

Isoxazoles I: Protonation of Isoxazole Derivatives in Aqueous Sulfuric Acid

RUBEN H. MANZO* and M. MARTINEZ de BERTORELLO[▲]

Abstract □ The protonation of 3-amino-5-methylisoxazole, 5-amino-3,4-dimethylisoxazole, sulfamethoxazole (*N*-sulfanilamido-5-methyl-3-isoxazole), and sulfisoxazole (*N'*-sulfanilamido-3,4-dimethyl-5-isoxazole) in aqueous sulfuric acid was studied. The pK_{SH^+} and $\log SH^+/S$ or $\log SH_2^{+2}/SH^+$ values were determined by UV spectrophotometry. The data were treated by the acidity function method and by the method of linear free energy relationships. The comparison of the correlations obtained and the basicity and the UV spectra of the four compounds indicate that the process of protonation is the same in the amino and sulfonamide derivatives.

Keyphrases □ Isoxazole derivatives—protonation in sulfuric acid, ionization ratios, $\log I$ correlated with Hammett's *H*_o function, UV spectrophotometry □ Sulfisoxazole—protonation in sulfuric acid, ionization ratios, $\log I$ correlated with Hammett's *H*_o function, UV spectrophotometry □ Sulfamethoxazole—protonation in sulfuric acid, ionization ratios, $\log I$ correlated with Hammett's *H*_o function, UV spectrophotometry

It is well known that the derivatives of 3- and 5-aminoisoxazoles are found in their protonated form in mineral acid solutions. After the pK_a values for these compounds were determined, the protonation site of the heterocycle was found to be the nitrogen atom, according to UV spectroscopic studies (1).

Similar studies on the sulfonamide derivatives have not been done, nor are there any data about the behavior of the ionization ratio I (SH^+/S or SH_2^{+2}/SH^+) in various conditions of acidity in the medium for the four compounds studied.

This paper reports studies of the basicity and behavior of the ionization ratio I of these derivatives in connection with the study of the isoxazole ring cleavage in mineral acid solutions (2).

The fact that amino- and sulfonamidoisoxazoles are cleaved at the oxygen-nitrogen bond in hydrolytic reactions catalyzed by acids (3) and the importance in this type of reaction in determining the equilibrium existing between the basic substrate and the hydrogen ions of the medium led to a comparative investigation of the protonation equilibrium for these substrates. The equilibria considered were $S + H^+ \rightleftharpoons SH^+$ for the amino derivatives and $SH^+ + H^+ \rightleftharpoons SH_2^{+2}$ for the sulfonamido derivatives.

The determinations of the ionization ratio I were done using UV spectrophotometry by the indicator method (4), utilizing the difference in the spectra of the basic forms and their respective protonated forms. The data were evaluated by the Davis and Geissman (5) method for 5-amino-3,4-dimethylisoxazole (II) and the Alder *et al.* (6) method for the remaining compounds. The acidity function method (7) was used to correlate the data of $\log I$ with Hammett's *H*_o function (plots of $\log I$ against $-H_o$). Correlations by the linear free energy method (8) were carried out for the sulfonamide deriva-

tive {plots of $-(\log I + H_o)$ or $-(\log I - \log [H^+])$ against $-(\log [H^+] + H_o)$ }.

EXPERIMENTAL¹

Materials and Apparatus—Sulfisoxazole² (IV) was a commercial USP product recrystallized from ethanol, m.p. 193–194°. Sulfamethoxazole³ (III) was a commercial NF product recrystallized from ethanol-water (1:1), m.p. 165.5–166.5°. 5-Amino-3,4-dimethylisoxazole (II) was prepared according to the method described (9) for other sulfonamides. Ten grams of sulfisoxazole was dissolved in 200 ml. glacial acetic acid and 25 ml. of acetic anhydride. The solution was boiled for 5 min., cooled, and diluted with 500 ml. of distilled water. A precipitate was formed, which was separated, dried, and subsequently solubilized in 25 ml. of 40% (w/v) sulfuric acid and boiled for 3 min.; the solution was then cooled and alkalized with a sufficient amount of 10% sodium hydroxide solution. This solution was extracted three times with 40 ml. of ether; the ethereal extracts, once combined and evaporated, yielded 3.2 g. of II, which was recrystallized first from benzene and then from water, m.p. 123.5–124.5°.

3-Amino-5-methylisoxazole (I) was prepared in the same way and purified by successive vacuum sublimations up to a constant melting point of 60–61°.

Preparation of Solutions—The solutions of the purified compounds were prepared in distilled water (I and II) and in 1 *N* sulfuric acid (III and IV). The concentrations were designed so that when 1.0 ml. of the solution was added to a 50-ml. volumetric flask filled to the mark with sulfuric acid of known concentration, the final absorbance would be 0.2–0.8.

The blank solutions were prepared in the same way as the sample solutions; but 1 ml. of water was added instead of I or II, and 1 ml. of 1 *N* sulfuric acid was added instead of III or IV.

Complete absorption spectra of III and IV were recorded over 205–300 nm. Table I shows acidity conditions and characteristics of the spectra of these compounds. In all cases a substantial change in absorption occurred when acidity conditions were modified. After diluting the 22 *N* and 24 *N* acidic solutions of III and IV with distilled water, new spectra were obtained which were similar to those corresponding to lower acidity conditions (8 *N*).

The wavelengths used for quantitative measurements were selected from comparative analysis of the spectra taken in extreme acidity conditions. For II, wavelengths corresponding to a maximum of the basic and protonated forms were selected; Table I shows the respective absorptivities. For the remaining compounds, five wavelengths were selected, taken symmetrically at the maximum band of the protonated form for I and the biprotonated form for III and IV (Table I).

Processing of Data—The Davis and Geissman (5) correction treatment for effects of the medium on II was used to assess the values of I obtained by the indicator method (4). The method⁴ of Alder *et al.* (6) was applied to the remaining compounds.

¹ Melting points were determined in a melting-point apparatus devised by Dr. Tottoli. The values given are uncorrected. Spectrophotometric readings (UV) were made in a Hilger & Watts photoelectric spectrophotometer. The complete UV absorption spectra were taken in a Cary 14 recording spectrophotometer.

² Preferred USAN chemical name is *N'*-(3,4-dimethyl-5-isoxazolyl)-sulfanilamide.

³ Preferred USAN chemical name is *N'*-(5-methyl-3-isoxazolyl)sulfanilamide.

⁴ Sulfuric acid (Carlo Erba G.R.) (96%, d 1.84) product was used.

⁵ In every case, experimental data that were correlated were adjusted by the method of least squares, giving them all the same statistical weight.

Table I—UV Spectra of Isoxazole Derivatives in Water and in Sulfuric Acid

Substrate	Water		Sulfuric Acid								λ Used ^a , nm.
	λ	ϵ	2 N		8 N		24 N		22 N		
			λ	ϵ	λ	ϵ	λ	ϵ	λ	ϵ	
I ^b	209 ^c	6820	230 ^c	8040	—	—	—	—	—	—	228.5, 231, 233.5, 236, 238.5
II ^b	244 ^c	8230	263 ^c	13,800	—	—	—	—	—	—	224, 263 ^d
	263 ^c	5230	244 ^c	3990	—	—	—	—	—	—	—
III	—	—	—	—	218 ^c	13,600	238 ^c	18,700	—	—	233, 235.5, 238, 240.5, 243
	—	—	—	—	238 ^c	5950	—	—	—	—	—
IV	—	—	—	—	220 ^c	—	—	—	220 ^c	—	—
	—	—	—	—	264 ^c	2690	—	—	264 ^c	11,400	257, 260.5, 264, 267.5, 271

^a Wavelengths used for ionization ratio I determination. ^b λ_{\max} and absorptivity were taken from Reference 1. ^c λ_{\max} . ^d Ionization ratio determined by the Davis and Geissman (5) method. ^e Absorptivity at λ_{\max} for the protonated form.

Table II—Correlations of $\log I$ versus $-Ho$ (Acidity Function) and $(\log I - \log [H^+])$ versus $-(\log [H^+] + Ho)$ (Linear Free Energy Relationship)

Substrate	Acidity Function Plots			Linear Free Energy Relationship			$pK_{BH^+}^b$
	Slope	Half-Protonated	r^a	Slope ϕ	$pK_{BH^+}^b$	r	
I	0.86	0.46	0.995	—	—	—	00.47
II	1.02	1.03	0.998	—	—	—	1.16
III	0.90	-3.81	0.997	0.12	-3.52	0.996	—
IV	1.07	-3.33	0.992	-0.08	-3.50	0.990	—

^a r is the regression coefficient. ^b The pK_{BH^+} determined by the spectrophotometric method (1).

Log I values obtained in this way were correlated with Hammett's Ho acidity function using values given by Bascome and Bell⁶ (10) for I and II and Ryabova *et al.* (11) for III and IV. Table II gives parameters obtained from all correlations made. The value of Ho corresponding to the protonation of half of the compound is given in all cases.

RESULTS AND DISCUSSION

The UV absorption spectra of the protonated forms of I, II, and III show a bathochromic shift of 20 nm. and an increase of the absorptivity with respect to the spectrum of the basic forms. With IV, the shift cannot be seen due to the existence of a strong absorption band with λ_{\max} 220 nm.; however, the appearance of a band with λ_{\max} 264 nm. in 22 N sulfuric acid can be observed, similar to that of the corresponding aminoisoxazole II.

The plot of $\log I$ against $-Ho$ for I is linear with a 0.86 slope. Consequently, the protonation process does not follow Hammett's acidity function, and the value of the intercept is not representative of the thermodynamic pK_{BH^+} (12). The Ho value corresponding to the protonation halfway through the titration as a measure of the basicity of the compound is given in Table II. Similar behavior was observed with III.

For II, $\log I$ against $-Ho$ is a linear plot with unitary slope (1.02). The compound behaves like a Hammett base, and it is approximately accurate to take $\log I$ value when Ho is extrapolated to zero as the pK_{BH^+} , because it satisfies the acidity function method postulates. Compound IV behaved in a similar manner, although the value of the slope (1.07) was somewhat above one.

Compounds III and IV both possess an aromatic primary amino group which, in the acidity conditions of these determinations, are completely in the protonated form; thus $\log I$ measurements correspond to a second protonation. Some research has been done on protonation of positively charged bases (13-17). On the whole, the behavior of this type of compound in media of considerable ionic strength does not differ appreciably from the behavior of neutral bases of a similar structure; nevertheless, the correlations made with Ho by the acidity function method are subject to the same

limitations as the correlations having unitary slope. The correlation process by the linear free energy relationship method avoids these limitations, supplying a treatment that is applicable to any type of base (8, 18).

The linear free energy relationship method was applied to III and IV; Table II lists the pK_{BH^+} values obtained. Protonation of I and II cannot be determined by this method.

The similarities existing in the changes in the UV spectra as a consequence of protonation when I is compared with III and when II is compared with IV might indicate that the nature of the protonation process is the same in amino and sulfonamido derivatives. This similarity in behavior can also be observed when comparing slopes obtained by the acidity function method between I (0.86) and III (0.90) and between II (1.02) and IV (1.07).

On the other hand, ΔHo between half-protonation of I and II is 0.57, a comparable value to ΔHo between half-protonation of III and IV (0.48); ΔHo between I and III (4.27) is comparable to ΔHo between II and IV (4.36).

If the 3-amino and 3-sulfonamido derivatives are compared to the 5-amino and 5-sulfonamido derivatives, differences between slope values are outstanding (0.86, 0.90, and 1.02, 1.07, respectively). At present, considering the small number of derivatives studied, it would be rash to conclude that structural differences between 3-sulfonamido and 5-sulfonamido derivatives are the factors conducive to different relationships between activity coefficients ($\gamma SH^+/\gamma S$ or $\gamma SH_2^+/\gamma SH^+$) for both types of derivatives.

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^a To interpolate percent w/w values of sulfuric acid used in the determinations and to obtain the respective Ho values given by Bascome and Bell, given the curvature that presents Ho functions in that zone, this function was transformed into ho ($Ho = -\log ho$); it was proven that a more linear relationship exists between percent w/w sulfuric acid and ho up to a concentration of 5-10% (w/w) than with Ho .

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▲ To whom inquiries should be directed.

Isoxazoles II: Kinetics and Mechanism of Degradation of Sulfoxazole in Moderately Concentrated Acids

RUBEN H. MANZO* and M. MARTINEZ de BERTORELLO[▲]

Abstract □ The acid degradation of sulfoxazole (*N*-sulfanilamido-3,4-dimethyl-5-isoxazole) in hydrochloric acid solutions in concentrations from 10 to 24% and at $108 \pm 0.1^\circ$ was studied. Two parallel pathways of molecular degradation which lead simultaneously to the formation of sulfanilic acid (pathway A) and sulfanilamide (pathway B) as final products were determined. The isoxazole ring is degraded as much in the sulfoxazole molecule (pathway B) as in the 5-amino-3,4-dimethylisoxazole (pathway A), leading to formation of 2-butanone and hydroxylamine (and ammonia in the latter case) as final products. Both degradative pathways show pseudo-first-order kinetics. A study was also made of how the reaction rates are affected with the acid concentration. Degradative pathway B prevails at low acid concentrations and can be associated with a mechanism in which water participates in the rate-determining step; degradative pathway A prevails at higher acid concentrations and the mechanism implies nonparticipation of water in the rate-determining step.

Keyphrases □ Sulfoxazole—kinetics and mechanism of acid degradation, ionization ratios □ Isoxazole derivatives—kinetics and mechanism of acid degradation of sulfoxazole, ionization ratios □ Degradation—sulfoxazole in hydrochloric acid solutions, rates, mechanisms, ionization ratios

The isoxazoles form a group of heterocycles that may be characterized by their chemical behavior; they exhibit properties that are typical of aromatic systems and also, under certain conditions, show ring lability, particularly at the oxygen-nitrogen bond (1).

At present, more attention is paid to the investigation of the mechanism of chemical reactions under extreme conditions (high and low temperatures, high and low pressures, effects of radiation, etc.); available data show that under such conditions the course of reactions often becomes uncommon.

Based on these findings and on some experimental data obtained in this laboratory, it appeared interesting

to perform a thorough study of the cleavage reactions of the isoxazole ring in strong acid solutions and at high temperatures. These studies may contribute more basic information on the stability of the ring, especially since data related to the problem are quite scarce (1). Moreover, since numerous derivatives of the isoxazole ring have pharmacological properties (2), the importance of the conditions and mechanism by which these heterocycles are degraded is greatly increased.

This paper presents the results of a study of the influence of hydrochloric acid concentrations and high temperatures on the hydrolytic degradation of one isoxazole derivative: sulfoxazole¹ (*N*-sulfanilamido-3,4-dimethyl-5-isoxazole).

EXPERIMENTAL²

Materials—All of the solvents used were commercial products, purified by the usual techniques. Hydrochloric acid, sulfuric acid, and sodium β -naphthoquinone-4-sulfonate were analytical³ reagent grade. 2,4-Dinitrophenylhydrazine⁴ was recrystallized from methanol. Sulfoxazole USP⁵ was recrystallized from ethanol, m.p. 193–194°. 5-Amino-3,4-dimethylisoxazole was prepared according to the method described (3) for other sulfonamides: 10 g. of sulfoxazole was dissolved in 200 ml. of glacial acetic acid and 25 ml. of acetic anhydride. The solution was boiled for 5 min., cooled, and diluted with 500 ml. of distilled water. A precipitate

¹ Preferred USAN chemical name is *N*-(3,4-dimethyl-5-isoxazolyl)-sulfanilamide.

² Melting points were taken on a melting-point apparatus (Dr. Tottoli) and are uncorrected. The IR spectra were run on a Beckman IR 8 spectrophotometer in potassium bromide pellets. UV measurements were made in a Hilger & Watts H.700.308 spectrophotometer, using quartz cells 1 cm. thick. The complete absorption spectrum in the UV region was taken in a Cary 14 recording spectrophotometer. Absorbance measurements in the visible region were made in a Bausch & Lomb spectrophotometer.

³ Carlo Erba G.R.

⁴ Merck & Co.

⁵ SOCRAM.