

tyric acid occupies an intermediate position between  $\beta$ -alanine and  $\epsilon$ -aminocaproic acid. The changes in enthalpy and entropy probably reflect the decrease in flexibility of the hydrocarbon chain with removal of the carboxyl hydrogen in the first ionization and the increase in flexibility resulting from removal of the proton from the ammonium group in the second ionization. Further discus-

sion of these properties in relation to those of the other amino acids will be dealt with in another communication.

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## Spectrophotometric Studies of Dissociation Constants of Nitroguanidines, Triazoles and Tetrazoles

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The dissociation constants of several derivatives of nitroguanidine and related compounds have been determined by spectrophotometric means. The method of Stenstrom and Goldsmith has been applied to compounds exhibiting weakly acidic (monoprotic and diprotic) and basic dissociation. Each  $pK$  value was obtained graphically from a smooth curve plotted from several absorption observations over the useful  $pH$  range using buffered solutions. Sodium chloride was added to maintain a constant ionic strength of one. Dissociation constants too low ( $pK$  10 to 12) to be determined by potentiometric titration were easily measured. Where potentiometrically determined values were available for comparison, good agreement was obtained.

Ultraviolet absorption spectra have been reported for a large number of nitro-substituted guanidines and tetrazoles. In some cases absorption differences were noted when acidic *versus* basic solutions of these materials were measured.<sup>1-3</sup> No instances are reported where these differences were employed to arrive at a measure of the dissociation constants of these compounds.

The acidic properties of nitroguanidines and tetrazoles have been discussed and in cases where acid dissociation was extensive, potentiometric titration has been used to determine dissociation constants.<sup>4-6</sup> In cases where there was only slight dissociation, potentiometric methods were not feasible. The need for information concerning relative acidities of these weaker acids and bases was evident. The application of a spectrophotometric procedure provided a convenient method for determining dissociation constants for several nitroguanidines. A variety of nitramines has been included in this study to illustrate the applicability of the method.

### Apparatus

The absorption spectra were measured using a Beckman model DU spectrophotometer. A Beckman model G,  $pH$  meter equipped with general purpose glass electrode was used for all  $pH$  measurements. Sodium ion corrections for the glass electrode were applied where necessary.

### Experimental

The method of Stenstrom and Goldsmith<sup>7</sup> has been used by several workers in determining dissociation constants

- (1) R. N. Jones and G. D. Thorn, *Can. J. Research*, **B27**, 828 (1949).
- (2) A. F. McKay, J. P. Picard and P. E. Brunet, *Can. J. Chem.*, **29**, 746 (1951).
- (3) V. J. Sabetta, D. Himmelfarb and G. B. L. Smith, *THIS JOURNAL*, **57**, 2478 (1935).
- (4) W. D. Kumler and P. P. T. Sah, *J. Org. Chem.*, **18**, 669 (1953).
- (5) E. Lieber, S. H. Patinkin and H. H. Tao, *THIS JOURNAL*, **73**, 1792 (1951).
- (6) J. S. Mihina and R. M. Herbst, *J. Org. Chem.*, **15**, 1082 (1950).
- (7) W. Stenstrom and N. Goldsmith, *J. Phys. Chem.*, **30**, 1683 (1926).

of weak acids. The method has been extended to include two step ionization processes.<sup>8,9</sup>

The values for the ionization constants  $K_1$  and  $K_2$  are calculated as

$$pK_1 = pH - \log \frac{A_1 - A^\circ}{A' - A_1}$$

$$pK_2 = pH - \log \frac{A_2 - A'}{A'' - A_2}$$

where

- $A_1$  = absorbance<sup>10</sup> of the mixture of the two species, un-ionized and singly ionized species
- $A^\circ$  = absorbance of the un-ionized molecule
- $A'$  = absorbance of the singly ionized ion
- $A_2$  = absorbance of the mixture of singly and doubly ionized species
- $A''$  = absorbance of the doubly ionized ion

Absorbance values are used throughout the equations rather than molar absorptivity as in the original derivation<sup>7,11</sup> since cell length and molar concentration are constant for each series of measurements.

The use of these equations is simplified by plotting the relationship between  $pH$  and absorbance. At the midpoint of the break in the curve,  $pH = pK$  since the log term equals zero.

In the present work, the absorption spectrum of each buffered solution was recorded in the ultraviolet range 200-400  $m\mu$ . Wave length peaks characteristic of the un-ionized molecule or ionized species were selected for use. In general, one major absorption peak was exhibited in the ultraviolet region by the compounds investigated and this peak most strongly illustrated the change in absorbance with change in  $pH$  of the medium. By employing a large number of buffered solutions over the  $pH$  range (1-14), it was possible to plot a smooth curve showing the relationship between  $pH$  and absorbance. By careful measurement then the  $pK$  value could be easily obtained graphically.

In the case of the compounds for which the second dissociation constant was investigated, the removal of the second proton resulted in little or no shift in the main absorption peak.

- (8) C. V. Banks and A. B. Carlson, *Anal. Chim. Acta*, **7**, 291 (1952)
- (9) M. T. Rogers, T. W. Campbell and R. Maatman, *THIS JOURNAL*, **73**, 5122 (1951).
- (10) Absorbance =  $A = \log(I_0/I) = abc$ ; molar absorptivity =  $\epsilon = aM$ .
- (11) L. J. Edwards, *Trans. Faraday Soc.*, **46**, 726 (1950).

All compounds studied were handled in substantially the same manner. The materials were dissolved in the water or alcohol-water solvent. Aliquots of these solutions were transferred to a volumetric flask and to this was added the desired Britton and Robinson<sup>12</sup> buffer mixture to which a concentration of sodium chloride had been added to give a salt concentration of 1 M with final concentration of the compound approximately  $7 \times 10^{-5}$  M. Solutions with pH above 12.0 were prepared by using known amounts of standard NaOH solution. The buffer plus salt solution was used as the blank in the spectrophotometer reading. In view of the probability of decomposition upon standing in various buffer media, the peak absorbance of the solutions was determined without delay after preparation. No additional temperature control was exercised other than to allow all solutions to equilibrate at room temperature,  $24 \pm 0.5^\circ$ . Adequate replication was gained by using numerous points to plot each curve.

A typical example follows: 0.035 g. of nitrosoguanidine was dissolved in water and diluted to 100 ml. One ml. of this solution was transferred to a 50-ml. flask. The final dilution to the mark was made using the desired buffers containing 2.9 g. of sodium chloride. Thirteen different solutions were thus prepared to cover the pH range to 13.0. The values of absorbance at 257 m $\mu$  were used for plotting to determine *pK*. These are summarized in Fig. 1. A notable feature of this compound is shown in the graph wherein both acidic and basic dissociations are indicated.

Rigorous standardization of master solutions was not necessary since the precise knowledge of concentration, hence molar absorptivity, was of no direct utility. The aliquots were precisely measured since this quantity was

TABLE I  
DISSOCIATION CONSTANTS OF NITROGUANIDINE AND RELATED COMPOUNDS

	<i>pK</i>	Wave length, m $\mu$
Nitroguanidine	12.20 <sup>a</sup>	265
1-Methyl, 1-amino-3-	12.60	272
1-Methyl-3-	12.40	267
1-( $\beta$ -Phenylethyl)-3-	12.25	269
1-Benzyl-3-	12.00	271
1-( $\beta$ -Cyanoethyl)-3-	11.65	268
1-( $\alpha$ -Phenylethyl)-3-	11.46	272
1-Carboethoxymethyl-3-	11.20	270
1-(2-Pyridyl)-3-	10.70	298
1-Amino-3-	10.60 <sup>b</sup>	267
1-Cyanomethyl-3-	9.30	266
1-(2-Phenylaminoethyl)-2-phenyl-3-	9.30	274
1-Benzoyl-3-	8.10	276
1-Formamido-3-	7.50	267
1-( <i>p</i> -Tolyl)-3-	10.85	271
1-( <i>p</i> -Anisyl)-3-	10.70	275
1-( <i>p</i> -Dimethylaminophenyl)-3-	10.70	266
1-Phenyl-3-	10.50	275
1-( <i>m</i> -Anisyl)-3-	9.80	277
1-( <i>p</i> -Chlorophenyl)-3-	9.70	280
1-( <i>p</i> -Cyanophenyl)-3-	8.60	290
Nitrosoguanidine	<i>pK</i> <sub>a</sub> 11.70	257
	<i>pK</i> <sub>b</sub> 11.90	
3-Methyl-5-nitroamino-1,2,4-triazole	4.75 <sup>c</sup> ; 11.30	288
3-Nitroamino-5-methyl-1,2,4-triazole	4.30; 11.10	286
3-Nitroamino-1,2,4-triazole	3.95; 10.80	284
Guanidinium-5-nitroaminotetrazole	5.69 <sup>d</sup>	270

<sup>a</sup> Value ca. 14 reported by Kumler and Sah.<sup>4</sup> <sup>b</sup> Value 10.47 reported by Kumler and Sah.<sup>4</sup> <sup>c</sup> Value 4.8 reported by Lieber, *et al.*<sup>5</sup> <sup>d</sup> Value 6.1 calculated for potassium 5-nitroaminotetrazole from data of Lieber, *et al.*<sup>5</sup> All compounds were furnished by Dr. Ronald A. Henry of these laboratories. The precision of these measurements is estimated to be  $\pm 0.05$  *pK* unit.

(12) H. T. S. Britton and R. A. Robinson, *J. Chem. Soc.*, 1456 (1931).

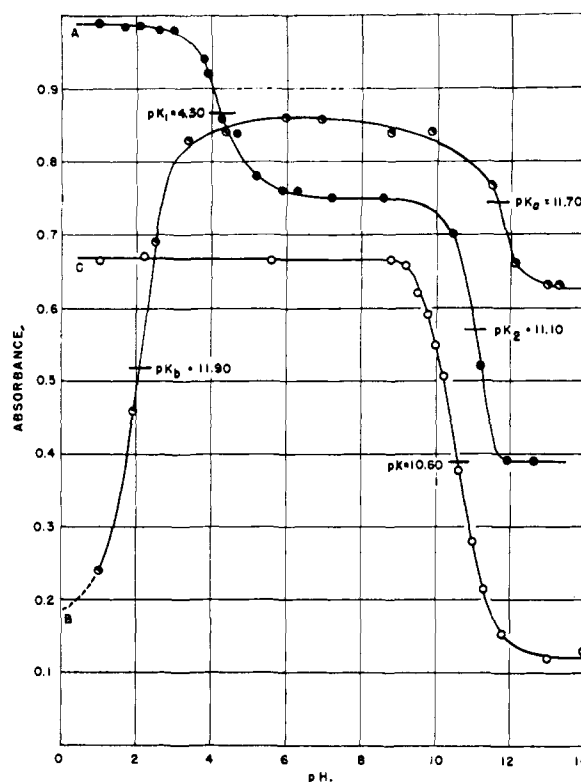


Fig. 1.—Graphical determination of dissociation constants: curve A, 3-nitroamino-5-methyl-1,2,4-triazole; curve B, nitrosoguanidine; curve C, 1-amino-3-nitroguanidine. Beckman model DU spectrophotometer; 1-cm. matched silica cells; temperature  $24^\circ$ . Absorbance =  $\log(1/\text{transmittance})$ . Absorbance readings taken at wave length of maximum absorption, curve A at 286 m $\mu$ , B at 257 m $\mu$ , and C at 267 m $\mu$ .

invariant in each series. In cases of slightly soluble materials, up to 100% alcohol was used in the master solution to dissolve the sample. While this amount of alcohol in each aliquot is appreciable, the amount is less than 2% in the final dilution so that its effect on dissociation is considered well within the accuracy of the method.

The graphical derivation of *pK* values for monoprotic nitroaminoguanidine is shown in Fig. 1. The graphical derivation of *pK*<sub>1</sub> and *pK*<sub>2</sub> for a diprotic nitramine are shown in Fig. 1. The *pK* values found for the various nitramine compounds are summarized in Table I.

### Discussion

An important feature of these observations is that the acidity function of nitroguanidine and all related compounds appears instantaneously. Long standing in alkaline solution, reportedly necessary,<sup>13</sup> was not required in this work to bring out the acidic character. Moreover, the main absorption peak of all nitroguanidines handled did not shift appreciably in the range required to obtain *pK* values. Both of these facts would seem to rule out the slow tautomerization.

The relative acidities of the substituted phenyl-nitroguanidines agree well with what would be predicted from the electron-attracting tendencies of the substituents. The effect of these groups on the dissociation constant is shown in Fig. 2 in

(13) S. S. Barton, R. H. Hall and G. F. Wright, *THIS JOURNAL*, **73**, 2201 (1951).

which values of  $pK$  are plotted against Hammett's substituent constants,  $\sigma$ ,<sup>14</sup> for the groups. Approximate linearity between  $pK$  and  $\sigma$  is observed.

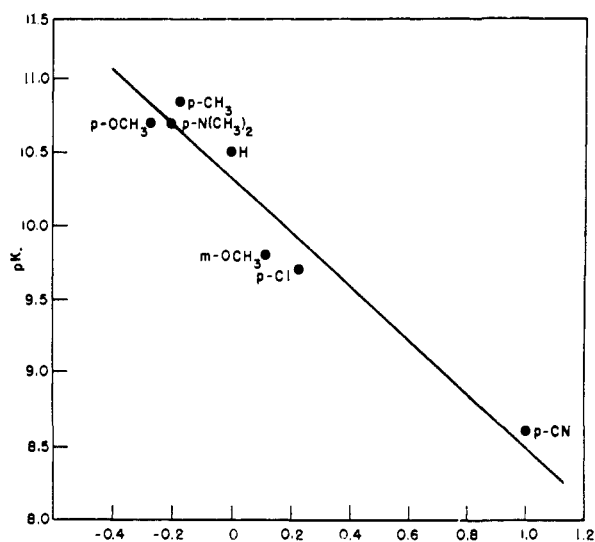


Fig. 2.—Effect of substituents on the acidity of phenyl-nitroguanidine.

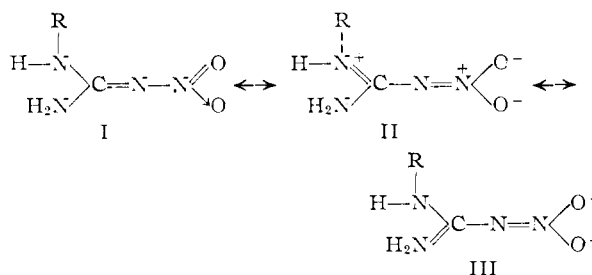
The value of  $\rho$ , measuring the susceptibility of the dissociation to change in substituent, is +1.9. This value was obtained from the negative slope of the line, calculated by the method of least squares. By comparison with similar measurements,<sup>10,14</sup> it is seen that this value of  $\rho$  is moderately large. The value found here would suggest a structure where the electron density of the proton-releasing atom is readily affected by change in electron pull of phenyl substituent. This situation would pertain in the resonance hybrid represented by the three structures I, II and III. In these structures the nitrogen atom having a substituent group capable of attracting or repelling electrons is the one most likely to release a proton. The electron density on the nitrogen atom then varies strongly depending on the negative or positive character of the substituent. This indeed is

(14) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 184-191.

indicated by the high value found for  $\rho$  and by the range of acidities of the nitroguanidines listed in Table I.

The substituted nitroguanidines show the effects of electron-attracting tendencies of the groups through not in as regular a fashion as the substituted phenylnitroguanidines. Within pairs, predicted comparisons appear. In terms of their effect on extent of dissociation, the groups compare as follows: cyanophenyl > cyanomethyl; cyano-methyl > cyanoethyl;  $\alpha$ -phenylethyl >  $\beta$ -phenylethyl; methyl > methyl plus amino; benzyl >  $\beta$ -phenylethyl; benzoyl > phenyl; phenyl > pyridyl; formamido > amino. In general, the substituent groups impart the regular effects one would predict in terms of electron attractions.

There are several features of the spectrophotometric method which are particularly favorable for determining dissociation constants of nitramines. There is excellent control of pH through use of buffered solutions throughout the full pH range. All solutions are checked by use of the pH meter. Extensive replication is possible by use of numerous aliquots over the full pH range. The effect of decomposition on readings is reduced to a negligible amount in that the absorption reading is taken immediately after the sample is mixed with the buffer. Further applications of the method for determining dissociation constants of a large number of nitramines are suggested.



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