[Chem. Pharm. Bull. 20(7)1572—1574(1972)]

UDC 547.789.103

Proton Ionization and Thermal Decomposition of 2-Amino-2-thiazolinium Ion and Its N-Methyl Derivatives

Akira Hanaki

National Institute of Radiological Sciences[1]

(Received December 13, 1971)

N-Alkylation of 2-amino-2-thiazolinium (2-ATH$^+$) ion affects probably the physicochemical property of the compound, depending on the position of the substituent. The chemical shift in nuclear magnetic resonance (NMR) spectra of -N-CH_2-CH_2-S-moiety in 2-ATH$^+$ and 2-amino-2-thiazoline (2-AT) skeltons was changed considerably by 3-N-methylation but not by N-methylation at 2-amino group.[2] The substitution at 3-N-position would influence considerably the localization of electrons in 2-thiazolinium ring and especially in the functional group undergoing proton ionization; *i.e.*, amidinium group. The present paper is intended to check how the substituent affects the acidity of 2-ATH$^+$ and whether the substitution affects the thermal stability of the compound. The thermal decomposition was followed by the differential thermal analysis (DTA). In order to identify whether a peak in DTA curve is due to the phase transition; *i.e.*, from solid to liquid, or chemical change, the thermogravimetric analysis (TGA) was carried out simultaneously.

Table I. Proton Ionization Constant

Compound	pK_a
2-ATH$^+$	9.10
2-Methyl-2-ATH$^+$	9.12
3-Methyl-2-ATH$^+$	10.17

temperature; 15.0°
ionic strength; 0.1 (NaCl.)

The proton ionization constant, pK_a, was listed in Table I. The pK_a value was increased markedly and specifically by 3-N-methylation. Amidinium group, from which one proton is ionized to form a conjugate base, is stabilized by 3-N-alkyl group. It means that in 2-ATH$^+$ skelton $(\text{-NH}{=}\overset{|}{\text{C}}{=}\text{NHR})^+$ moiety may possess same acidity as $(\text{-NH}{=}\overset{|}{\text{C}}{=}\text{NH}_2)^+$ and that $(\text{-NR}{=}\overset{|}{\text{C}}{=}\text{NH}_2)^+$ moiety is the most basic of all.

The DTA and TGA curves of 2-ATH$^+$ derivatives were presented in Fig. 1. The first endothermic peak in each compound indicates the phase transition, because weight loss of the sample, which was estimated from TGA curve, was not observed in this temperature region. As heating rate becomes slow, the temperature of the peak approaches that of melting point. The second peak was also endothermic and appeared from 330 to 340°. The DTA curve of 2-ATH$^+$ in this region was composed of two peaks, which shifted to higher temperature region as heating rate increased. Those second peaks in every compounds were due to the chemical change. The decomposition of the compound was begun from 280°. The third peak in 2-methyl- or 3-methyl-2ATH$^+$ was observed as a shoulder, while 2-ATH$^+$ displayed a different intense peak. The TGA curve showed similar pattern in 2-methyl- and 3-methyl-2-ATH$^+$, while in 2-ATH$^+$ a different curve showing separate two parts was measured. Beyond 400°, the base line of DTA curve became drifted because of differences in the thermal diffusibilities of the sample and the reference. However, the TGA curve showed the continuous weight loss up to 500°. The amounts of weight loss from 280 to 400° were approximately 75% in each compound.

---

1) Location: *Anagawa-4, Chiba.*
2) T. Hino, K. Tana-ami, K. Yamada, and S. Akaboshi, *Chem. Pharm. Bull.* (Tokyo), **14**, 1201 (1966).

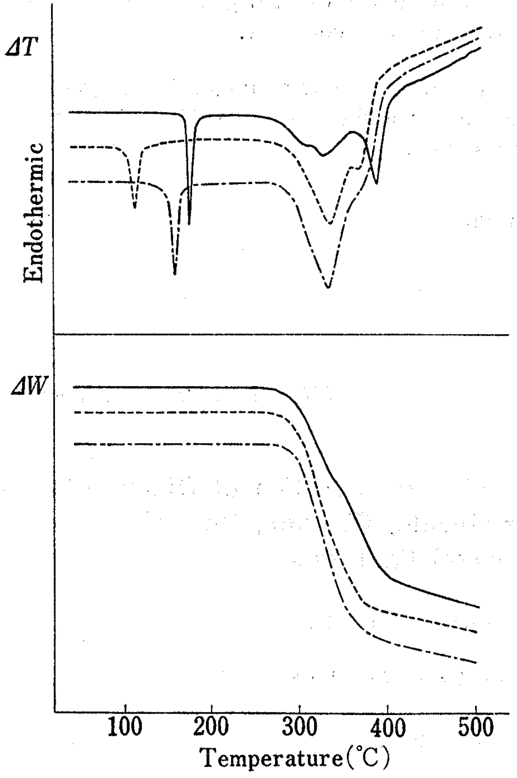


Fig. 1. DTA and TGA Curves of 2-ATH+, 2-Methyl- and 3-Methyl-2-ATH+

ΔT : temperature difference between the sample and the reference
ΔW : weight loss of the sample
——— : 2-ATH+
– – – – : 2-methyl-2-ATH+
—·—·— : 3-methyl-2-ATH+

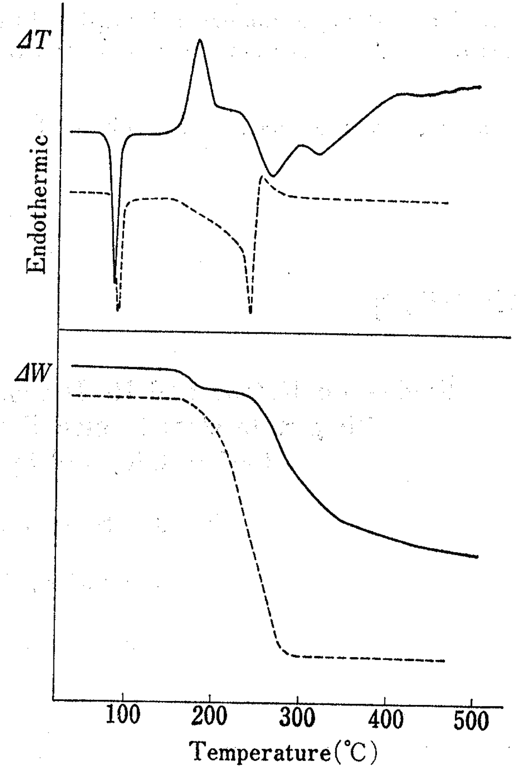
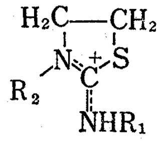


Fig. 2. DTA and TGA Curves of 2-AT and 2-Methyl-2-AT

——— : 2-AT
– – – – : 2-methyl-2-AT

The DTA curves of 2-AT and 2-methyl-2-AT gave different patterns as shown in Fig. 2. 2-AT showed typically an exothermic peak at 180°. 2-AT skelton would be partly decomposed and approximately 9% of the total weight was lossed. The second chemical change which was indicated by two endothermic peaks appeared at 264 and 320° was begun from 230°. The amounts of weight loss from 230 to 350° was less than 50%. On the other hand, 2-methyl-2-AT was decomposed almost completely below 250° and the weight loss was more than 96%. 3-Methyl-2-AT, liquid at room temperature, did not give a clear DTA curve. Those findings indicate that 3-N-methylation, which affects markedly the acidity and NMR spectra of 2-ATH+, is not able to alter the thermal stability of the compound.



R_1	R_2	
H	H	: 2-ATH+
CH_3	H	: 2-methyl-2-ATH+
H	CH_3	: 3-methyl-2-ATH+

Experimental

Thermal Analysis——The thermal analysis was performed with a Shimadzu DT-2B thermal analyzer equipped with a Pt/Pt-10% Rh thermocouple. Both DTA and TGA curves were recorded simultaneously on a same chart. The sample was prepared by using a layer-packing method in a platinum cell (6 mm diameter). The compound weighed, 73—76 mg, was packed loosely over reference material, approximately 900 mg. As a reference material fused silica was used. The reference cell was packed with fused silica. The measurement was done in a static air atmosphere and heating rate was 5°/min.

Proton Ionization Constant——The pK_a value was calculated from the potentiometric titration curve.

The titration was done at 15° using a Radiometer TTTlc titrator and SBR2 titrigraph. The detailed procedure was reported previously.[3] The pKa calculated was practical constant.

Acknowledgement The thermal analysis was carried out at the Instrumental Analysis Center of Application Laboratory, Shimadzu Seisakusho, Ltd. The author wishes to thank Mrs. M. Tsuyama and T. Hattori of the Analysis Center for doing the thermal analysis.

---

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

[Chem. Pharm. Bull. 20(7)1574—1578(1972)]

UDC 547.445.04 : 547.484' 262.04

Studies on Ketene and Its Derivatives. XLIX.[1] Reaction of Diketene with β-Ketoesters to give Ethyl Orsellinate, Divarate, Olivetol Carboxylate, and Sphaeropherol Carboxylate

TETSUZO KATO and TOYOHARU HOZUMI

Pharmaceutical Institute, Tohoku University[2]

(Received December 18, 1971)

Diketene reacts easily with an active hydrogen which is attached to a hetero atom such as oxygen or nitrogen to give O-acetoacetyl or N-acetoacetyl derivatives. However, only a few references are available concerning the reaction of diketene with an active hydrogen attached to a carbon atom to give C-acetoacetyl derivative. Hamamoto[3] reported the reaction of diketene with acetylacetone in the presence of an acidic catalyst to give 3-acetyl-2,6-dimethyl-4-pyrone. This reaction suggests that diketene reacts with the active methylene of acetylacetone to give 3-acetyl-pentan-2,4-dione as an intermediate, which cyclizes to the pyrone derivative. In the previous paper of this series[4] we have reported the reaction of 2-(2-pyridyl)-acetonitrile with diketene to give 2-(2-pyridyl)-2-acetoacetylacetonitrile in good yield.

The objectives of the present paper are twofold—to investigate the activity of diketene toward the active methylene of β-ketoester and establish the simple method of preparation of some metabolites of lichen such as orsellinic acid derivatives.

When ethyl acetoacetate (Ia) was allowed to react with diketene in the presence of sodium hydride in tetrahydrofuran, colorless crystals of mp 131—132°, $C_{10}H_{12}O_4$ (IIa), and a colorless oil of bp 130—131° (4 mmHg), $C_{10}H_{12}O_4$ (IIIa), were obtained in 38% and 7% yield, respectively. Both IIa and IIIa are already known, and characterized as ethyl orsellinate and ethyl 2,6-dimethyl-4-pyrone-3-carboxylate,[5] respectively.

Reaction of IIIa with ammonia afforded ethyl 2,6-dimethyl-4-pyridinol-3-carboxylate (IVa) and ethyl 4-amino-2,6-dimethylpyridine-3-carboxylate (Va). Treatment of Va with nitrous acid gave IVa.

When the reaction was carried out in the presence of triethylamine in place of sodium hydride, both yields of IIa and IIIa decreased. The use of water as a solvent instead of organic solvent such as tetrahydrofuran decreased the yield of IIa but increased that of IIIa.

---

[1] XLVIII: T. Kato, N. Katagiri, and N. Minami, *Chem. Pharm. Bull.* (Tokyo), **29**, 1368 (1972).

[2] Location: *Aobayama, Sendai, 980, Japan.*

[3] K. Hamamoto, T. Isoshima, and M. Yoshioka, *Nippon Kagaku Zasshi*, **79**, 840 (1958).

[4] T. Kato and T. Atsumi, *Yakugaku Zasshi*, **87**, 961 (1967).

[5] S. Gelin and R. Gelin, *Bull. Soc. Chim. France*, **1969**, 231.