PROTOLYTIC EQUILIBRIUM OF THE

ISOMERIC PHENYL-1,2,4-TRIAZINES*

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*The protonation constants for the first and second stages (pK_{BH+}, pK_{BH2+}) of a series of 1,2,4-triazines with a phenyl substituent at various positions in the ring were determined in aqueous solution by a spectrophotometric method. The values of the basicity constants characterizing the first protonation of the heterocycles investigated was in the range of acidity of the medium of pH 3.5 to H_0 -2, and the second from H_0 -7.3 to H_0 -8.7. The position of the phenyl substituent proved to have a significant effect on the size of pK_{BH+}. According to the results of ab initio calculations using HF/6-31G** for the heterocycles investigated the $1H^+$ form is thermodynamically most stable among the monocations, with the exception of 6-phenyl-1,2,4-triazine for which the existence of the monocation in the $1H^+$ and $2H^+$ forms are equally probable. In the case of the dications of all the triazines the $2,4$-H,H^{2+} tautomer is the most preferred. The aromaticity of the 1,2,4-triazine ring is changed insignificantly on mono- and diprotonation.*

Keywords: 1,2-triazines, nonempirical calculations, protolytic eqiuilibria, prototropic tautomerism, basicity, acidity function.

Many practically important properties of 1,2,4-triazines, including the known high biological activity of compounds of this series [1,2], are mainly determined by their ability to act as bases. In spite of the obvious urgency of investigating protolytic equilibria involving the 1,2,4-triazine ring, there is insufficient quantitative data on the size of pK_{BH+} for compounds of this series. Basicity constants are discussed in the literature only for certain functionally substituted compounds for which protonation is possible not only on the triazine ring but also at the exocyclic group [3]. It is evident that it is difficult to form an opinion on the basicity of strictly the 1,2,4-triazine heterocyclic system on the basis of these data. We succeeded in discovering the pK_{BH+} value of only one of the simplest nonannelated 1,2,4-triazines (3,5,6-trimethyl-1,2,4-triazine: pK_{BH+} 2.85 [4]). Quantitative data are known on protolytic equilibria involving certain annelated 1,2,4-triazines. The highest basicity in the imidazo[1,2-*b*]-1,2,4-triazine system is possessed by the nitrogen atom at position 5 of the imidazole ring. The basicity of the latter is reduced significantly on excitation [5,6]. Analogously the first protonation of 1,2,4-triazolo[4,3-*b*]-1,2,4-triazine occurs predominantly in the azole fragment, while diprotonation occurs in the azine fragment [7].

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* Dedicated to the 70th birthday of Professor G. I. Koldobskii

The spectral characteristics of monocyclic 1,2,4-triazines are discussed in a series of publications, enabling judgement on electron-donating properties of both the heterocycle as a whole and of each of the nitrogen atoms in it. It was shown that the signals of the ring nitrogen atoms in ^{15}N NMR spectra varied significantly [8-10]. It may be expected that the nitrogen atoms in positions 1 and 2 possess the highest electron-donating properties. In [11,12] it was shown experimentally (^{14}N and ^{15}N NMR spectroscopy) that both protonation and quaternization of 1,2,4-triazines take place predominantly at the N^1 and N^2 atoms. It was shown that steric factors prove to have a significant effect on the direction of quaternization of 1,2,4-triazines. However a quantitative determination of the sizes of pK_{BH+} of these heterocycles was not carried out.

Theoretical investigations of the basicity of the 1,2,4-triazine ring and the tautomerism of the corresponding conjugate acids were carried out in [13,14]. According to the calculations the most probable center for protonation of unsubstituted 1,2,4-triazine in the gas phase is the nitrogen at position 2 and the least preferred is that in position 4 [14]. The basicity of unsubstituted 1,2,4-triazine was estimated (pK_{BH+} -1.77) on the basis of the dependence of the mean local ionization energy on known values of pK_{BH+} of azoles and azines [15]. A somewhat higher basicity for this heterocycle (pK_{BH+} -0.02) is expected on the basis of a correlation of the theoretically calculated protonation energies in the gas phase and the values of representative basicity constants in solution obtained for azines [16].

It may be noted that in spite of the abundance of varied publications devoted to the structure and physicochemical properties of 1,2,4-triazines, it is extremely difficult to make a judgement on the basicity of this heterocycle and its derivatives in solution.

In the present work we have experimentally determined (spectrophotometric method) in aqueous solution the first and second protonation constants (pK_{BH+}, pK_{BH2+}) of a series of 1,2,4-triazines with a phenyl substituent at various positions in the ring (1-7). Theoretical calculations (*ab initio* HF/6-31G**) have been carried out of the total energy of the isomeric 3-, 5-, and 6-phenyl-1,2,4-triazines (1,2,8) and their conjugate acids, and also of the unsubstituted triazine 9 in the gas phase.
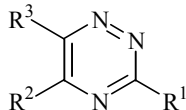
1 R^1 = Ph, R^2 = R^3 = H; 2 R^1 = R^3 = H, R^2 = Ph; 3 R^1 = R^2 = R^3 = Ph; 4 R^1 = Ph, R^2 = Me, R^3 = H;
5 R^1 = Me, R^2 = H, R^3 = Ph; 6 R^1 = R^3 = Ph, R^2 = H; 7 R^1 = 4-Cl-C$_6$H$_4$, R^2 = H, R^3 = Ph;
8 R^1 = R^2 = H, R^3 = Ph; 9 R^1 = R^2 = R^3 = H

A special feature of the electronic structure of the 1,2,4-triazine ring is the presence of three nonequivalent nitrogen atoms of the pyridine type, each of which is a potential center of basicity. On protonation of these heterocycles it is theoretically possible to generate three forms of monocation and three forms of dication (Scheme 1).

According to literature data of [12,14] protonation at the nitrogen atom in position 4 is of low probability. The low stability of the 4H[+] tautomer (1d-9d) may be explained by the retention on protonation of the mutual repulsion of the lone electron pairs of the ring nitrogen atoms in positions 1 and 2, which destabilizes the system significantly [17]. In the case of the dications it may be expected that the 1,2-H,H^{2+} form (1e-9e) will be unstable due to the mutual repulsion of the neighboring NH fragments, which was recorded previously for azoles and diazines [3,16,18].

In the electronic absorption spectra of heterocycles 1-7 in media of various acidities it is possible to separate three bands corresponding to the absorption of free base, mono-, and diprotonated forms (Figs. 1, 2). In all cases, a bathochromic shift of the absorption maxima occurs on going from free base to the conjugate acid (Table 1), which is characteristic in the case of aromatic nitrogen-containing heterocycles [16,19]. The intensity of the observed absorption bands on mono- and diprotonation is changed insignificantly. Attention should be

Scheme 1
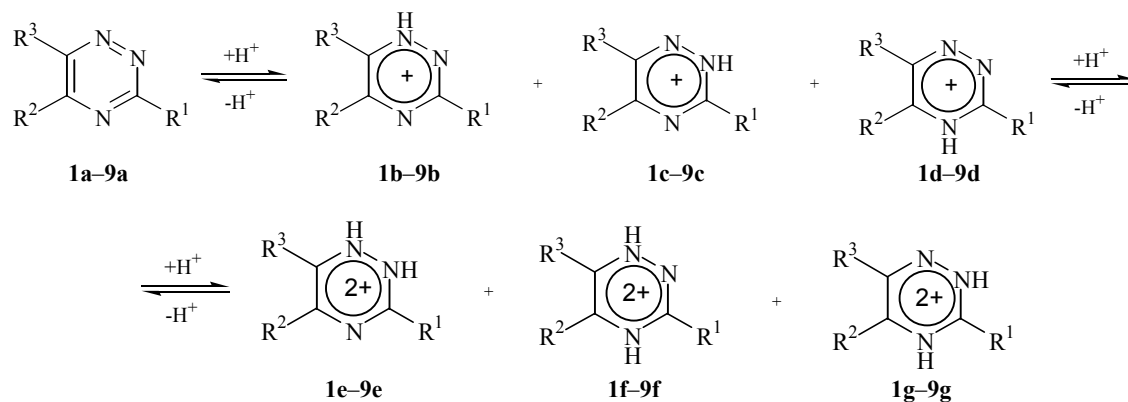
paid to the absence of sharp isobestic points in the electronic spectra of triazines **1-7**. This may be explained both by the influence of solvation effects, and by the presence of a mixture of tautomeric forms of the mono- and dications having different spectral characteristics [20].

The dependences of molar extinction coefficient (ε) on the acidity of the medium (pH, H_0), corresponding to the first and second protonation of heterocycles **1-7** has the typical S-shape characteristic of equilibrium processes (Fig. 3).

The values of pK_{BH+} and pK_{BH2+} of the compounds being investigated (Table 2) were calculated from the dependencies of the ionization relationships on acidity of the medium in pH or H_0 scales according to equations 1-3 [21,22].

$$\lg I = -m \cdot H_0 + pK'_{BH+}, \quad pK_{BH+} = pK'_{BH+} / m \tag{1}$$

$$\lg I = -x \cdot pH + pK'_{BH+}, \quad pK_{BH+} = pK'_{BH+} / x \tag{2}$$

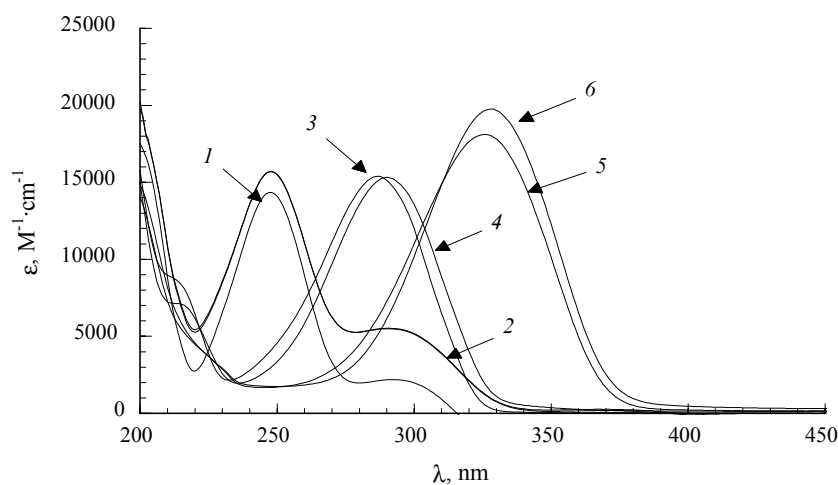$$\lg I = -m \cdot H_0 + pK'_{BH2+}, \quad pK_{BH2+} = pK'_{BH2+} / m \tag{3}$$

Fig. 1. UV absorption spectra of 3-methyl-6-phenyl-1,2,4-triazine (**5**) in aqueous buffer solutions and in aqueous solutions of sulfuric acid: 1) pH 7.43; 2) pH 4.93; 3) pH 2.93; 4) H_0 -5.63; 5) H_0 -8.3; 6) H_0 -9.15.
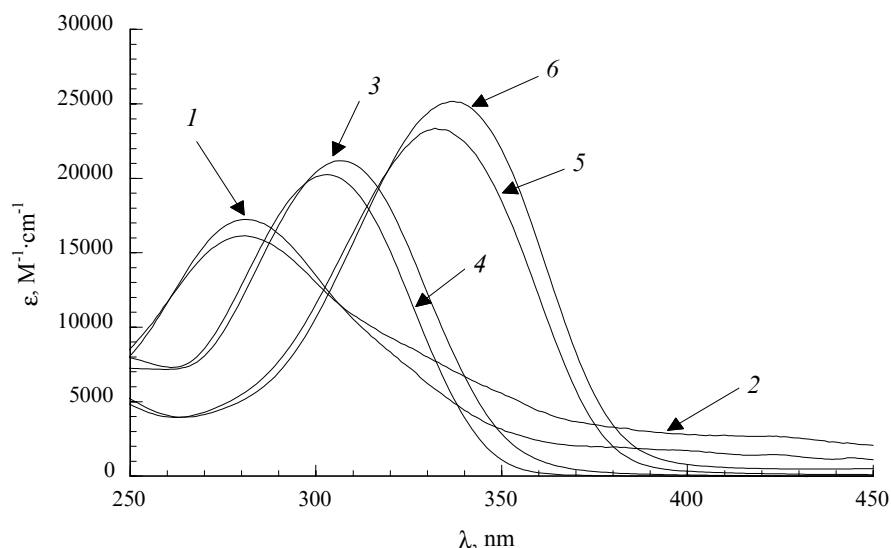
Fig. 2. UV absorption spectra of 3,6-diphenyl-1,2,4-triazine (**6**) in aqueous buffer solutions and in aqueous solutions of sulfuric acid: 1) pH 3.34; 2) pH 4.27; 3) H_0 -6.2; 4) H_0 -3.4; 5) H_0 -5.8; 6) H_0 -9.45.

The ratio of the free term to the slope of the linear dependence of log I on the acidity of the medium was applied to the values of pK_{BH+} and pK_{BH2+}, which enables errors in the final values to be avoided when the slopes differ from 1 [22].

TABLE 1. Spectral Characteristics of Compounds **1**-**7** in the Form of Free Bases, Mono-, and Dications

| Com-pound	λ^{B}_{max} (ε^{B}_{max}), medium	λ^{BH+}_{max} (ε^{BH+}_{max}), medium	λ^{BH2+}_{max} (ε^{BH2+}_{max}), medium
1	255 (17500), buffer solution: pH 5.68	265 (13000), 65.85% H_2SO_4: H_0 -5.25	280 (13000), 94.55% H_2SO_4: H_0 -9.6
2	290 (17500), 230 (7000), 255 (6000), buffer solution: pH 2.46	345 (23500), 64.5% H_2SO_4: H_0 -5.05	375 (18000), 94.55% H_2SO_4: H_0 -9.6
3	285-320 (10000), H_2SO_4: pH 1	325 (32000), 64.5% H_2SO_4: H_0 -5.05	335 (28000), 94.55% H_2SO_4: H_0 -9.6
4	250 (17000), buffer solution: pH 5.68	280 (14500), 30.20% H_2SO_4: H_0 -1.8	270 (15000), 305 (11500), 94.55% H_2SO_4: H_0 -9.6
5	250 (16000), buffer solution: pH 7.43	290 (16000), H_2SO_4: pH 1	330 (20500), 94.55% H_2SO_4: H_0 -9.6
6	280 (15000) buffer solution: pH 3.96	300 (18700) 5.45% H_2SO_4: H_0 -0.15	340 (25000), 91.9% H_2SO_4: H_0 -9.1
7	300 (6500), buffer solution: pH 1	306 (20600) 41.47% H_2SO_4: H_0 -2.6	370 (29000), 91.9% H_2SO_4: H_0-9.1

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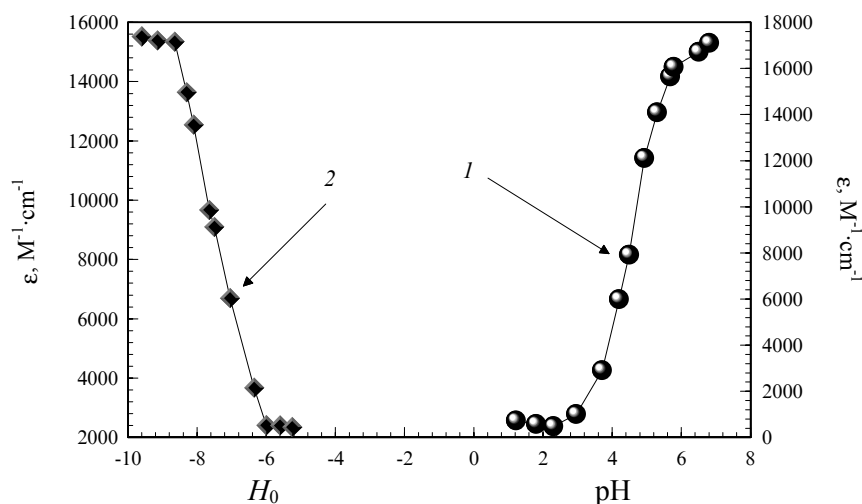
Fig. 3. Dependence of molar extinction coefficient of 3-methyl-6-phenyl-1,2,4-triazine (**5**) on the acidity of the medium at the analytical wavelengths 340 nm for curve 1, and 240 nm for curve 2.

The solvation coefficients (m, x) in equations (1-3) for triazines **1-7** were close to unity in the majority of cases, which indicates that these heterocycles are protonated analogously to the standard base of Hammett [21].

TABLE 2. Parameters of Equations (1-3) for Heterocycles **1-7**

Com-pound	R^3	R^5	R^6	λ_{anal}, nm	pK_{BH+}	m, x	r	n
First protonation								
1	Ph	H	H	250	2.43±0.04	1.10±0.01	0.998	6
2	H	Ph	H	290	0.18±0.01	1.07±0.01	0.998	7
3	Ph	Ph	Ph	330	-1.79±0.03	1.04±0.01	0.996	5
4	Ph	Me	H	305	1.26±0.02	0.94±0.01	0.991	7
5	Me	H	Ph	340	3.45±0.03	1.03±0.01	0.998	6
6	Ph	H	Ph	—*	2.38±0.01	1.09±0.03	0.980	8
7	4-ClC$_6$H$_4$	H	Ph	—*	-0.41±0.01	0.81±0.03	0.977	5

Com-pound	R^3	R^5	R^6	λ_{anal}, nm	pK_{BH2+}	m	r	n
Second protonation								
1	Ph	H	H	320	-8.09±0.14	1.06±0.12	0.994	5
2	H	Ph	H	400	-8.03±0.53	0.68±0.03	0.993	5
3	Ph	Ph	Ph	290	-8.66±0.23	0.78±0.09	0.997	6
4	Ph	Me	H	250	-8.61±0.21	1.15±0.10	0.997	6
5	Me	H	Ph	240	-7.47±0.60	0.85±0.11	0.994	5
6	Ph	H	Ph	351	-7.34±0.24	0.84±0.12	0.996	6
7	4-ClC$_6$H$_4$	H	Ph	-*	-7.37±0.47	0.68±0.06	0.991	5

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* Calculated from the dependence of the shift of λ_{max} on the acidity of the medium.

According to the results obtained 1,2,4-triazines in the form of free bases **1a-7a** are relatively strong organic bases. This is in agreement with the assessment of the basicity considered above for this heterocyclic system. 1,2,4-Triazines are close to diazines as bases [18] and are significantly weaker than 1,2,4,5-tetrazines [23]. Considering that protonation of the ring occurs preferentially at the nitrogen atoms in positions 1 and 2, it is expedient to compare this heterocycle with pyridazine (pK_{BH+} 2.24 [18]). It may be noted that the influence of the additional nitrogen atom in the ring for 1,2,4-triazines compared with pyridazine is extremely insignificant and consequently the basicity of the azine ring is mainly determined not so much by the number of nitrogen atoms in the ring as by their mutual disposition. The sizes of the basicity constants characterizing the first protonation of heterocycles **1-7** are within the range of acidity of the medium from pH 3.5 to H_0 -2. The fairly broad spread of pK_{BH+} values is caused evidently by the specific influence of the phenyl substituent in the different positions of the heterocycle. This may lead to the formation of monocations of various structure (Scheme 1) (protonation at the atoms in positions 1 and 2). Such a strongly differing influence of a substituent in different positions of the 1,2,4-triazine ring on its electron-donating characteristics has been recorded previously [12,24,25].

In the case of the second stage of protonation of phenyl-1,2,4-triazines the spread of values of pK_{BH2+} is insignificant (from H_0 -7.3 to H_0 -8.7). The difference between the values of pK_{BH+} and pK_{BH2+} is about 8-9 units. A similar picture was recorded previously for diazines [18].

To interpret the experimental data obtained we carried out a series of theoretical calculations by the *ab initio* method, which adequately describes the various properties and characteristics of the heterocyclic system being studied [14,17]. We have calculated values of the total and relative energy of the free base of unsubstituted 1,2,4-triazine **9a**, and of its mono- and diprotonated forms **9b-g** using HF/6-31G** (Table 3, Fig. 4). As was noted previously in [14], the 2H$^+$ form of monocation **9c** was the most stable thermodynamically. Among the dications the most stable was the 2,4-H,H^{2+} tautomer **9g**. On the basis of the calculated ring geometry the aromaticity of all the possible prototropic forms was calculated by the method of Pozharskii [14]. It may be noted that on mono- and diprotonation the aromaticity of the ring is changed insignificantly. This distinguishes 1,2,4-triazine from other azines, for which the reduction of aromaticity on protonation is substantial [23,26,27]. It is possible that the unimportant change of aromaticity among other factors serves to explain the relatively high basicity of 1,2,4-triazines.

TABLE 3. Values of the Total and Relative Energies of 1,2,4-Triazine (**9**) in Various Prototropic Forms, Calculated Using HF/6-31G**; Aromaticity according to Pozharskii (benzene, A 100%)

Form	E_T, a.u.	ΔE^*, kcal/mol	A, %
9a	-278.647176	—	78
9b	-278.933362	5.10	63
9c	-279.001484	0	58
9d	-278.980810	12.97	67
9e	-279.121440	12.39	48
9f	-279.137712	2.18	52
9g	-279.141182	0	63

* Relative to the thermodynamically most stable form of the mono- and dication (1 a.u. = 627.52 kcal/mol).
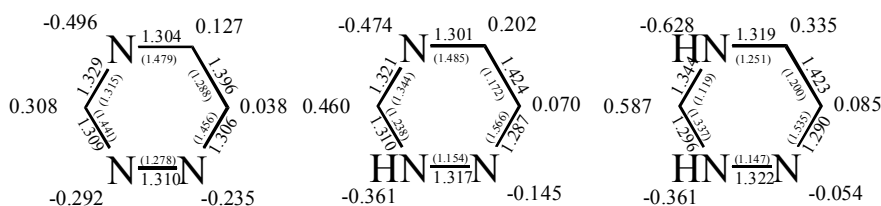
Fig. 4. Molecular diagrams of the free base of 1,2,4-triazine (**9a**) and of the thermodynamically most stable forms of its mono- and dications (**9c,g**) calculated *ab initio* using HF/6-31G**.

TABLE 4. Values of the Total and Relative Energies of the Neutral Bases and Monoprotonated Forms of Phenyl-1,2,4-triazines (**1**, **2**, **8**) Calculated Using HF/6-31G**

Com-pound	E_T, a.u.	ΔE^*, kcal/mol	Com-pound	E_T, a.u.	ΔE^*, kcal/mol
1a	-508.212808	—	**2c**	-508.586189	0
1b	-508.571361	8.30	**2d**	-508.563580	14.19
1c	-508.584590	0	**8a**	-508.207627	—
1d	-508.562085	14.12	**8b**	-508.574128	0
2a	-508.210410	—	**8c**	-508.574118	0.01
2b	-508.571257	9.37	**8d**	-508.552643	13.48

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* Relative to the thermodynamically most stable forms of the mono- and dication (1 a.u. = 627.52 kcal/mol).

With the aim of interpreting the abovementioned significant influence of a phenyl substituent on the scheme of monoprotonation of 1,2,4-triazines we calculated the absolute energies of the free bases of 3-, 5-, and 6-phenyl-substituted 1,2,4-triazines (**1a**, **2a**, **8a**) and their monoprotonated forms (**1b-d**, **2b-d**, **8b-d**) with full optimization of the geometry on the same basis in the gas phase (Table 4). As is seen from the Table, for the 3- and 5-phenyl derivatives, as for the unsubstituted 1,2,4-triazine, protonation at the nitrogen atom in position 2 is the most probable. In the case of 6-phenyltriazine the difference in energies of the 1H$^+$ and 2H$^+$ tautomers (**8b** and **8c**) at 0.01 kcal/mol was insignificant. Consequently practically equal probabilities exist for protonation at position N^1 and for position N^2. The different character of the influence of a phenyl substituent in the 1,2,4-triazine ring on its electron-donating properties is therefore confirmed.

EXPERIMENTAL

The UV absorption spectra were recorded on a Perkin-Elmer Lambda 40 spectrophotometer. The concentration of sulfuric acid in aqueous solutions was determined by potentiometric titration with a precision of ±0.2 wt. %. The values of the acidity function H_0 were taken from [28]. For studying basicity aqueous buffer solutions of ionic strength μ 0.01 were used, prepared according to [29]. The model heterocycles **1-7** were synthesized and purified by known methods: compound **1** as described in [30], compounds **2**, **3**, **4**, **7** as in [31], and compounds **5**, **6** as in [32].

The *ab initio* calculations were carried out using the GAMESS programs [33].

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