

Thermodynamics of Proton Ionization from Some Substituted, Unsaturated, Five-Membered Nitrogen Heterocycles (1)

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INTRODUCTION

The purpose of this study was to determine pK , ΔH° and ΔS° values for proton ionization from substituted tetrazoles, protonated and neutral 1,2,4-triazole, protonated 1,2,3-triazole, and pyrazole. A similar study of substituted 1,2,3-triazoles has been published (3).

A study of these compounds was considered to be of interest for several reasons: a) although they are iso-electronic, their acidic and basic properties are remarkably varied; b) the bond structure of the unsaturated five-membered nitrogen heterocycles is poorly characterized and c) very few thermodynamic data have been previously reported for these compounds.

No ΔH values and only a few pK values (4-9) have been reported for proton ionization from the series of compounds included in the present study.

RESULTS

Table I gives the average pK , ΔH° and ΔS° values obtained in this study. The limits of error are expressed as average deviations from the mean, except the deviation in the ΔH° value given for 5-trifluoromethyltetrazole. Since the calculation of ΔH° depends on the pK value and the uncertainty in the pK value was rather large, ΔH° was calculated from the two different species distributions that resulted from using pK values of 1.9 and 1.5 (upper and lower limits, respectively). The resulting ΔH° values were then averaged and the deviation reported is the average deviation of these two values.

Previously reported pK values are given in parentheses in Table I. In general, these values are in fair agreement with the ones obtained in the present study. None of the previously reported values are true thermodynamic pK values because no activity coefficient corrections were made. In addition, the pK value previously reported for 5-phenyltetrazole was done in an alcohol-water mixture and that for 5-trifluoromethyltetrazole was merely stated with no reference as to the method of obtaining it.

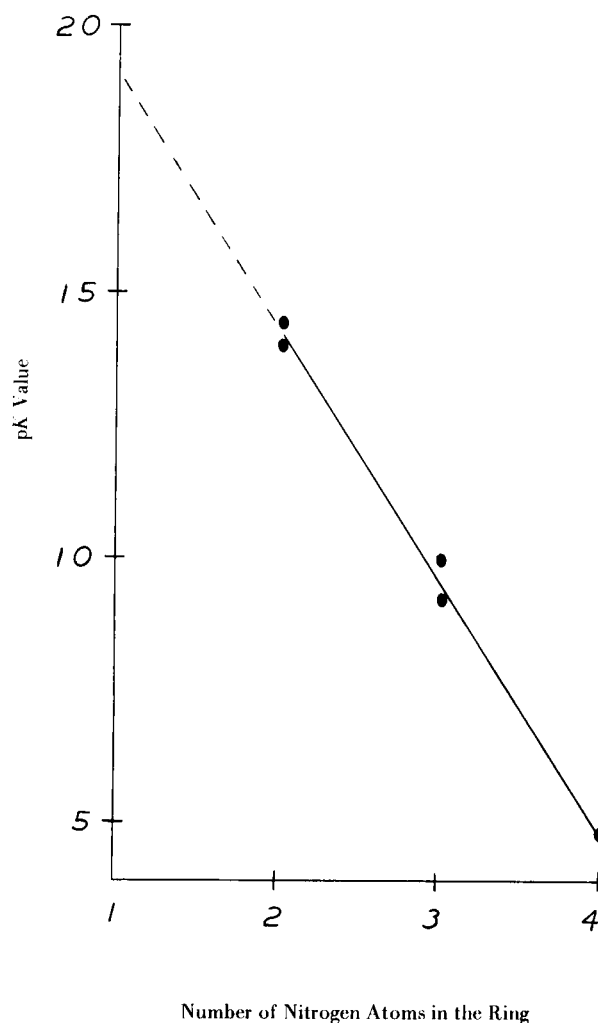
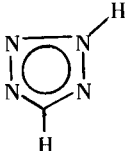
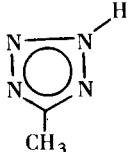
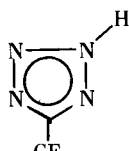
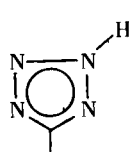
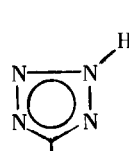
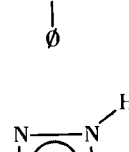
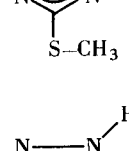


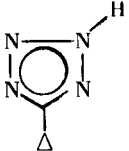
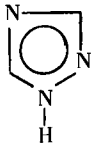
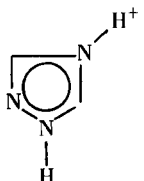
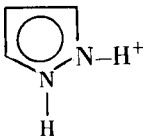
Figure 1. Plot of pK vs. Number of Nitrogen Atoms in the Ring for Five-Membered Unsaturated Nitrogen Heterocycles.

Results from both calorimetric experiments and pH titrations indicate that 1,2,3-triazole and tetrazole cannot be protonated in dilute aqueous solution. pH Titrations

TABLE I

pK , ΔH° , and ΔS° Values for Proton Ionization from Some Unsaturated, Five-Membered Nitrogen Heterocycles

Acid	Structure (a)	pK	ΔH° kcal/mole	ΔS° cal/deg. mole
Tetrazole		4.90 ± 0.01 (4.89) (b) (4.79) (c)	$+3.09 \pm 0.07$	-12.1
5-Methyltetrazole		5.63 ± 0.02 (5.56) (c)	$+3.32 \pm 0.07$	-14.6
5-Trifluoromethyltetrazole		1.7 ± 0.2 (1.14) (d)	-1.13 ± 0.16	-11.2
5-Phenyltetrazole		4.38 ± 0.01 (4.54) (e)	$+3.20 \pm 0.12$	- 9.3
5-Phenoxytetrazole		3.49 ± 0.07	$+2.59 \pm 0.28$	-7.3
5-Methylthiotetrazole		4.00 ± 0.04	$+2.71 \pm 0.19$	-9.2
5-Hydroxytetrazole		$pK_1 = 5.40 \pm 0.01$ (N-H) $pK_2 = 10.26 \pm 0.04$ (O-H)	$+3.87 \pm 0.10$ $+6.19 \pm 0.07$	-11.7 -26.3

5-Cyclopropyltetrazole		5.41 ± 0.01	$+3.66 \pm 0.05$	-12.5
1,2,4-Triazole		10.04 ± 0.05	$+7.90 \pm 0.22$	-19.4
Protonated 1,2,4-triazole		2.45 ± 0.03 (2.30) (f)	$+2.30 \pm 0.01$	-3.5
Protonated Pyrazole		2.61 ± 0.05 (2.48) (f)	$+3.52 \pm 0.03$	-0.2

(a) It is unknown whether the tetrazoles exist as the 1*H*- or as the 2*H*- form in aqueous solution. (b) E. Lieber, S. H. Patinkin and H. H. Tao, *J. Am. Chem. Soc.*, **73**, 1792 (1951). (c) J. S. Mihina and R. M. Herbst, *J. Org. Chem.*, **15**, 1082 (1950). (d) W. P. Norris, *J. Org. Chem.*, **27**, 3248 (1962). (e) R. M. Herbst and K. R. Wilson, *J. Org. Chem.*, **22**, 1142 (1957). (f) G. Dedichen, *Ber. deut. chem. Ges.*, **39**, 1831 (1906).

of approximately 10^{-2} *M* solutions with 1 *M* perchloric acid showed no buffer effect and calorimetric determinations showed that no heat was evolved when 5 ml. of 1 *M* perchloric acid was added to 175 ml. of 10^{-2} *M* solution. In the case of 1,2,3-triazole, the results of this study are in disagreement with a previously reported value ($pK_a = 1.17$) (4,5). This value was originally obtained from unpublished data, and it therefore was impossible to assess the accuracy. No attempt was made to obtain thermodynamic data for proton ionization from protonated pyrrole, because it is known to be the weakest base in the series of the unsaturated five-membered nitrogen heterocycles (4,7).

DISCUSSION

Substituent Effects on Tetrazoles.

Previous discussions of the substituted tetrazoles have compared the tetrazolyl anion with the carboxylate group (9). These discussions have been based solely on pK data and suggest that the carboxylate group and the tetrazolyl anion transmit inductive effects in a similar manner. For example, the difference in the pK values of 5-methyltetrazole and 5-trifluoromethyltetrazole and 5-trifluoromethyltetrazole is about the same magnitude (3.9) as the

difference in the pK values of acetic acid and trifluoroacetic acid (4.2) (6). The results of this study show that the difference in the pK values of 5-trifluoromethyltetrazole and tetrazole is due to the difference in the enthalpy changes (5.4 kcal/mole). Although enthalpy change data are not available for proton ionization from trifluoroacetic acid, it is known that the enthalpy change for ionization from a carboxyl group is approximately constant (range -1.4 to +1.4 kcal/mole) (10). If the enthalpy change for proton ionization from trifluoroacetic acid falls in this range, then the difference in the pK values of trifluoroacetic and acetic acid is due to the magnitude of the entropy changes.

The analogy of the tetrazole ring and the carboxylate group also breaks down when one compares tetrazole and 5-phenyltetrazole with benzoic and formic acids. Formic acid is a stronger acid than benzoic acid while tetrazole is a weaker acid than 5-phenyltetrazole. Herbst has recognized this fact and explains the discrepancy from the viewpoint of resonance stabilization (9). According to Herbst, tetrazole is a weaker acid than 5-phenyltetrazole because of the greater resonance stabilization of the 5-phenyltetrazolyl anion. The results of the present study show that the small difference in acidity of tetrazole and

5-phenyltetrazole is due to the difference in the entropy changes rather than the enthalpy changes. This could be interpreted to mean that the difference in acidity is due to electrostatic or hydration effects instead of intramolecular effects.

An interpretation of the data for proton ionization from 5-hydroxytetrazole is complicated by the fact that it can be present in either the keto or enol form. The results of the present study indicate that 5-hydroxytetrazole is present largely in the enol form in dilute aqueous solution and that the proton bonded to the nitrogen atom ionizes in the first stage, while the O-H proton ionizes in the second stage. This conclusion is based on the observations (a) that the enthalpy change for the second stage of proton ionization (6.19 kcal/mole) from 5-hydroxytetrazole is of about the same magnitude as that of proton ionization from substituted phenols (range 4.8 to 5.6 kcal/mole) (11,12), and (b) that the enthalpy change for the first stage ionization from 5-hydroxytetrazole (3.87 kcal/mole) is close to the enthalpy change observed for proton ionization from tetrazole (3.09 kcal/mole).

A direct comparison of substituent effects on 1,2,3-triazole and on tetrazole is not possible at this time because those substituents which produced large changes in ΔH° for ionization of triazole, namely $-\text{COOH}$ and $-\text{Br}$ (3), do not form stable compounds when substituted on tetrazole. However, the data for trifluoromethyltetrazole in Table I indicate that the ΔH° value for ionization of tetrazoles is likely to be sensitive to the substitution of highly electronegative groups and/or groups with π bonds. Further work is currently being done on this topic.

Comparison of the Acidities of the Unsaturated Five-Membered Nitrogen Heterocycles.

There is a linear correlation between the acidities of the unsubstituted, unsaturated five-membered nitrogen heterocycles and the number of nitrogen atoms in the ring. Imidazole and pyrazole, with two nitrogen atoms in the ring, have pK values of 14.4 and 14, respectively (13,14,4), 1,2,3- and 1,2,4-triazole, with three nitrogen atoms, have pK values of 9.26 (3) and 10.04, respectively, and tetrazole, with four nitrogen atoms, has a pK value of 4.90. These data are presented graphically in Figure 1.

Extrapolation of the line in Figure 1 to one nitrogen atom suggests that pyrrole should have a pK value of ~ 19 . Although no data are available on pyrrole itself, a pK value of 16.5 has been estimated for 2,4-dimethyl-3,5-dicarbethoxypyrrole (15).

The reason for the linear correlation between the acidities of the unsaturated five-membered nitrogen heterocycles and the number of nitrogen atoms in the ring can be found in an analysis of the entropy and enthalpy

changes for proton ionization from these compounds. The entropy changes for proton ionization from uncharged triazoles and tetrazoles is approximately constant at -12 cal/deg. mole (3). This entropy change is also the same as the entropy change reported for proton ionization from imidazole (-7 ± 5 cal/deg. mole) (14). This shows that the linear correlation which is observed between the pK values for proton ionization from the unsaturated five-membered nitrogen heterocycles and the number of nitrogen atoms in the ring is due to the linear variation of ΔH° .

The fact that the entropy changes are approximately constant is not surprising since the reactions are all of the same charge type. The linear dependence of the enthalpy changes for proton ionization on the number of nitrogen atoms in the ring indicates that the difference in acidity of these compounds is due to an intramolecular effect. The successive replacement of carbon atoms with more electronegative nitrogen atoms, probably causes a decrease in the N-H bond energy by an electron withdrawing effect.

Basicities of the Unsaturated Five-Membered Nitrogen Heterocycles.

The results of the present study show that the large differences in the basicity of the unsaturated five-membered nitrogen heterocycles are due to the magnitude of the enthalpy changes for protonation. For example, the enthalpy change for proton ionization from protonated pyrazole is 2.30 kcal/mole, while the enthalpy change for proton ionization from protonated imidazole is 8.79 kcal/mole (16). The entropy changes are about the same (-3.5 cal/deg. mole for pyrazole and -2.5 cal/deg. mole for imidazole) (16). This means that any explanation of the relative base strengths of the unsaturated five-membered nitrogen heterocycles must be based on intramolecular effects rather than on solvation effects. Some of these intramolecular effects have been discussed previously (4,7,8,9,17). The results of this study also show that there is no general correlation between the base strengths and the number of nitrogen atoms in the ring as was observed for proton ionization from the neutral molecules.

The weak basicity of pyrrole is not difficult to understand. It has been shown that pyrrole is planar with conjugated π -electron sextets in the cyclic system (7). The only lone pair that would be available for bonding in the nitrogen atom is part of the aromatic sextet. The addition of one more nitrogen atom to the ring introduces a tertiary nitrogen which contains a lone pair available for bonding. Therefore, pyrazole and imidazole are more basic than pyrrole. There is, however, a striking difference in the basicities of pyrazole and imidazole. Molecular orbital calculations (18) of charge densities of the nitrogen atoms of imidazole and pyrazole predict that imidazole is

the stronger base, which agrees with the observed basicities. Figure 2 shows the charge densities on the nonprotonated nitrogen atoms in pyrazole, imidazole, 1,2,3-triazole, and 1,2,4-triazole.

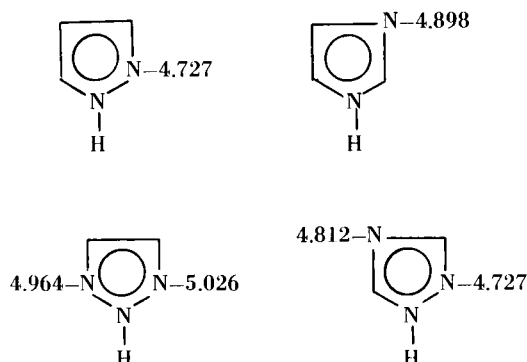


Figure 2. Charge Densities on Nitrogen Atoms in Some Nitrogen Heterocycles.

In comparing the basicity of 1,2,3-triazole with that of 1,2,4-triazole, it is experimentally observed that 1,2,4-triazole is the stronger base. The molecular orbital calculations are in disagreement with this since 1,2,3-triazole is calculated to have the higher electron densities on the nitrogen atoms.

From the basicity comparison of imidazole with pyrazole and 1,2,3-triazole with 1,2,4-triazole, it can be observed that the position of the nitrogen atoms in the ring is the factor that governs the basicity of the unsaturated five-membered nitrogen heterocycles. In each of the previous comparisons, the compound that has a nitrogen atom which is not adjacent to another nitrogen is the more basic. It is interesting to note that, with the exception of pyrrole, the order of basicity would be related to the number of nitrogen atoms in the ring were it not for this factor. For example, the order of basicity is pyrazole > 1,2,3-triazole and tetrazole, but 1,2,4-triazole and pyrazole are of about equal basicity, because 1,2,4-triazole contains a nitrogen in a nonadjacent position.

EXPERIMENTAL

Materials.

The compounds used for this study came from several sources. The 1,2,3-triazole was prepared by Dr. B. D. West by the method given in Reference 19. Dr. Peter Scheiner prepared 5-phenyltetrazole, 5-phenoxytetrazole, and 5-methylthiotetrazole by the methods given in References 20-22. Mr. Newton Fawcett prepared the sodium salt of 5-trifluoromethyltetrazole, 5-hydroxytetrazole, 5-methyltetrazole, and tetrazole by the methods given in Refer-

ences 19, 23, and 24. 1,2,4-Triazole and pyrazole were obtained from Aldrich Chemical Company and benzotriazole from Eastman Organic Chemicals.

5-Cyclopropyltetrazole.

The 5-cyclopropyltetrazole, a new compound, was prepared as follows: cyclopropyl cyanide, 13.4 g. (0.20 mole), sodium azide, 14.3 g. (0.22 mole), ammonium chloride 3.5 g. (0.065 mole) and 100 ml. anhydrous DMF were stirred and heated at 120-125° for 44 hours. Solvent was removed under reduced pressure leaving a white paste. The latter was taken up in 50 ml. of water, acidified with concentrated hydrochloric acid and cooled. (HN₃, with caution.) The crystalline precipitate was collected, washed with ice water and dried; yield, 12.1 g. (55%), m.p. 148-150°. Two crystallizations from ethylacetate gave the analytical sample, m.p. 149-150°.

Anal. Calcd. for C₄H₆N₄: C, 43.63; H, 5.49; N, 50.88. Found: C, 43.66; H, 5.49; N, 50.85.

All compounds used in this study were tested for purity by equivalent weight determinations and found to be 99+% pure.

Equipment and Procedures.

The equipment and procedures used in this study were the same as described in a previous paper (3).

Calculations.

The computer programs and input data for the pH and ΔH° calculations are available (25).

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