

BASICITY OF 3,6-DIPHENYL-1,2,4,5-TETRAZINE

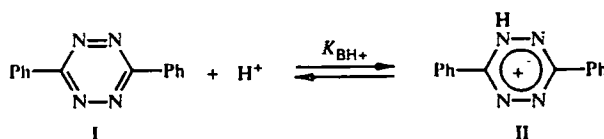
R. E. Trifonov, V. Yu. Zubarev, A. A. Malin,
and V. A. Ostrovskii

We have determined the basicity of 3,6-diphenyl-1,2,4,5-tetrazine in aqueous solutions of sulfuric acid (pK_{BH^+} is -4.8). According to quantum chemical calculations done by the MNDO method and the *ab initio* method in a 6-31G++ basis, the tetrazine ring is a nonpolar, highly aromatic system similar to benzene. The aromaticity of the tetrazine heterocycle decreases significantly upon protonation, which considerably destabilizes the protonated form.

The high interest in 1,2,4,5-tetrazines is due to their high biological activity and reactivity [1, 2]. The tetrazine ring is an interesting model for physicochemical studies as the ring most saturated with nitrogen atoms relative to stable azine [3], but information about the physicochemical properties of tetrazines is limited or fragmentary. In particular, such an important property of a heterocycle as basicity has not been discussed previously for tetrazines at a quantitative level.

In this work, we have determined the basicity constant for 3,6-diphenyl-1,2,4,5-tetrazine (I) in aqueous sulfuric acid solutions using the spectrophotometric method. This compound was chosen as a model since it is relatively stable in acid solutions and is suitable for spectrophotometric analysis. The structure and thermodynamic characteristics of the free base I and its conjugate acid II and also the corresponding forms of unsubstituted tetrazine (III, IV) were calculated by the semiempirical MNDO method and separately for the forms (III, IV) using the *ab initio* method in a 6-31G++ basis.

The basicity centers of 1,2,4,5-tetrazines are the pyridine nitrogen atoms, which are equivalent for compounds with identical substituents in the 3 and 6 positions of the ring.

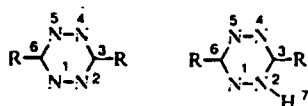


On going from base I to conjugate acid II, we observe a substantial bathochromic shift of the maximum for the $\pi-\pi^*$ transition in the electronic absorption spectrum, from λ_{max} 295 to 336 nm. Furthermore, the protonated form II, in contrast to the base I (the characteristics of the $n-\pi^*$ transition of base I in ethanol were: λ_{max} 548 nm, ϵ 2250) does not have a pronounced maximum corresponding to the $n-\pi^*$ transition. This may be explained by the substantial differences between the electronic structure of the base and the corresponding conjugate acid. Upon protonation, the color of the solutions changes: the base gives a bright raspberry color, the protonated form gives a yellow color. It is difficult to measure the electronic absorption spectrum of the unprotonated tetrazine I in aqueous sulfuric acid solutions because of the extremely low solubility of I. For the working concentrations (10^{-5} moles/liter), we could measure the spectrum of the base only in 1,4-dioxane and ethanol.

Because of the low solubility of base I in aqueous solutions of sulfuric acid, we calculated the basicity constants by the iteration method in [5]. As the pK_{BH^+} value, we took the ratio of the y-intercept (pK'_{BH^+}) to the slope (m) of the Eits-MacClelland [spelling unverified] linear equation [4]. The calculation results were (λ_{anal} 340 nm): $pK_{BH^+} -4.8 \pm 0.6$,

St. Petersburg State Technological Institute, St. Petersburg 198013, Russia, e-mail: ostrovskii@mail.convey.ru.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, Vol. 34, No. 1, pp. 120-123, January, 1998. Original article submitted June 5, 1997.

TABLE 1. Charges on Atoms, Geometry, and Thermochemical Characteristics of 3,6-Diphenyl-1,2,4,5-Tetrazine (I) and Its Protonated Form (II), 1,2,4,5-Tetrazine (III) and Its Protonated Form (IV) (calculated by the MNDO* method)



Compound	Charges on atoms						
	1	2	3	4	5	6	7
I	-0.07	-0.07	-0.01	-0.07	-0.07	-0.01	—
II	-0.02	-0.05	0.19	0.01	0.06	0.09	0.31
III	-0.07	-0.07	0.03	-0.07	-0.07	0.03	—
IV	-0.09	-0.08	0.22	-0.02	0.02	0.13	0.28

Compound	Bond lengths. Å					
	1-2	2-3	3-4	4-5	5-6	7-2
I	1.274	1.370	1.372	1.272	1.372	—
II	1.329	1.354	1.410	1.245	1.414	1.031
III	1.266	1.379	1.379	1.266	1.379	—
IV	1.329	1.364	1.431	1.230	1.433	1.023

Compound	Angles. degrees					ΔH , kcal/mole	μ , D	I_p , eV
	3-2-1	4-3-2	5-4-3	6-5-4	7-2-1			
I	119.1	121.7	119.2	119.1	—	68.8	0.012	11.11
II	123.6	117.4	120.8	120.2	114.3	265.3	—	17.19
III	120.4	119.2	120.4	120.4	—	114.3	0.008	9.15
IV	125.3	114.2	122.3	121.9	112.3	291.4	—	12.52

*All the considered structures are planar.

TABLE 2. Relative Aromaticity (benzene A 100%) of Tetrazines (I, III) and Their Protonated Forms (II, IV) (calculated by the Pozharskii method [10])

Compound	Aromaticity		Compound	Aromaticity	
	MNDO	6-31G++		MNDO	6-31G++
I	77	—	III*	87	96
II	25	—	IV	37	58

*The aromaticity was 88% when calculated from the bond lengths determined experimentally by x-ray diffraction.

$m = 1.9 \pm 0.2$, for linear regression coefficient $r = 0.99$. The anomalous value of the solvation coefficient may be explained by the effects of association of the poorly soluble unprotonated form I [6, 7].

As follows from the data presented, the tetrazine ring is the weakest base among all known aromatic polynitrogen heterocycles (azoles, azines) [8, 9]. The basicity of tetrazine I is somewhat lower than might be expected based on the increase in the number of electronegative nitrogen atoms in the heterocycle in the azine series [9]. Obviously such an anomaly in tetrazines is connected with the features of their electronic structure. Accordingly, we have used the MNDO and *ab initio* methods for the quantum chemical investigations.

The results of the MNDO calculations for the electronic structure, geometry, enthalpy of formation, dipole moments, and ionization potentials for the two forms of diphenyltetrazine (I, II), unsubstituted 1,2,4,5-tetrazine III and its protonated form IV are given in Table 1. The tetrazine ring is a low-polarity structure with a total dipole moment close to zero. The negative charge on the nitrogen atoms of the unprotonated heterocycle is fairly small. On the whole, the tetrazine ring resembles benzene with respect to the type of electron density distribution and geometry. Note the high symmetry of the tetrazine ring, which is apparent in the equivalence of the four C–N bonds, the two N–N bonds, and the corresponding angles. Protonation leads to appreciable distortion of the symmetry of the tetrazine ring. The N–N bond including the protonated nitrogen atom is appreciably elongated, while the other N–N bond is shortened. Introduction of phenyl substituents in principle does not affect the electron density distribution and geometry of the protonated and unprotonated heterocycle.

The geometry and electronic structure of tetrazine III and its protonated form IV were calculated by the *ab initio* method (complete optimization of geometry in a 6-31G++ basis). The calculated total energies (au) for form III and IV are –294.4198 and –294.7391 respectively. On the whole the data from the nonempirical calculations agree with the semiempirical calculations. Similarly, the unprotonated tetrazine ring is a nonpolar, highly symmetric system. The N–N bonds are slightly shorter than the C–N bonds, but the differences between the N–N and C–N bond lengths are less compared with the semiempirical calculations. As for the results obtained by the semiempirical MNDO method, the nonempirical calculations show that protonation significantly distorts the symmetry of the heterocycle. We should note that the agreement between the calculated parameters and the x-ray diffraction data for unsubstituted tetrazine [10] is better for the *ab initio* method.

The anomalously low basicity of the tetrazine ring may be interpreted based on the aromaticity criterion. From the calculated bond multiplicities, using the Pozharskii method [10] we calculated the relative aromaticity (*A* 100%) for all the structures under consideration (I–IV) (Table 2). The tetrazine ring is close in aromaticity to the benzene ring. Protonation destroys the symmetry of the heterocycle and reduces its aromaticity, which ultimately destabilizes the protonated form.

Obviously for a deeper understanding of the effects we have touched upon, we need an analysis of the entire azine series. This is difficult to do today because of limited and contradictory literature data.

EXPERIMENTAL

Compound I was obtained and purified by the familiar method in [11], and its physicochemical characteristics corresponded to the literature data. The UV absorption spectra were recorded on a Specord M-40 at 25°C. The sulfuric acid concentration was determined by potentiometric titration. The values of the Hammett acidity function (H_0) used to calculate the $pK_{BH^{++}}$ values were taken from [12]. Semiempirical MNDO calculations were done using the program MNDO-90 [13]. Nonempirical calculations in a 6-31G++ basis were done using the GAMESS software package [14] in the Linux operating system.

We would like to thank the International Science Foundation for financial support of this research (grants: 128p, a97-2408, a97-2411, a97-2484).

REFERENCES

1. H. Neunhoffer, in: *Comprehensive Heterocyclic Chemistry*, A. Katritzky, C. W. Rees, A. Boulton, and A. McKillop (eds.), Vol. 3, Pergamon, Oxford (1984), p. 269.
2. Th. Eicher and S. Hauptmann, *The Chemistry of Heterocycles*, George Thieme Verlag, Stuttgart–New York (1995).
3. T. L. Gilchrist, *Heterocyclic Chemistry* [Russian translation], Mir, Moscow (1996).
4. V. A. Ostrovskii and G. I. Koldobskii, *Weak Organic Bases* [in Russian], Izdat. LGU, Leningrad (1990).
5. U. L. Haldna, *Usp. Khim.*, **49**, 1174 (1980).
6. R. E. Trifonov, S. É. Ivanova, V. A. Ostrovskii, and G. I. Koldobskii, *Zh. Org. Khim.*, **30**, 1556 (1994).
7. U. Haldna, M. Grebenkova, and A. Ebber, *Eestia Tead. Akad. Toim. Keem.*, **39**, 185 (1990).
8. J. Catalan, J. L. Abboud, and J. Elguero, *Adv. Heterocycl. Chem.*, **41**, 187 (1987).
9. A. E. A. Porter, *Comprehensive Organic Chemistry*, D. Barton and W. D. Ollis, (eds.) [Russian translation], Vol. 8, Khimiya, Moscow (1985).
10. A. F. Pozharskii, *Theoretical Principles of Heterocyclic Chemistry* [in Russian], Khimiya, Moscow (1985), p. 22.

11. J. H. Markgraf, S. H. Brown, H. W. Kaplinsky, and R. G. Peterson, *J. Org. Chem.*, **29**, 2629 (1964).
12. R. A. Cox and K. Yates, *Can. J. Chem.*, **61**, 2225 (1983).
13. A. A. Bliznyuk and A. A. Voityuk, *Zh. Strukt. Khim.*, **27**, 190 (1986).
14. M. W. Schmidt, K. K. Baldrige, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. J. Su, T. L. Windus, M. Dupuis, and J. A. Montgomery, *J. Comput. Chem.*, **14**, 1347 (1993).