Reference	Temperature (°C)
N′-Methyl-AET	8.05	12	present work	15
	9.88	18	present work	15
AET	7.94	13	2)	15
	8.94	7	2)	15
Ethylenediamine	7.13	11.0	10)	25
	9.91	11.9	10)	25
Propane-1,3-diamine	(8.49)[11]	12.4	12)	25
	(10.47)[11]	13.2	12)	25
Methylamine	(10.64)[8]	13.3	12)	25
Ethylamine	(10.63)[14]	13.7	12)	25
n-Propylamine	(10.57)[15]	13.8	12)	25
Mercaptoethylamine	8.23	7.4	13)	25
Mercaptoethylguanidine	8.94	7.0	2)	15

When the pK and ΔH values were obtained in different studies, the pK value is enclosed in parentheses.

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10) J.A. Partridge, J.J. Christensen and R.M. Izatt, *J. Am. Chem. Soc.*, **88**, 1649 (1966).
11) C.R. Bertsch, W.C. Fernelius and B.P. Block, *J. Am. Chem. Soc.*, **62**, 444 (1958).
12) J.J. Christensen, R.M. Izatt, D.P. Wrathall and L.D. Hansen, *J. Chem. Soc.(A)*, **1969**, 1212.
13) R.J. Irving, L. Nelander and I. Wadso, *Acta Chem. Scand.*, **18**, 769 (1964).
14) A.G. Evans and S.D. Hamann, *Trans. Faraday Soc.*, **47**, 34 (1951).
15) R.G. Bates and H.B. Hetzer, *J. Phys. Chem.*, **65**, 667 (1961).

The distribution of the ionized species of N′-methyl-AET was calculated under the several experimental condition, where the amounts of alkali added for the initiation was different. In Fig. 2 was shown the plot of the distribution and the apparent half life of the reactive species against the alkali quantity. There existed a intimate relationship between the reactivity and the distribution of the second conjugate base. Therefore, it is suggested that the second conjugate base, thermodynamically unstable, is highly sensitive to the transguanylation, though the first base may also undergo the transformation, and that the reactions of N′-methyl-AET encountered during the potantiometric titration are pictured as follows:

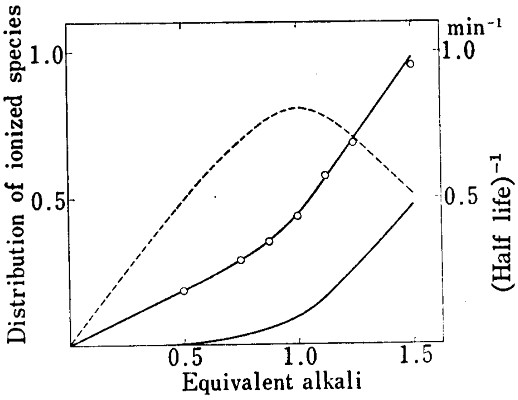
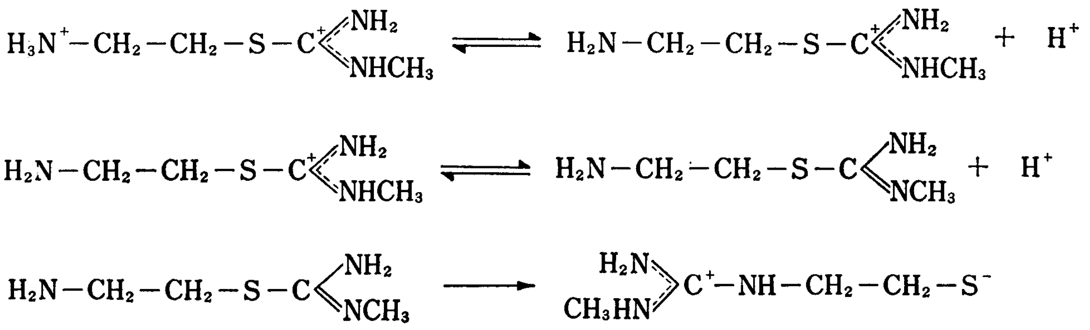


Fig. 2. Distribution of the Ionized Species of N′-Methyl-AET and the Half Life of the Transguanylation as a Fuction of pH

The half life was expressed by [R′SH]/([RH+]+[R]), where [R′SH], [RH+] and [R] indicate respectively the concentrations of the transguanylation product, the first and the second conjugate bases. The distribution of the first and the second conjugate bases; *i.e.*, [RH+]/[R]. and [R]/[R]., were represented respectively by the dotted and solid lines.



$$\mathrm{H_3N^+{-}CH_2{-}CH_2{-}S{-}C^{+}\!\!\begin{array}{l}\nearrow NH_2\\ \searrow NHCH_3\end{array} \rightleftharpoons H_2N{-}CH_2{-}CH_2{-}S{-}C^{+}\!\!\begin{array}{l}\nearrow NH_2\\ \searrow NHCH_3\end{array} + H^+}$$

$$\mathrm{H_2N{-}CH_2{-}CH_2{-}S{-}C^{+}\!\!\begin{array}{l}\nearrow NH_2\\ \searrow NHCH_3\end{array} \rightleftharpoons H_2N{-}CH_2{-}CH_2{-}S{-}C\!\!\begin{array}{l}\nearrow NH_2\\ \searrow NCH_3\end{array} + H^+}$$

$$\mathrm{H_2N{-}CH_2{-}CH_2{-}S{-}C\!\!\begin{array}{l}\nearrow NH_2\\ \searrow NCH_3\end{array} \longrightarrow \begin{array}{r}H_2N\searrow\\ CH_3HN\nearrow\end{array}\!\!C^+{-}NH{-}CH_2{-}CH_2{-}S^-}$$

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