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Solvent Catalytic Degradation of Sulfamic Acid and Its N-Substituted Derivatives

KINZO NAGASAWA and HISAE YOSHIDOME

Faculty of Pharmaceutical Sciences, Kitasato University[1]

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In a solution containing the polar solvent such as pyridine, quinoline, dioxane, dimethylformamide, and dimethylsulfoxide, sulfamic acid and its N-substituted derivatives were converted to an equimolar amount of inorganic sulfate and corresponding amine. The factors and the reaction mechanisms concerning this degradation process were discussed on the basis of the experimental results, and the following scheme of the reaction was proposed:

$$\mathrm{RR'N{-}SO_3H} \rightleftarrows \mathrm{RR'\overset{+}{N}H{-}\overset{-}{S}O_3} \xrightleftharpoons[]{\text{solvent}} \mathrm{RR'NH}$$

$$+\ \text{solvent–}\mathrm{SO_3}\ \text{adduct} \xrightleftharpoons[]{\mathrm{H_2O}} \mathrm{RR'\overset{+}{N}H_2} + \mathrm{H\overset{-}{S}O_4} + \text{solvent}$$

It was also proved that this reaction and the determination procedures is possible to apply as the general analytical method for sulfamic acid derivatives.

It has been shown that sulfamic acid and its N-substituted derivatives are reactive to the compounds with HO group such as alcohols and phenols to produce O-sulfated products,[2–5] and that the presence of pyridine accelerates this sulfation reaction.[2,4–6]

In the course of investigation of this sulfation reaction, it has been found that sulfamic acid and its N-substituted derivatives were decomposed catalytically by pyridine. In a pyridine solution which contains a small amount of water, sulfamic acid and its N-substituted derivatives were converted to an equimolar mixtures of inorganic sulfate and corresponding amine. A similar catalytic activity was shown by several aromatic heterocyclic compounds such as picoline, quinoline, and also by various kind of polar solvents such as dioxane, dimethyl formamide, dimethyl sulfoxide, *etc.*

Sulfamic acid and its N-substituted derivatives are in general stable against the hydrolysis by acid and alkaline reagent, with an exception of N-phenyl substituted derivatives which are susceptible to acids.[7] Cyclohexylsulfamic acid, a sweetening food–additive, is degraded by nitrous acid to inorganic sulfate and some diazotized degradation fragments.[9–12] Another hydrolytic procedure using hydrogen peroxide as a catalyst was reported.[8] However, any method generally applicable to the analysis of sulfamic acid compounds has not yet been reported.

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[1] Location: *Sankocho, Shiba-Shirokane, Minato-ku, Tokyo.*
[2] K. Nakano and H. Yamaguchi, *Kogyo Kagaku Zasshi*, **67**, 2055 (1964).
[3] K. Yamaguchi, *Nippon Kagaku Zasshi*, **80**, 171, 204 (1959).
[4] K. Nagasawa, J. Patent 464379 (1966).
[5] K. Nagasawa, A. Ūki and K. Yamazaki, the 18th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1963; K. Nagasawa, Y. Tohira and H. Yoshidome, the 24 th Annual Meeting of Pharmaceutical Society of Japan, Kyoto, April 1967.
[6] K. Yamaguchi, *Nippon Kagaku Zasshi*, **84**, 155 (1963).
[7] L.F. Audrieth and M. Sveda, *J. Org. Chem.*, **9**, 93 (1944).
[8] H. Ichibagase and S. Kojima, *Yakugaku Zasshi*, **82**, 1616 (1962).
[9] J.B. Wilson, *J. Assoc. Offic. Org. Chemists*, **40**, 1 (1951).
[10] D.I. Rees, *Analyst*, **90**, 568 (1965).
[11] M.L. Richardson and P.E. Luton, *Analyst*, **91**, 520 (1966).
[12] A.J. Shenton and R.M. Johnson, *Chem. Ind.* (London), **1967**, 364.

This work was undertaken to investigate the various factors concerning the degradation reaction and the applicability of this reaction to the quantitative analyses of sulfamic acid derivatives.

The degradation processes of cyclohexylsulfamic acid in the pyridine solution containing 1% and 25% water, respectively, are shown in Fig. 1. The amounts of liberated cyclohexylamine was converted to its dinitrophenylated derivative and measured colorimetrically.

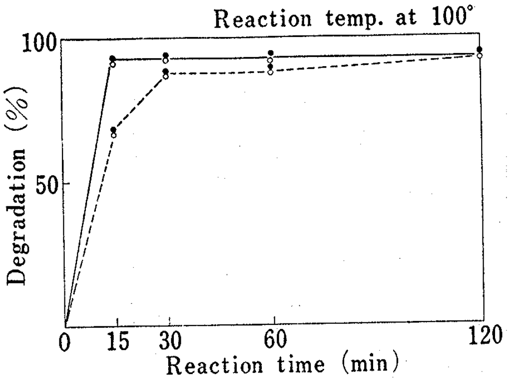

Fig. 1. Liberation of Inorganic Sulfate and Cyclohexylamine during the Pyridine-catalyzed Degradation of Cyclohexylsulfamic Acid

●: inorganic sulfate ○: cyclohexylamine
——: pyridine containing 1% H_2O
------: pyridine containing 25% H_2O

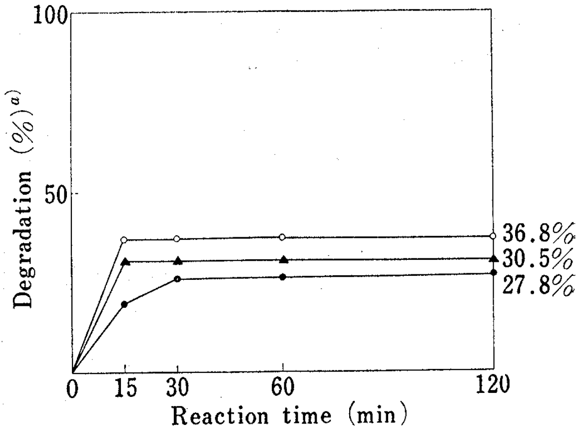

Fig. 2. Degradation of Cyclohexylsulfamic Acid in Anhydrous Pyridine at Various Temperature

○: reaction temp. at 100°
▲: reaction temp. at 60°
●: reaction temp. at 19—20°
a) Degradation was determined by measuring inorganic sulfate.

The inorganic sulfate was measured turbidmetrically as barium sulfate. It was confirmed that both degradation products were equimolar until 94% of cyclohexylsulfamic acid was decomposed. The degree of the degradation of cyclohexylsulfamic acid in anhydrous pyridine at various temperatures is shown in Fig. 2. In consideration of the experimental result on the degradation of piperidine N-sulfonic acid (described in later), this suggests that the reaction in this condition is reversible and that equilibrium is established at 27.8%, 30.5% and 36.8% degradation at the temperature of 19—20°, 60° and 100° respectively. Piperidine N-sulfonic acid was degraded in anhydrous pyridine at 60° and the result is shown in

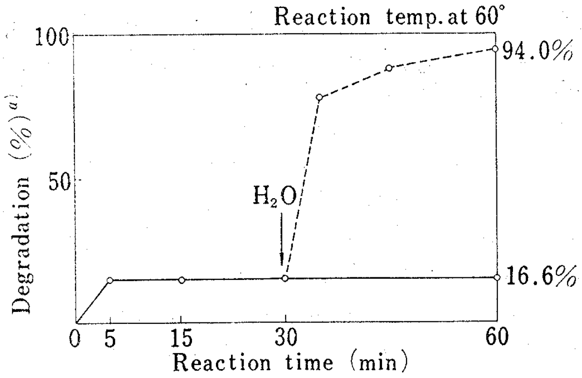

Fig. 3. Influence of Water in the Degradation Process of Piperidine N-Sulfonic Acid

------: pyridine containing 1% H_2O
——: anhydrous pyridine
a) Degradation was determined by measuring inorganic sulfate.

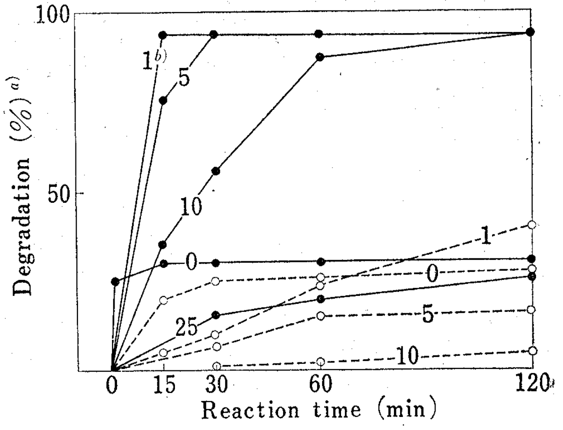

Fig. 4. Degradation of Cyclohexylsulfamic Acid in Water-containing Pyridine

—●—: reaction temp. at 60°
---○---: reaction temp. at 19—20°
a) Degradation was determined by measuring inorganic sulfate.
b) Figure means % of water in pyridine medium.

Fig. 3. As shown in the figure, the addition of water (1 v/v%) after the reaction reached to its equilibrium point (16.6% degradation) resulted in the advancement of the reaction up to 94% degradation. These results indicate that this reaction is consisted of two kinds of the reaction which is concerned with pyridine and water, respectively.

The effect of water content in the reaction medium on the degradation of cyclohexylsulfamic acid was examined at 20° and 60° (Fig. 4). Similar experimental results for other sulfamic acid derivatives are shown in Fig. 5. These results suggest that the presence of water is necessary for the completion of the reaction, and that the smaller the amount of water, the more the reaction is favored.

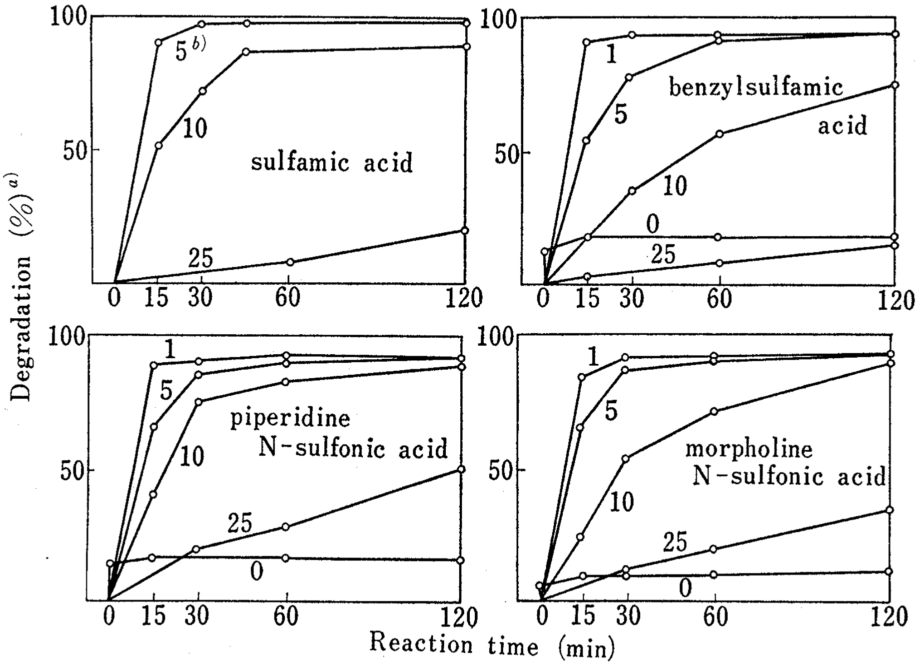

Fig. 5. Pyridine Catalyzed Degradation of Sulfamic Acid and N-Substituted Derivatives

reaction temperature: 60°

a) Degradation was determined by measuring inorganic sulfate.

b) Figures on lines mean % of water in pyridine medium.

From the evidence of X-ray[13] and infrared[14] studies for the structure of free sulfamic acid, a dipolar structure, $NH_3^+SO_3^-$, in solid sulfamic acid were certified. The species in solution is less certain, but from dielectric constant measurement in certain organic solvents,[15] the dipolar ion is believed to be present also. Consequently, the presence of a dipolar structure, $C_6H_{11}NH_2^+ SO_3^-$, in cyclohexylsulfamic acid which is one of N-substituted derivatives of sulfamic acid is probable. For the investigation of the reaction mechanism, it seems to be important to compare the susceptibility of cyclohexylsulfamic acid with those of metal salts of the sulfamic acid derivative which are firmly constituted from an acid anion C_6H_{11}-$NHSO_3^-$ and metal ions, to this reaction. Cycohexylsulfamic acid and its various types of salts were reacted at 100° in a medium of pyridine containing 25% of water.[16] The results shown in Fig. 6 indicate that the metal salts are more resistant against the degradation reaction than the free acid or its ammonium salts. From a consideration of this results, it seems reason-

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[13] Kanda and King, *J. Am. Chem. Soc.*, **73**, 2315 (1951); Osaki, Tadokoro and Nitta, *Bull. Chem. Soc. Japan*, **28**, 524 (1955).

[14] E.g., Siebert, *Z. Anorg. Chem.*, **292**, 167 (1957).

[15] Hovermale and Sears, *J. Phys. Chem.*, **60**, 1579 (1956).

[16] This reaction condition was selected in order to obtain the homogeneous solution of various types of salt of cyclohexylsulfamic acid in the solution.

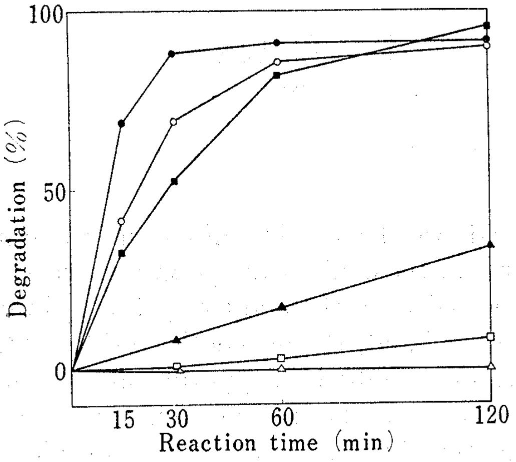

Fig. 6. Pyridine-catalyzed Degradation of Several Kinds of Cyclohexylsulfamic Aicd Salts

The degradation reaction was performed in the pyridine medium containing 25% of water at 100°, and determined by measuring inorganic sulfate.

●: free cyclohexylsulfamic acid
○: NH_4 salt ■: $(C_2H_5)_3NH$ salt
▲: Ca salt □: Na salt △: K salt

able to presume that the dipolar structure of cyclohexylsulfamic acid participates in the early process prior to the fission of N–S linkage.

It was also proved that this type of degradation occurs by α-picoline,[19,20] quinoline,[17,18] dimethyl formamide,[17,21] dimethyl sulfoxide[23] and dioxane,[17,22] all of which have been known to form an adduct with sulfur trioxide. As shown in Fig. 7 and 8, both α-picoline and quinoline are effective same degree as pyridine, and dimethyl formamide, dimethyl sulfoxide and dioxane are also effective but by lower degree. These observations suggest that the above mentioned solvents exert a similar effect as pyridine on the molecule of a sulfamic acid derivatives and "solvent-SO_3 adduct" is probably playing a role as the intermediate in the degradation process. In order to confirm the above supposition an authentic sample of pyridine-SO_3 (1:1) adduct was prepared from pyridine and $ClSO_3H$ according to Baumgarten[24] and the product was subjected to the reaction figured in Chart 1. The analytical data of the sample were as follows: Calculated value for $C_5H_5N \cdot SO_3$: S, 20.15%. Found: S, 19.28%.

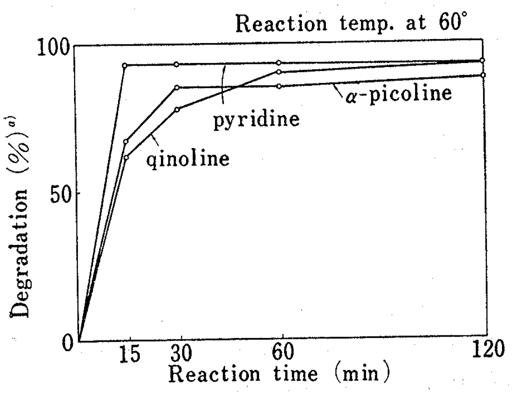

Fig. 7. Degradation of Cyclohexylsulfamic Acid in Various Polar Solvents$^{b)}$

a) Degradation was determined by measuring inorganic sulfate.
b) Each solvent contains 1% of H_2O.

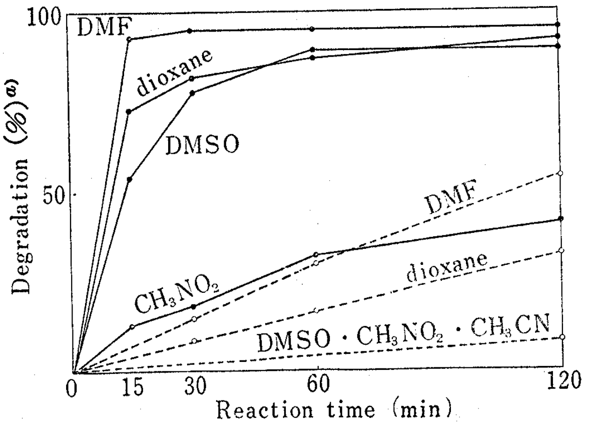

Fig. 8. Degradation of Cyclohexylsulfamic Acid in Various Polar Solvents$^{b)}$

—●—: reaction temp. at 100°
---○---: reaction temp. at 60°
a) Degradation was determined by measuring inorganic sulfate.
b) Each solvent contains 1% of H_2O.

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17) G.A. Ratchiff and Ph. D. Dissertaion, *Cornell University Diss. Abstracts*, **14**, 2018 (1954).
18) J.E.G. Harris and J. Thomas, British Patent 317736; *Chem. Abstr.*, **33**, 3495 (1935).
19) J. Taras, U.S. Patent 2507944; *Chem. Abstr.*, **45**, 873 (1951).
20) R.F.M. Sureau and P.M.J. Obellianne, U.S. Patent 2789132; *Chem. Abstr.*, **51**, 15571 (1957).
21) S. Coffey, G.W. Driver, D.A.W. Fairweather and F. Irving, British Patent 642206; *Chem. Abstr.*, **45**, 3412 (1951).
22) E.E. Gilbert, B. Veldhuis, E.J. Carlson and S.L. Giolito, *Ind. Eng. Chem.*, **45**, 2065 (1953).
23) P.L. Whistler, A.H. King, G. Ruffini and F.A. Lucas, *Arch. Biochem. Biophys.*, **121**, 358 (1967).
24) P. Baumgarten, *Ber.*, **59 B**, 1166 (1926).

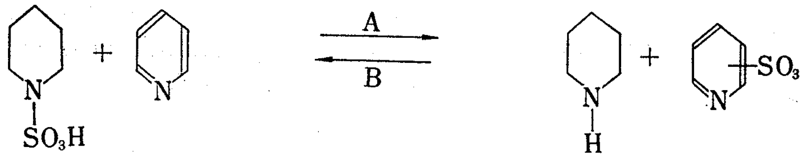

Chart 1

mp 163—168° (mp 175°).[24] Piperidine N-sulfonic acid was heated in anhydrous pyridine at 100° for 4 hr and the formation of pyridine–SO_3 adduct at the equilibrium point was measured indirectly from the amount of inorganic sulfate liberated from the adduct by the addition of an excess amount of water (reaction A). On the other hand, the authentic pyridine–SO_3 adduct was reacted with an equimolar amount of piperidine in anhydrous pyridine at the same condition above and measured the decomposed amount of the adduct at the equilibrium point (reaction B). In the above experiments, it was found that by reaction A 16.8% of adduct was while by reaction B 22.9% of adduct was measured unchanged. In consideration of the purity of the pyridine–SO_3 adduct used,[25] it is not unresonable to understand that these figures are approximately equal.

From the experimental evidences thus obtained, the following scheme of the degradation is presented. As shown in Chart 2, this reaction is consisted of two reactions, one is the reaction (C)—(D) concerned with pyridine, and the other is the reaction (E) concerned with water as a reactant. According to the polar effect of pyridine, a sulfamic acid derivative (I) is converted to a dipolar type (II), followed by a cleavage of the N–S linkage, which results in the formation of constitutional amine (III) and pyridine–SO_3 adduct (IV).

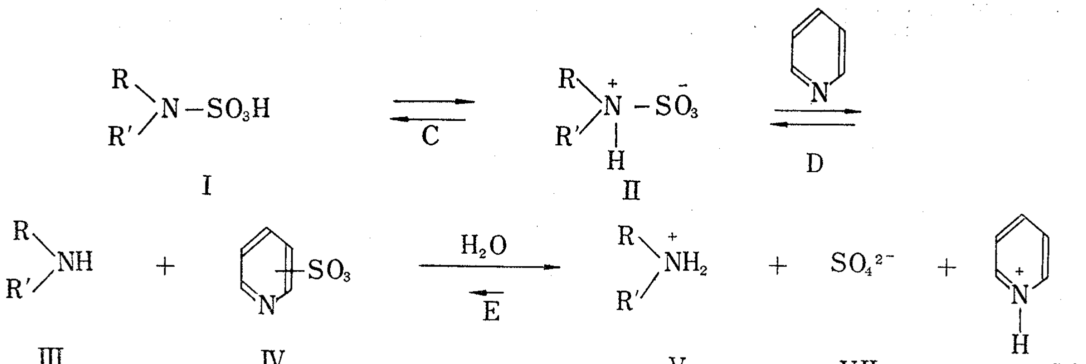

Chart 2

The reaction (D) is stopped by the addition of an excess of water, and a mixture of unreacted sulfamic acid derivative and the decomposition products consisted of equimolar amount of amine (III) and inorganic sulfate (VII) is formed. The above mentioned inorganic sulfate is probably originated from the hydrolysis of "pyridine–SO_3 adduct" (IV).

Subsequently the applicability of the above described degradation reaction to the quantitative analysis of sulfamic acid compound was investigated. The analytical method of cyclohexylsulfamic acid so far widely used is based on a diazotized degradation of it with nitrous acid, however, this method is not applicable to N-disubstituted derivatives such as piperidine N-sulfonic acid (see experimental part). As described above, all types of sulfamic acid derivatives tested were degraded successfully by heating in aqueous pyridine to form their constituents proportionally to the amount of mother compound at a given condition. As is confirmed by the experimental results shown in Fig. 9, this degradation reaction and the

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[25] The contaminants in the authentic preparation of pyridine–SO_3 adduct are presumed to be pyridine sulfate and its hydrogen chloride, which are very difficult to remove.[26]

[26] E.E. Gilbert, *Chem. Rev.*, 62, 552 (1962).

determination procedure is possible to apply as the general analytical method for sulfamic acid derivatives.

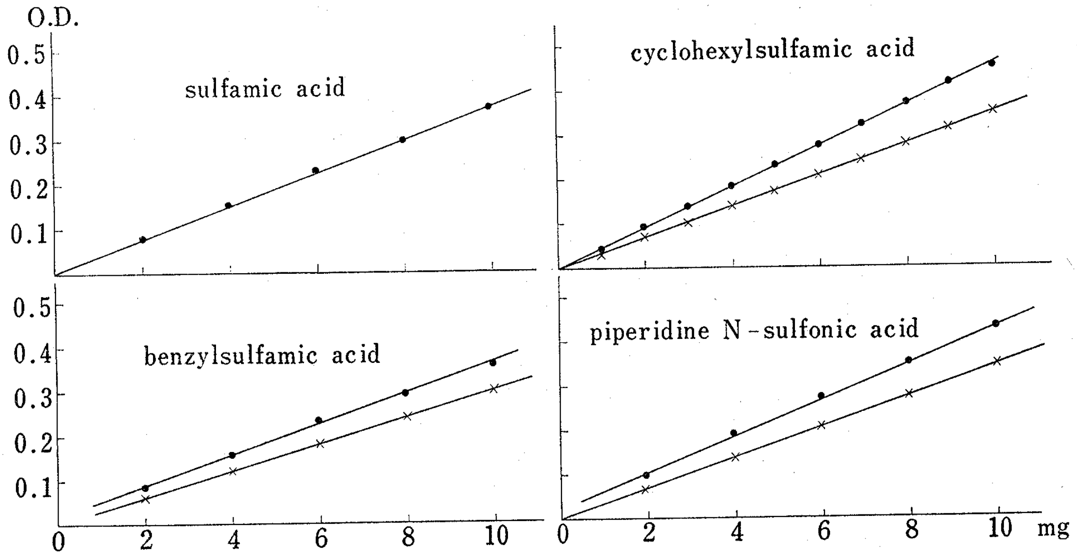

Fig. 9. Calibration Curves of Sulfamic Acid and Several N-Substituted Sulfamic Acids

● : inorganic sulfate × : dinitrophenylated amines

Experimental

Reagents and Solvents——The reagents and solvents which are all special reagent grade were used without further purification except for pyridine. Pyridine was distilled from BaO and the fractions of bp 115.5—116° were used. N-Substituted sulfamic acids were synthesized as described in this experimental part.

Cyclohexylsulfamic Acid——Sodium cyclamate commercially available was treated with Dowex 50 (H^+) to make it free acid form, and the solution of free cyclamate was concentrated into dryness *in vacuo*, which was recrystallized from water. The crystals were dried over P_2O_5 *in vacuo* at 90° and the yield was alomst quantitative, mp 169—170° (lit.27), mp 167—168°).

Piperidine N-Sulfonic Acid——A mixture of 18.8 g of piperidine and 150 ml of $CHCl_3$ was cooled at –5—0°, and it was added to 50 ml of $CHCl_3$ solution containing 8.6 g of $ClSO_3H$. The reaction temperature of the mixture was controlled not to exceed 0° and the mixture was stirred for 1 hr. After the distillation of $CHCl_3$ from the mixture, the residue was dissolved in 120 ml of 10% Na_2CO_3, extracted with ethyl ether for several times to remove piperidine. The water layer was separated and adjusted to pH 4 with Dowex 50 (H^+), then added with 10% barium acetate solution to remove inorganic sulfate. After the removal of precipitates, the clear solution was passed through a column of Dowex 50 (H^+) to obtain the solution of free piperidine N-sulfonic acid. The solution was evaporated to dryness and the residue was dried on NaOH pellets *in vacuo* overnight, and recrystallized from hot water to afford long needles of mp 190—191.5° (decomp.) (lit.27), mp 193°). The yield was 7.6 g (62%). *Anal.* Calcd. for $C_5H_{11}O_3NS$ (piperidine N-sulfonic acid): C, 36.35; H, 6.72; N, 8.48; S, 19.36. Found: C, 36.32; H, 6.66; N, 8.26; S, 19.96.

Morpholine N-Sulfonic Acid——A mixture of 26.1 g of morpholine and 150 ml of $CHCl_3$ was cooled at –5° and added with the $CHCl_3$ solution (50 ml) containing 11.6 g of $ClSO_3H$. The mixture was cooled not to exceed 0° and reacted for 1 hr while being stirred. From the reaction mixture, $CHCl_3$ was evaporated and the residue was dissolved in 160 ml of 10% Na_2CO_3. The alkaline solution was concentrated to dryness *in vacuo* and the resultant material was redissolved in water and acidified with the addition of Dowex 50 (H^+) at pH 4. After the evolution of CO_2, 10% solution of barium acetate was added to the acidic solution until no precipitation occurred. The precipitates were removed, and the supernatant was decationized with the passage of a column of Dowex 50 (H^+). The acidic solution was evaporated into dryness below 40° and desiccated over pellets of NaOH *in vacuo* overnight. The dried powder obtained was dissolved in 40 ml of water and the pH of the solution was adjusted to 6.5 with the addtion of NaOH solution. The neutral solution, which amounted to *ca.* 50 ml, were added with 400 ml of EtOH and stored in a refrigerator overnight. The needles of sodium salt of morpholine N-sulfonic acid were separated from the solution and the yield was 10.4 g. The addition of 200 ml of ethyl ether to the mother liquor resulted in the separation of additional 3.1 g of the crystals. The total yield was 71.5%.

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27) H. Yamaguchi, *Nippon Kagaku Zasshi*, **82**, 483 (1961).

The free morpholine N-sulfonic acid was prepared from the Na salt above described as follows. The aqueous solution containing 3.8 g of the Na salt was passed through a column of Dowex 50 (H^+) and the acidic effluent was freeze-dried to form 3.1 g of white powder, which showed mp 188.5° (decomp.) (lit.[27] mp 190.5°). *Anal.* Calcd. for $C_4H_9O_4NS$ (morpholine N-sulfonic acid): N, 8.39; S, 19.15. Found: N, 8.34; S, 19.65.

Benzylsulfamic Acid——A mixture of benzylamine (67.5 g) and $CHCl_3$ (400 ml) was cooled at −5° and 14 ml of $ClSO_3H$ were added gradually to the mixture while being stirred. The mixture was reacted at 0° for 30 min and filtrated to separate crystalline product which was washed with $CHCl_3$ and air-dried. The above product was recrystallized from water to form 47.7 g of benzylammonium benzylsulfamic acid which had mp 177—181°. The yield was 76.2%.

The free acid was prepared from the benzylammonium salt by the passage through a column of Dowex 50 (H^+). From 17 g of the salt, 10.5 g of crystalline free acid having mp 190—191° (decomp.) (lit.[27], mp 190—190.5°) were obtained. *Anal.* Calcd. for $C_7H_9O_3NS$ (benzylsulfamic acid): C, 44.91; H, 4.85; N, 7.48; S, 17.13. Found: C, 45.03; H, 5.21; N, 7.26; S, 17.01.

Degradation of Sulfamic Acid Compounds——Into a graduated flask of 1 ml-capacity, 0.1 mmole of a sulfamic acid compound is weighed, and the anhydrous or the water containing pyridine is added accurately to the flask up to 1 ml volume. From the flask, each 0.2 ml of the test solution is delivered into a test tube (diameter 1.5 cm, height 15 cm), respectively, and the stoppered test tube is heated on a water bath at a fixed temperature. At intervals, the test tube is removed and the contents are diluted with the addition of distilled water to an appropriate concentration. The amount of inorganic sulfate is estimated by the procedure described in the item of quantitative analysis. In the case of other solvents than pyridine and their water containing systems, the procedure above described is also used.

Quantitative Estimation of Inorganic Sulfate——According to Dodgson's turbidmetric procedure,[28] 3 ml of 3.8% CCl_3COOH solution, 1 ml of a test solution containing 10—50 γ/ml as S, and 1 ml of gelatin–$BaCl_2$ solution are mixed in a flask which is allowed to stand on for 20 min at room temperature. The optical density of the solution is measured at 500 mμ. The same procedure is performed on the standard solution of K_2SO_4 and the quantity of inorganic sulfate in the test solution is determined.

Gelatin–$BaCl_2$ Solution: Two grams of gelatin are dissolved in 400 ml of hot distilled water and the solution is allowed to stand overnight at 4°. To the solution, 2 g of powderized $BaCl_2$ are added and the resultant solution is used after the storage at 4° for 2 hr.

K_2SO_4 Standard Solution: To 1000 ml of distilled water, 271.74 mg of K_2SO_4 (dried at 80° for 3 hr *in vacuo*) are added. S content of the standard solution corresponds to 50 γ/ml.

Quantitative Estimation of Amines——Sangar's procedure for the micro-determination of amines was used.[29] To a test tube (diameter 2 cm, height 20 cm), 0.1 ml of the same test solution are introduced and the test tube is immersed in a boiling water bath for 30 min in order to evaporate pyridine in the tube. After the addition of 0.05 ml of 2,4-dinitrofluorobenzene solution and 0.1 ml of 0.1 M Na_2CO_3, the test tube is warmed at 60° for 20 min, then added with 0.4 ml of 0.2 N NaOH·dioxane solution. After warming at 60° for additional 1 hr, the mixture is diluted with distilled water to a volume of 10 ml and extracted with 10 ml of cyclohexane. After the separation of the cyclohexane layer, its optical density is measured at each specific maximum absorption range of DNP-amines.

The values of the wave-length at maximum absorption of various DNP-amines are as follows:

DNP-cyclohexylamine	340 mμ
DNP-benzylamine	330 mμ
DNP-piperidine	355 mμ

2,4-Dinitrofluorobenzene solution is prepared from 0.1 ml of 2,4-dinitrofluorobenzene and 10 ml of absolute ethanol. 0.2 N NaOH–dioxane solution is prepared from 2 g of NaOH and 250 ml of 60% aqueous dioxane.

Preparation of Calibration Curves——In the range of 1—10 mg, several samples of N-substituted sulfamic acid are weighed precisely in a graduated test tube and added with 1 ml of the pyridine containing 10% of water. In the case of sulfamic acid (H_2NSO_3H), the amounts of 1—5 mg are weighed and added with 2 ml of the water-containing pyridine. Each test tube is heated on a boiling water bath for 30 min and after cooling, the contents of the test tube are diluted with distilled water to a volume of 25 ml. The test solutions thus obtained are examined in both inorganic sulfate and DNP-amines, except for those obtained from sulfamic acid (H_2NSO_3H), which are estimated to inorganic sulfate only.

Degradation of Sulfamic Acid Compounds with Nitrite——Ten to twenty mg of a sulfamic acid compound or its sodium salt are weighed precisely in a flask and dissolved in 20 ml of distilled water. To the solution, five drops of 10% HCl and 1 ml of 10% $NaNO_2$ are added, and the mixture is reacted at room temperature for 30 min. The reaction mixture is diluted with distilled water to a volume of 100 ml and the amount of inorganic sulfate is determined according to the described method.

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28) K.S. Dodgson, *Biochem. J.*, **78**, 312 (1961).

29) F. Sanger, *Biochem. J.*, **39**, 507 (1945).

By means of this procedure, the amounts of inorganic sulfate formed from various N-disubstituted sulfamic acid compounds were determined as follows.

Sample	Degradation %
Piperidine N-sulfonic acid	66.6
Morpholine N-sulfonic acid	32.4
Di-*n*-butyl sulfamic acid	33.5
Cyclohexyl sulfamic acid	93.2

Degradation (Reaction A) in Piperidine N-Sulfonic Acid–Pyridine System and N-Sulfation Reaction (Reaction B) of Piperidine with Pyridine-SO_3 Adduct——1) Two mmoles of piperidine N-sulfonic acid are weighed precisely in the flask which is equipped with a Liebig's condenser and $CaCl_2$–tube. To the flask, 20 ml of anhydrous pyridine are added and the solution is heated at 100° for 4 hr. After cooling, the reaction mixture is diluted with distilled water to a volume of 100 ml and an aliquot is removed from the solution for the determination of inorganic sulfate formed. The amount of inorganic sulfate shows indirectly the amount of pyridine–SO_3 adduct formed in reaction A.

2) Each 2 mmoles of synthesized pyridine–SO_3 adduct and piperidine are weighed presicely in a flask, and added with 20 ml of anhydrous pyridine. The solution in the flask is reacted under the same conditions as described in (1), and analyzed for inorganic sulfate. The amount of the inorganic sulfate shows the residual amount of pyridine–SO_3 adduct in reaction B.