Heteroatom Chemistry
Volume 13, Number 3, 2002

Quantitative Structure–Property Relationships in the Pyridine Series

Alexei N. Pankratov

Department of Chemistry, N. G. Chernyshevskii Saratov State University, 83 Astrakhanskaya Street, Saratov 410026, Russia

Received 14 March 2001; revised 31 August 2001

ABSTRACT: *By means of the MNDO, AM1, and PM3 methods, standard heats of formation, entropies, ionization potentials, and molecular dipole moments of the pyridine series compounds have been computed. The information on the experimental values of the above quantities has been systematized. Linear dependencies allowing a priori evaluation of thermodynamic and molecular characteristics of pyridines have been stated. Correlations of the 2,2′-bipyridines* pK_a *values for aqueous solutions with the gaseous-phase proton affinities have been found.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:229–241, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10013

INTRODUCTION

Pyridine is one of the key compounds in chemistry. A pyridine ring enters the composition of many natural substances, in particular, alkaloids [1]. The pyridine series compounds are physiologically active [1,2], serve as drugs [1,3], antisepses, vitamins, insecticides, herbicides, fungicides, monomers, solvents, corrosion inhibitors, and water-resistant agents [3]. In agriculture, pyridines are used as the plant growth regulating agents and pesticides [3]. Pyridine and its derivatives have gained widespread and diversified acceptance in analytical chemistry [2,4,5].

For directed synthesis of pyridines with the given properties, an a priori evaluation of thermodynamic and molecular characteristics of the said compounds is of importance.

2,2′-Bipyridine and its derivatives are significant chelating reagents and redox indicators [2,4,5]. Their protonation exhibits a competing reaction in relation to complexation. Molecular design of 2,2′-bipyridines demands for quantitative relationships for the pK_a evaluations.

It would be reasonable to assume that in aqueous solutions, basicity of bipyridines (characterized by the pK_a values) is determined to a significant extent by the molecular electronic structure, and by electronic effects of substituents in the aromatic ring. An integral measure of intramolecular factors involved in amines basicity could be proton affinity (PA). The latter presents reaction enthalpy for proton breaking-off in the gaseous phase:

$$BH^+ \rightarrow B + H^+$$

and is calculated using semiempirical quantum chemical methods by the formula [6,7]:

$$PA = \Delta H_f(B) + \Delta H_f(H^+) - \Delta H_f(BH^+)$$

The present work is aimed at quantum chemical investigation of the pyridine series compounds electronic structure, correlations establishments of experimental values of heats of formation (ΔH_f), entropies (S), ionization potentials (I), and molecular dipole moments (μ) with the computed ones, as well as at relationships statement of the 2,2′-bipyridines

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Correspondence to: Alexei N. Pankratov; e-mail: pankratovan@info.sgu.ru.

Contract grant sponsor: International Soros Science Education Program.
Contract grant number: d96-16 and d97-1381.

pK_a values (characterizing their basicity in aqueous solutions) with the gaseous-phase proton affinities.

The species under study were pyridine and its 231 derivatives, the molecules of which contain C, H, N, O, F, Si, S, Cl, Br, and I atoms (Tables 1–4), along with 2,2′-bipyridine and its 8 substituted derivatives.

The semiempirical quantum chemical methods would be reasonable to use for obtaining simplified predictive quantitative relations. For the series of compounds, we have established a correctness of the most important thermodynamic and molecular characteristics reproduction [9–16] by the MNDO [17], AM1 [18], and PM3 [19] methods, as well as of electronegativity, inductive, and mesomeric parameters of atomic groups [20]. It has been the above mentioned methods that we have used for solving the problems of the present work.

COMPUTATIONAL METHODS

The computations were performed using the software from the MOPAC package [21,22] with the complete geometry optimization (Broyden–Fletcher–Goldfarb–Shanno function minimizer) [23] involving Thiel's fast minimization algorithm [24]. The preliminary optimization was realized by the molecular mechanics method (the MMX procedure) [25] with the software of the PCMODEL complex [25]. In quantum chemical computations, the condition of the gradient norm not exceeding 0.02 kcal/(mol Å) was preset. In some cases, the sufficient decrease in gradient norm was achieved by means of abandonment of the Thiel's fast minimization routine (the keyword NOTHIEL of the MOPAC package was applied), or under optimization with the Davidon–Fletcher–Powell method (keyword DFP) [23], or using combined approaches involving the keywords NOTHIEL and DFP.

For molecules with closed electronic shells, the restricted Hartree–Fock (RHF) formalism was used. Computations of pyridylmethyl radicals were conducted by the unrestricted Hartree–Fock (UHF) method [22]. In calculating the rotational contributions to thermodynamic functions the symmetry number was taken as unity. The regression analysis was performed with the confidence level of 0.95.

RESULTS AND DISCUSSION

The ΔG_f values were calculated from the relationship:

$$\Delta G_f = \Delta H_f - T\Delta S_f$$

TABLE 1 Experimental and Computed Values of Standard Heats of Formation

		$\Delta H_{f\,theor}$ *(kcal/mol)*		
Compound	$\Delta H_{f\,exper}$ *(kcal/mol)*	*MNDO*	*AM1*	*PM3*
Pyridine	33.50	28.82	32.04	30.37
2-Methylpyridine (2-picoline)	23.65	19.75	25.69	21.15
3-Methylpyridine (3-picoline)	24.76	20.49	24.09	20.83
4-Methylpyridine (4-picoline)	24.80	20.86	24.16	20.78
2,3-Dimethylpyridine (2,3-lutidine)	16.31	13.53	18.44	12.27
2,4-Dimethylpyridine (2,4-lutidine)	15.26	11.88	17.87	11.61
2,5-Dimethylpyridine (2,5-lutidine)	15.87	11.35	17.74	11.67
2,6-Dimethylpyridine (2,6-lutidine)	14.02	10.85	19.50	12.04
3,4-Dimethylpyridine (3,4-lutidine)	16.73	14.82	16.75	11.89
3,5-Dimethylpyridine (3,5-lutidine)	17.39	12.24	16.17	11.35
2-Cyanopyridine (picolinonitrile)	67.09	60.30	67.95	67.04
3-Cyanopyridine (nicotinonitrile)	66.42	59.73	63.94	66.33
4-Cyanopyridine (isonicotinonitrile)	67.76	60.92	64.85	66.73
3-Carboxypyridine (nicotinic acid, niacin)	−52.94	−60.03	−57.54	−58.72
2-Aminopyridine	28.23	25.80	32.98	26.43
3-Aminopyridine	34.46	29.31	30.08	28.19
4-Aminopyridine	31.05	28.35	29.07	27.46
2-Hydroxypyridine	−19.0	−24.97	−11.77	−18.07
3-Hydroxypiridine	−10.4	−18.55	−11.61	−14.22
4-Hydroxypyridine	−7.24	−19.96	−12.70	−15.22
6-Methyl-2-hydroxypyridine	−28.75	−33.80	−17.98	−27.93
2-Methyl-3-hydroxypyridine	−20.2	−25.96	−17.60	−22.88
6-Methyl-3-hydroxypyridine	−16.7	−27.59	−17.86	−23.26
2-Methyl-4-hydroxypyridine	−17.1	−28.83	−19.04	−24.41
2,2′-Bipyridine	64.03	58.84	71.90	62.66
2,4′-Bipyridine	67.93	60.09	68.99	62.40
4,4′-Bipyridine	70.05	61.22	68.09	61.81

TABLE 2 Experimental and Computed Values of Standard Entropies

		S_{theor} *(cal/(mol K))*		
Compound	S_{exper} *(cal/(mol K))*	*MNDO*	*AM1*	*PM3*
Pyridine	67.59	68.62	68.65	69.13
2-Methylpyridine (2-picoline)	77.68	76.39	76.69	78.65
3-Methylpyridine (3-picoline)	77.67	76.37	76.43	77.42

where the standard entropies of formation ΔS_f were calculated by the formula:

$$\Delta S_f = S - \Sigma_i \quad S_i$$

in which S_i are the entropies of the elements constituting molecule in their standard states [26,27] in view of H, N, O, F, rhombic S, Cl, Br, I being the two-atomic molecules; $T = 298.15$ K. The results obtained are presented in Tables 1–4.

In a number of cases, the problem might come to mind about the ambigous optimal conformations of molecules. To clarify the questions related to the conformational state of molecular systems, we came up against the necessity of analyzing a series of works ([28–40] and others). Once we have decided upon the use of quantum chemical methods to perform the conformational analysis, the bulk of research could be multiplied many times. The optimal conformations of several molecules are given as an example.

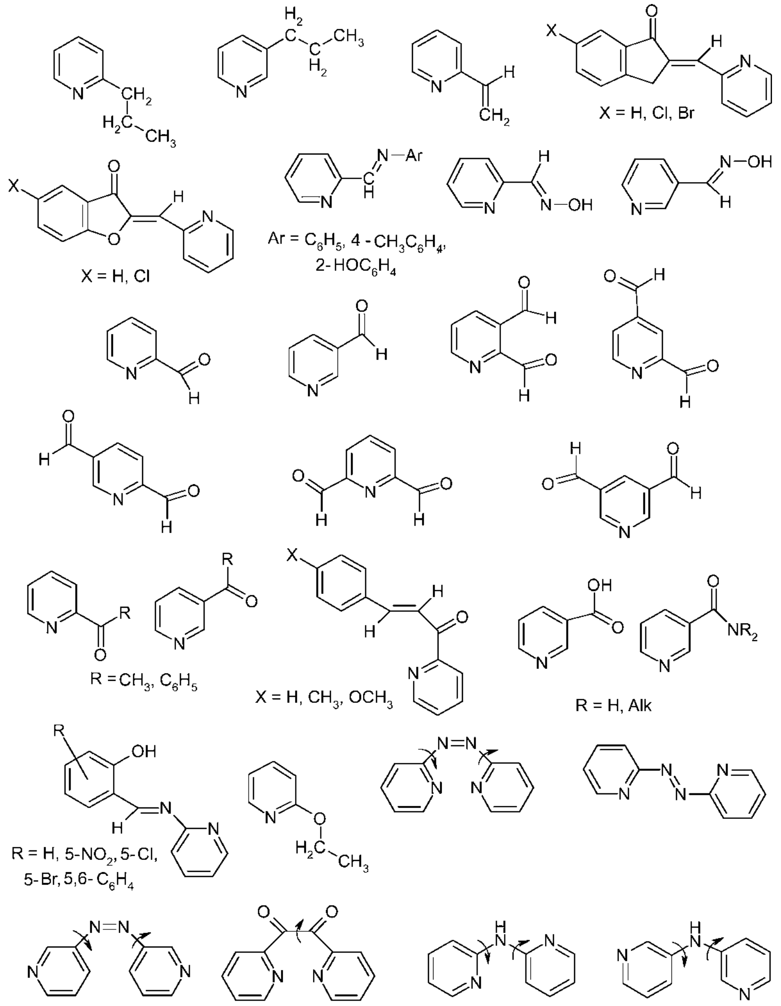

TABLE 3 Measured (Adiabatic or Vertical) and Computed[a] Ionization Potentials

			I_{theor} *(eV)*		
Compound	I_{exper} *(eV)*	*Determination Method*	*MNDO*	*AM1*	*PM3*
Pyridine	9.85	Electron impact	9.69	9.93	10.10
2-Methylpyridine (2-picoline)	9.56	Electron impact	9.57	9.63	9.80
3-Methylpyridine (3-picoline)	9.04	Photoionization	9.59	9.64	9.81
4-Methylpyridine (4-picoline)	9.67	Electron impact	9.68	9.89	10.06
2,3-Dimethylpyridine (2,3-lutidine)	8.85	Photoionization	9.48	9.41	9.60
2,4-Dimethylpyridine (2,4-lutidine)	8.85	Photoionization	9.56	9.59	9.75
2,5-Dimethylpyridine (2,5-lutidine)	8.80[b]	Photoelectron spectroscopy	9.47	9.35	9.53
2,6-Dimethylpyridine (2,6-lutidine)	8.85	Photoionization	9.47	9.40	9.60
4-tert-Butylpyridine	9.30	Photoelectron spectroscopy	9.66	9.84	10.03
2,4,6-Tri-*tert*-butylpyridine	9.3[b]	Photoelectron spectroscopy	9.55	9.59	9.77
2-Cyanopyridine (picolinonitrile)	10.12[b]	Photoelectron spectroscopy	10.10	10.31	10.44
3-Cyanopyridine (nicotinonitrile)	10.10[b]	Photoelectron spectroscopy	10.11	10.31	10.44
4-Cyanopyridine (isonicotinonitrile)	10.30[b]	Photoelectron spectroscopy	10.15	10.43	10.63
2-Formylpyridine	9.75	Electron impact	10.00	10.23	10.36
4-Formylpyridine	10.12	Electron impact	9.98	10.25	10.38
2-Aminopyridine	8.34[b]	Photoelectron spectroscopy	9.09	8.84	8.83
3-Aminopyridine	8.44[b]	Photoelectron spectroscopy	9.06	8.79	8.90
4-Aminopyridine	8.97	Electron impact	9.52	9.14	9.10
2-Hydroxypyridine	9.11[b]	Photoelectron spectroscopy	9.23	9.44	9.52
3-Hydroxypyridine	9.15[b]	Photoelectron spectroscopy	9.24	9.45	9.55
4-Hydroxypyridine	9.70	Electron impact	9.75	9.95	9.85
2-Methoxypyridine	8.82[b]	Photoelectron spectroscopy	9.16	9.29	9.43
4-Ethoxypyridine	9.25[b]	Photoelectron spectroscopy	9.63	9.73	9.70
2-Fluoropyridine	9.85[b]	Photoelectron spectroscopy	9.85	9.92	10.21
2-Trimethylsilylpyridine	8.90[b]	Photoelectron spectroscopy	9.64	9.75	9.55
4-Trimethylsilylpyridine	9.30[b]	Photoelectron spectroscopy	9.64	9.82	9.81
2-Chloropyridine	9.91	Electron impact	9.92	9.88	9.65
4-Chloropyridine	10.15	Electron impact	10.06	10.22	9.92
2-Bromopyridine	9.65	Electron impact	9.84	9.89	10.11
4-Bromopyridine	9.94	Electron impact	9.98	10.23	10.37
2-Pyridylmethyl radical	8.17[b]	Electron impact	9.15	9.05	9.09
3-Pyridylmethyl radical	7.92[b]	Electron impact	8.95	8.88	9.00
4-Pyridylmethyl radical	8.40[b]	Electron impact	9.39	9.28	9.29

[a] Koopmans theorem [8].
[b] Vertical ionization potential.

In Tables 1–4, the known experimental values of standard heats of formation (ΔH_f) [26,41–46], entropies (S) [26], ionization potentials (I) [47–54], and molecular dipole moments (μ) [29–40,55–61] of pyridine and its derivatives are systematized, and also the computed values are presented.

On the MNDO consideration, all the heats of formation deviate from the experimental values to the negative side. A similar situation takes place for PM3, with the only difference that for 2-hydroxy- and 6-methyl-2-hydroxypyridines the computations overestimate to some extent the experimental quantities, and for 2- and 3-cyanopyridines the computed enthalpies of formation practically coincide with the measured ones.

For almost all the species studied, the AM1 and PM3 methods overevaluate the computed ionization potentials as compared to the experimental ones. The only exceptions are 2- (AM1, PM3) and 4-chloropyridines (PM3).

According to all three methods MNDO, AM1, and PM3, the positive deviations of computed quantities from the experimental ones predominate by value for the ionization potentials, and the negative deviations for the dipole moments.

The symbate behavior of the P_{theor} and P_{exper} values (P is ΔH_f, S, I, or μ) along with a good agreement of the computed values with experimental ones allows the linear relation between them to be assumed. And really the dependence $P_{\text{exper}} = \boldsymbol{b} P_{\text{theor}}$ is adequate.

In Table 5 the values of $\boldsymbol{b}$, correlation coefficients **r**, as well as the following conventional quantities: MS (mean signed; average value for $P_{\text{theor}} - P_{\text{exper}}$), and MU (mean unsigned; average value for $|P_{\text{theor}} - P_{\text{exper}}|$) are shown.

TABLE 4 Measured by the Second Debye Method and Computed Values of Dipole Moments

			μ_{theor} (D)		
Compound	μ_{exper} (D)	*Conditions*	*MNDO*	*AM1*	*PM3*
Pyridine	2.20	Benzene, 298 K	1.97	1.97	1.94
2-Methylpyridine (2-picoline)	1.96	Benzene, 298 K	1.85	1.78	1.75
3-Methylpyridine (3-picoline)	2.41	Benzene, 298 K	1.94	2.15	2.10
4-Methylpyridine (4-picoline)	2.57	Benzene, 298 K	2.03	2.32	2.28
2,3-Dimethylpyridine (2,3-lutidine)	2.20	Benzene	1.78	1.94	1.91
2,4-Dimethylpyridine (2,4-lutidine)	2.30	Benzene	1.91	2.10	2.08
2,5-Dimethylpyridine (2,5-lutidine)	2.15	Benzene	1.80	1.85	1.83
2,6-Dimethylpyridine (2,6-lutidine)	1.65	Benzene, 298 K	1.72	1.48	1.48
3,5-Dimethylpyridine (3,5-lutidine)	2.58	Benzene	1.89	2.24	2.19
2,4,6-Trimethylpyridine (collidine)	1.93	Benzene, 283–313 K	1.78	1.78	1.78
2-Ethylpyridine	1.71	Liquid	1.80	1.69	1.68
3-Ethylpyridine	2.41	Benzene, 298 K	1.94	2.15	2.12
4-Ethylpyridine	2.65	Benzene	2.07	2.40	2.32
2-Propylpyridine	1.91	Benzene, 298 K	1.78	1.66	1.66
3-Propylpyridine	2.45	Benzene, 298 K	1.94	2.17	2.12
4-Propylpyridine	2.70	Benzene, 298 K	2.12	2.43	2.39
3-Isopropylpyridine	2.43	Benzene, 298 K	1.96	2.17	2.10
4-Isopropylpyridine	2.70	Benzene, 298 K	2.10	2.34	2.26
2-Butylpyridine	1.90	Benzene, 298 K	1.79	1.65	1.72
3-Butylpyridine	2.47	Benzene, 298 K	1.94	2.16	2.05
4-Butylpyridine	2.72	Benzene, 298 K	2.13	2.45	2.40
4-*sec*-Butylpyridine	2.72	Benzene, 298 K	2.05	2.47	2.42
4-*tert*-Butylpyridine	2.73	Benzene, 298 K	2.15	2.43	2.36
2-Amylpyridine	1.90	Benzene, 298 K	1.79	1.65	1.65
4-Amylpyridine	2.72	Benzene, 298 K	2.14	2.46	2.41
4-Diethylmethylpyridine	2.74	Benzene, 298 K	2.14	2.40	2.32
2-Aminomethylpyridine	2.25	Benzene	0.973	1.67	1.06
3-Aminomethylpyridine	2.52	Benzene	3.16	3.23	3.13
4-Aminomethylpyridine	2.84	Benzene	2.78	2.68	2.69
2-(2-Amino)ethylpyridine	2.51	Carbon tetrachloride, 298 K	1.62	1.18	1.51
2-(2-*N*,*N*-Dimethylamino)ethylpyridine	2.31	Carbon tetrachloride, 298 K	1.86	1.07	1.68
4-(2-Amino)ethylpyridine	3.18	Carbon tetrachloride, 298 K	2.12	2.20	2.15
4-(2-*N*,*N*-Dimethylamino)ethylpyridine	3.03	Carbon tetrachloride, 298 K	2.17	2.29	2.12
Nicotine	2.62	Benzene, 298 K	2.07	2.45	2.47
Anabasine	2.26	Benzene, 293 K	1.61	1.89	1.79
2-Hydroxymethylpyridine (piconol)	3.03	Benzene, 298 K	2.28	2.61	2.51
3-Hydroxymethylpyridine	2.74	Benzene, 298 K	3.14	3.44	3.36
4-Hydroxymethylpyridine	2.60	Benzene, 298 K	2.98	3.18	3.16
2,6-Di(hydroxymethyl)pyridine	2.82	Dioxane, 298 K	1.34	2.17	2.02
2-(2-Hydroxy)ethylpyridine	3.37	Benzene, 298 K	1.68	1.61	1.44
2-(3-Hydroxy)propylpyridine	3.17	Benzene, 298 K	2.73	2.97	2.77
3-(3-Hydroxy)propylpyridine	2.82	Benzene, 298 K	3.27	3.58	3.47
4-(3-Hydroxy)propylpyridine	3.09	Benzene, 298 K	3.00	3.21	3.20
2-Vinylpyridine	1.92	Liquid, 293–333 K	1.40	1.50	1.51
4-Vinylpyridine	2.00	Liquid, 293–333 K	2.16	2.25	2.17
4-Styrylpyridine	2.70	Benzene, 298 K	2.33	2.55	2.44
4-*p*-Methoxystyrylpyridine	3.55	Benzene, 298 K	2.93	3.28	3.13
4-*p*-Chlorostyrylpyridine	1.20	Benzene, 298 K	0.342	1.08	1.39
ω-(2-Pyridyl)benzofulvene	2.63	Benzene, 293 K	2.26	2.35	2.37
ω-(3-Pyridyl)benzofulvene	1.73	Benzene, 293 K	1.82	2.10	2.08
ω-(4-Pyridyl)benzofulvene	2.13	Benzene, 293 K	1.65	1.65	1.57
2-(2′-Pyridylmethylene)-1-indanone	3.57	Dioxane,298 K	3.79	2.98	2.86
2-(2′-Pyridylmethylene)-6-chloro-1-indanone	4.98	Dioxane, 298 K	5.07	4.22	3.74
2-(2′-Pyridylmethylene)-6-bromo-1-indanone	4.87	Dioxane, 298 K	4.57	4.37	3.96
2-(3′-Pyridylmethylene)-1-indanone	3.83	Dioxane, 298 K	2.97	4.33	3.94
2-(3′-Pyridylmethylene)-6-chloro-1-indanone	4.08	Dioxane, 298 K	3.49	4.39	3.87
2-(4′-Pyridylmethylene)-1-indanone	3.36	Dioxane, 298 K	2.42	2.64	2.46

(Continued)

TABLE 4 Continued

			μ_{theor} (D)		
Compound	μ_{exper} (D)	*Conditions*	*MNDO*	*AM1*	*PM3*
2-(4′-Pyridylmethylene)-6-chloro-1-indanone	3.00	Dioxane, 298 K	2.14	2.29	2.09
2-(4′-Pyridylmethylene)-6-bromo-1-indanone	4.87	Dioxane, 298 K	2.03	2.32	2.08
2-(2′-Pyridylmethylene)benzofuran-3(2H)-one	4.39	Dioxane, 298 K	3.07	3.98	3.64
2-(2′-Pyridylmethylene)-5-chlorobenzofuran-3(2H)-one	4.78	Dioxane, 298 K	3.90	4.01	3.86
2-(3′-Pyridylmethylene)benzofuran-3(2H)-one	3.59	Dioxane, 298 K	3.27	3.84	3.52
2-(3′-Pyridylmethylene)-5-chlorobenzofuran-3(2H)-one	3.12	Dioxane, 298 K	2.52	3.24	2.97
2-(4′-Pyridylmethylene)benzofuran-3(2H)-one	2.93	Dioxane, 298 K	2.55	2.88	2.57
2-(4′-Pyridylmethylene)-5-chlorobenzofuran-3(2H)-one	1.98	Dioxane, 298 K	0.865	1.61	1.63
4-Phenylethynylpyridine	2.79	Benzene, 298 K	2.61	2.59	2.47
4-*p*-Methoxyphenylethynylpyridine	3.90	Benzene, 298 K	3.22	3.29	3.12
4-*p*-Chlorophenylethynylpyridine	1.23	Benzene, 298 K	0.441	1.13	1.42
2-Phenylpyridine	1.94	Benzene, 298 K	1.83	1.69	1.56
3-Phenylpyridine	2.28	Benzene, 298 K	2.03	2.05	2.01
4-Phenylpyridine	2.57	Benzene, 298 K	2.26	2.34	2.32
2,6-Diphenylpyridine	1.55	Benzene, 298 K	1.69	1.38	1.24
2-*o*-Tolylpyridine	2.02	Benzene, 298 K	1.81	1.66	1.39
2-*m*-Tolylpyridine	1.87	Benzene, 298 K	1.84	1.48	1.29
2-*p*-Tolylpyridine	1.78	Benzene, 298 K	1.85	1.56	1.42
2-(4-Diphenyl)pyridine	1.91	Benzene, 298 K	1.80	1.67	1.52
2-*p*-Aminophenylpyridine	2.11	Benzene, 298 K	0.631	1.26	1.77
2-*m*-Nitrophenylpyridine	4.65	Benzene, 298 K	5.96	5.23	4.96
3-*m*-Nitrophenylpyridine	3.41	Benzene, 298 K	5.11	3.88	3.41
4-*m*-Nitrophenylpyridine	4.65	Benzene, 298 K	4.34	4.97	4.49
2-*p*-Nitrophenylpyridine	5.60	Benzene, 298 K	6.59	6.78	6.87
3-*p*-Nitrophenylpyridine	3.79	Benzene, 298 K	4.73	5.08	5.15
4-*p*-Nitrophenylpyridine	1.93	Benzene, 298 K	3.17	3.49	3.63
2-Cyanopyridine (picolinonitrile)	5.23	Benzene, 298 K	4.56	4.53	4.74
3-Cyanopyridine (nicotinonitrile)	3.48	Benzene, 298 K	2.91	2.89	3.07
4-Cyanopyridine (isonicotinonitrile)	1.65	Benzene, 298 K	1.08	1.09	1.43
2-Pyridinalaniline	1.43	Benzene, 298 K	0.931	0.760	0.504
2-Pyridinal-4-toluidine	1.27	Benzene, 298 K	2.24	0.516	0.357
2-Pyridinal-2-aminophenol	2.03	Benzene, 298 K	1.87	1.86	1.56
2-Pyridinealdoxime	2.47	Dioxane, 298 K	2.16	2.09	2.09
3-Pyridinealdoxime	2.37	Dioxane, 298 K	1.71	1.68	1.52
4-Pyridinealdoxime	2.46	Dioxane, 298 K	1.67	1.67	1.71
2-Formylpyridine	3.35	Benzene, 298 K	3.56	2.94	2.88
3-Formylpyridine	2.37	Benzene, 298 K	1.39	1.33	1.06
4-Formylpyridine	1.74	Benzene	1.80	1.76	1.68
2,3-Diformylpyridine	3.49	Benzene, 298 K	3.87	3.34	2.89
2,4-Diformylpyridine	2.53	Benzene, 298 K	1.08	0.980	0.885
2,5-Diformylpyridine	2.19	Benzene, 298 K	0.958	1.85	1.87
2,6-Diformylpyridine	2.04	Benzene, 298 K	3.23	0.697	0.803
3,5-Diformylpyridine	2.24	Benzene, 298 K	1.56	1.69	1.64
2-Acetylpyridine	2.87	Benzene, 298 K	3.55	2.83	3.33
3-Acetylpyridine	2.33	Benzene, 298 K	2.83	4.09	3.44
4-Acetylpyridine	2.37	Benzene	2.22	2.27	2.31
2,6-Diacetylpyridine	1.13	Benzene	2.87	0.505	1.75
1-(2′-Pyridyl)-3-phenyl-1-propenone	2.31	Benzene, 298 K	3.68	3.45	3.82
1-(2′-Pyridyl)-3-(4″-tolyl)-1-propenone	2.47	Benzene, 298 K	3.69	3.64	4.06
1-(2′-Pyridyl)-3-(4″-anisyl)-1-propenone	2.64	Benzene, 298 K	4.29	4.87	5.09
1-(3′-Pyridyl)-3-phenyl-1-propenone	2.88	Benzene, 298 K	3.39	2.14	3.14
1-(3′-Pyridyl)-3-(4″-tolyl)-1-propenone	3.31	Benzene, 298 K	3.38	2.44	3.28
1-(3′-Pyridyl)-3-(4″-anisyl)-1-propenone	3.62	Benzene, 298 K	3.03	3.56	4.08
1-(4′-Pyridyl)-3-phenyl-1-propenone	3.27	Benzene, 298 K	2.90	3.43	3.33
1-(4′-Pyridyl)-3-(4″-tolyl)-1-propenone	3.77	Benzene, 298 K	2.91	3.82	3.71
1-(4′-Pyridyl)-3-(4″-anisyl)-1-propenone	4.23	Benzene, 298 K	3.27	4.40	4.21
1-(2′-Pyridyl)-3-(2″-thienyl)-1-propenone	2.13	Benzene, 298 K	3.47	3.26	4.41
1-(3′-Pyridyl)-3-(2″-thienyl)-1-propenone	3.15	Benzene, 298 K	3.31	2.06	3.35

TABLE 4 Continued

			μ_{theor} (D)		
Compound	μ_{exper} (D)	*Conditions*	*MNDO*	*AM1*	*PM3*
1-(4′-Pyridyl)-3-(2″-thienyl)-1-propenone	3.54	Benzene, 298 K	3.02	3.46	3.58
2-Benzoylpyridine	2.95	Benzene	3.66	3.35	3.68
3-Benzoylpyridine	3.01	Benzene	3.43	4.26	3.90
4-Benzoylpyridine	3.06	Benzene	2.66	2.85	2.67
3-Carboxypyridine (nicotinic acid, niacin)	4.0	Benzene	2.23	3.05	3.00
4-Carboxypyridine (isonicotinic acid)	2.7	Dioxane, 298 K	1.40	1.13	1.21
3-Carbamidopyridine (nicotinamide)	3.07	Benzene, 298 K	3.57	2.17	2.52
N-Methylnicotinamide	3.43	Benzene, 298 K	3.50	2.09	2.69
N,*N*-Dimethylnicotinamide	4.00	Benzene, 298 K	3.29	2.68	3.34
N-Ethylnicotinamide	3.45	Benzene, 298 K	3.55	1.93	2.35
N,*N*-Diethylnicotinamide	4.16	Benzene, 298 K	3.57	3.01	3.34
4-Carbamidopyridine (isonicotinamide)	3.00	Benzene, 298 K	3.06	3.23	3.17
Hydrazide of isonicotinic acid	2.92	Dioxane, 298 K	1.45	1.60	1.45
Methyl ester of isonicotinic acid	1.63	Benzene	1.75	1.58	1.65
Ethyl ester of isonicotinic acid	2.49	Benzene, 298 K	1.92	1.84	1.88
2-Aminopyridine	2.04	Benzene, 298 K	1.93	1.89	1.84
3-Aminopyridine	3.12	Benzene, 298 K	2.53	2.86	2.55
4-Aminopyridine	3.93	Benzene, 298 K	2.75	3.28	2.89
2-Amino-3-methylpyridine	2.17	Benzene, 298 K	1.76	2.00	1.97
2-Amino-4-methylpyridine	2.27	Benzene, 298 K	1.98	2.14	2.10
2-Amino-5-methylpyridine	2.02	Benzene, 298 K	1.89	1.90	1.87
2-Amino-6-methylpyridine	1.65	Benzene, 298 K	1.84	1.62	1.60
2-*N*-Methylaminopyridine	2.05	Benzene	1.63	1.64	1.65
2-Amino-4,6-dimethylpyridine	2.20	Benzene, 303 K	1.89	1.86	1.86
2-*N*,*N*-Dimethylaminopyridine	1.93	Benzene, 298 K	1.36	1.64	1.66
3-Amino-4-methylpyridine	3.35	Benzene	2.22	3.05	2.76
3-*N*-Methylaminopyridine	3.26	Benzene	2.77	2.84	2.52
3-*N*,*N*-Dimethylaminopyridine	3.25	Benzene	1.37	3.02	2.61
4-Amino-2-methylpyridine	3.54	Benzene	2.62	3.05	2.68
4-Amino-3-methylpyridine	3.89	Benzene	2.69	3.34	2.97
4-*N*-Methylaminopyridine	4.26	Benzene	2.99	3.42	2.98
4-Amino-2,6-dimethylpyridine	1.94	Benzene	2.49	2.71	2.40
4-*N*,*N*-Dimethylaminopyridine	4.33	Benzene	2.09	3.59	3.07
2,3-Diaminopyridine	2.71	Benzene, 298 K	1.75	1.78	1.77
2,5-Diaminopyridine	2.45	Benzene, 298 K	1.47	1.59	1.58
2,6-Diaminopyridine	1.46	Benzene, 298 K	2.78	2.44	2.29
Salicylal-2-aminopyridine	2.24	Benzene	2.38	1.40	2.03
5-Nitrosalicylal-2-aminopyridine	4.88	Benzene	5.35	6.31	6.27
5-Chlorosalicylal-2-aminopyridine	3.12	Benzene	2.65	2.16	2.72
5-Bromosalicylal-2-aminopyridine	2.95	Benzene	2.45	2.30	3.74
Benzo[5,6]salicylal-2-aminopyridine	2.0	Benzene	2.14	1.49	3.36
cis-2-Phenylazopyridine	2.8	Benzene, 298 K	3.58	3.22	3.59
trans-2-Phenylazopyridine	2.2	Benzene, 298 K	1.56	1.65	1.59
cis-4-Methyl-2-phenylazopyridine	3.1	Benzene, 298 K	3.59	3.38	3.83
trans-4-Methyl-2-phenylazopyridine	2.7	Benzene, 298 K	1.64	1.97	1.94
cis-2-*o*-Chlorophenylazopyridine	2.9	Benzene, 298 K	4.67	3.69	4.06
trans-2-*o*-Chlorophenylazopyridine	2.1	Benzene, 298 K	1.01	1.98	1.64
cis-5-Bromo-2-phenylazopyridine	2.8	Benzene, 298 K	2.66	2.13	2.92
trans-5-Bromo-2-phenylazopyridine	2.6	Benzene, 298 K	2.06	2.09	1.78
cis-3,5-Dibromo-2-phenylazopyridine	2.0	Benzene, 298 K	3.03	2.92	3.09
trans-3,5-Dibromo-2-phenylazopyridine	1.8	Benzene, 298 K	1.25	1.29	1.42
cis-3-Phenylazopyridine	2.5	Benzene, 298 K	3.12	3.94	2.92
trans-3-Phenylazopyridine	2.3	Benzene, 298 K	2.07	2.12	2.11
cis-3-*o*-Chlorophenylazopyridine	2.7	Benzene, 298 K	3.16	4.28	3.17
trans-3-*o*-Chlorophenylazopyridine	2.4	Benzene, 298 K	1.58	1.67	1.77
cis-4-Phenylazopyridine	2.6	Benzene, 298 K	2.31	2.84	2.31
trans-4-Phenylazopyridine	2.7	Benzene, 298 K	2.65	2.61	2.43

(Continued)

TABLE 4 Continued

			μ_{theor} (D)		
Compound	μ_{exper} (D)	*Conditions*	*MNDO*	*AM1*	*PM3*
3-Nitropyridine	5.06	Benzene	4.69	4.54	4.52
4-Nitropyridine	1.61	Benzene	2.78	2.92	3.02
2-Amino-3-nitropyridine	2.61	Benzene, 298 K	4.28	3.90	3.64
2-Amino-5-nitropyridine	5.57	Benzene, 298 K	5.52	7.09	6.44
3-Amino-2-nitropyridine	5.89	Benzene, 298 K	6.76	6.42	6.15
4-Amino-3-nitropyridine	4.51	Benzene, 298 K	4.86	5.51	4.84
3,5-Dinitropyridine	1.11	Benzene, 298 K	2.41	2.57	2.68
2-Hydroxypyridine	1.73	Benzene, 303 K	1.23	1.38	1.24
2-Methoxypyridine	1.06	Benzene, 298 K	0.869	0.782	0.869
4-Methoxypyridine	2.94	Benzene, 298 K	2.49	2.54	2.50
3-Ethoxypyridine	2.41	Benzene, 298 K	2.24	1.48	1.49
4-Cyclohexyloxypyridine	3.46	Benzene, 298 K	2.50	3.03	2.84
4-Phenoxypyridine	2.54	Benzene, 298 K	2.68	2.40	2.45
2-Chloropyridine	3.25	Benzene, 298 K	3.27	2.82	2.44
3-Chloropyridine	2.02	Benzene, 298 K	1.91	1.76	1.70
4-Chloropyridine	0.89	Benzene, 298 K	0.279	0.822	1.16
2,6-Dichloropyridine	3.65	Benzene, 298 K	3.81	3.23	2.69
3,5-Dichloropyridine	0.95	Benzene, 298 K	0.416	0.938	1.23
2-Nitro-5-chloropyridine	3.96	Benzene, 298 K	4.81	5.21	5.53
2,6-Dinitro-3-chloropyridine	5.32	Benzene, 298 K	6.71	6.13	6.65
2-Bromopyridine	3.21	Benzene, 298 K	2.86	2.88	2.66
3-Bromopyridine	2.00	Benzene, 298 K	1.76	1.78	1.71
4-Bromopyridine	0.77	Benzene, 298 K	0.733	0.710	0.918
2,5-Dibromopyridine	2.33	Benzene, 298 K	2.05	2.06	2.04
2,6-Dibromopyridine	3.54	Benzene, 298 K	3.28	3.29	2.90
3,4-Dibromopyridine	1.16	Benzene, 298 K	1.05	1.05	1.09
3,5-Dibromopyridine	1.02	Benzene, 298 K	0.817	0.800	1.13
2,3,6-Tribromopyridine	3.11	Benzene, 298 K	2.75	2.76	2.49
2,4,6-Tribromopyridine	2.29	Benzene, 298 K	2.11	2.10	1.99
3,4,5-Tribromopyridine	0.58	Benzene, 298 K	0.115	0.0820	0.884
3-Iodopyridine	1.93	Benzene, 298 K	1.81	1.77	1.77
2,2′-Bipyridine	0.69	Benzene, 298 K	1.95	0.176	0.0719
2,4′-Bipyridine	3.84	Benzene, 298 K	3.54	3.41	3.33
3,4′-Bipyridine	2.38	Benzene, 298 K	2.08	2.12	2.04
4,4′-Bipyridine	0.31	Benzene, 298 K	0.00909	0.00271	0.00093
cis-2,2′-Azobipyridine	4.04	Benzene, 298 K	3.28	2.82	3.27
trans-2,2′-Azobipyridine	1.78	Benzene, 298 K	1.56	0.981	0.0186
cis-3,3′-Azobipyridine	2.85	Benzene, 298 K	2.03	3.43	1.97
trans-3,3′-Azobipyridine	2.42	Benzene, 298 K	0.0427	0.0798	0.0139
cis-4,4′-Azobipyridine	2.0	Benzene, 298 K	0.121	0.440	0.166
trans-4,4′-Azobipyridine	0.36	Benzene, 298 K	0.00668	0.00511	0.00269
Bis(2-pyridyl)ketone	2.91	Benzene	4.73	3.22	2.82
2,2′-Dipyridoyl	4.43	Benzene, 298 K	5.40	4.21	4.16
2,2′-Dipyridylamine	1.49	Benzene	0.863	0.996	0.899
3,3′-Dipyridylamine	2.60	Benzene	3.80	2.41	1.68

We have found only three values of pyridines entropies in the literature. For the number of points equal to three, the correlation coefficient differs from zero significantly for regression, provided that it is exactly equal to unity. But even such a rigorous condition is met for the data obtained by the MNDO and AM1 methods. The latter confirms the fact that the interrelations revealed are not of coincidental character.

During evaluation of ionization potentials (I) and, especially, of dipole moments, the correlation coefficient, remaining sufficiently high, is still lower, and the slope differs greater from unity, than during computations of thermodynamic characteristics.

With regard to ionization potentials, this can be stipulated by the following factors.

1. A rather narrow range of changes for the *I* quantities.
2. The *I* values computed from Koopmans theorem [8] were compared to the experimental ones, among which both the vertical and adiabatic potentials are presented.

TABLE 5 Coefficients $\boldsymbol{b}$ in Equations $P_{\mathrm{exper}} = \boldsymbol{b}P_{\mathrm{theor}}$ and the $\boldsymbol{r}$, MU, MS Values

					Error	
P	*Method*	*Number of Compounds*	**b**	**r**	*MU*	*MS*
ΔH_f	MNDO	27	1.0432 ± 0.0696	0.9967	5.83	−5.83
ΔH_f	AM1	27	0.9890 ± 0.0408	0.9931	2.91	0.61
ΔH_f	PM3	27	1.0312 ± 0.0479	0.9970	3.79	−3.66
S	MNDO	3	1.0078 ± 0.0440	1.00	1.21	−0.52
S	AM1	3	1.0060 ± 0.0415	1.00	1.10	−0.39
S	PM3	3	0.9904 ± 0.0314	0.9930	0.92	0.75
I	MNDO	33	0.9671 ± 0.0135	0.9159	0.36	0.33
I	AM1	33	0.9603 ± 0.0101	0.9355	0.39	0.39
I	PM3	33	0.9517 ± 0.0112	0.8955	0.51	0.47
I^a	PM3	31	0.9469 ± 0.0095	0.9357	0.52	0.52
μ	MNDO	217	1.0056 ± 0.0393	0.7693	0.64	−0.23
μ^b	MNDO	203	1.0220 ± 0.0339	0.8394	0.55	−0.22
μ	AM1	217	1.0027 ± 0.0351	0.8217	0.50	−0.21
μ^b	AM1	206	1.0210 ± 0.0308	0.8712	0.50	−0.21
μ	PM3	217	1.0123 ± 0.0377	0.7870	0.60	−0.23
μ^b	PM3	203	1.0366 ± 0.0311	0.8609	0.51	−0.23

[a] Data for 2- and 4-chloropyridines are excluded.
[b] Data for molecules with $|\mu_{\mathrm{theor}} - \mu_{\mathrm{exper}}|$ > 1.45 D are excluded.

As to the dipole moments, when discussing a nature of μ_{theor} deviations from μ_{exper}, one must take into consideration the following:

1. In quantum chemical computations, usually ignored are the atomic vibrations, internal rotation in molecules, and the possibility of the latter's' existence as mixtures of conformers.
2. The measurements of the minor values of dipole moments (to 1 D) are in great error. This is so for all the experimental techniques except for the microwave spectroscopy.
3. The experimental values [29–40,55–61] are obtained under different conditions and for different states of aggregation of matter.

The effect of the latter factor is minimized by the following circumstances. From the total number of 217 pyridine series compounds, dipole moments are measured using the second Debye method: for 149 substances in benzene at 298 K (including for one at 283–313 K), for 41 in benzene at temperatures close to 298 K, for 4 in carbon tetrachloride at 298 K, for 20 in dioxane at 298 K. All the measurements are carried out in dilute solutions in inert solvents, therewith the dipole moments evaluation presumes the extrapolation of molar polarization to infinite dilution. Only for 2-ethyl-, 2-vinyl-, and 4-vinylpyridines, the μ values in the liquid state are considered. Herewith the MNDO, AM1, and PM3 methods satisfactorily reproduce the experimental values of dipole moments.

Thus, the solvate–solvent interactions do not change significantly the experimentally determined dipole moments, which may be referred to the single molecules. Therefore, all the above mentioned experimental data are comparable to the results of gaseous-phase quantum chemical computations. Provided that the μ_{theor} and μ_{exper} values for the compounds featured by the condition $|\mu_{\mathrm{theor}} - \mu_{\mathrm{exper}}| > 1.45$ D (Table 6) are excluded from the correlation series, the correlation coefficient increases to some extent.

The existence of quantitative relations P_{exper} vs P_{theor} as such shows that the semiempirical quantum chemical methods do reproduce correctly alteration trends of heats of formation, entropies, ionization potentials, and dipole moments in the pyridine series.

Using the correlations found one could predict the properties not always available to experimental measurement. In doing so, the computed values have to be corrected by the multiplier $\boldsymbol{b}$. In the case of $P = \mu$ (Table 5, the relationships attributed to 217 molecules), the **b** values are close to unity; that allows one to calculate the corresponding characteristic directly, without any correlation equations, although the use of the latter is feasible. Probably, such a situation would take place for entropy, at the condition of the experimental and computational data array accumulation.

As indicated above, the actual problem is theoretical estimation of the pK_a values in the 2,2′-bipyridine series. We have performed quantum

TABLE 6 Unsuccessful Reproductions of Molecular Dipole Moments by Semiempirical Quantum Chemical Methods

Compound	*Computation Methods*
2-Hydroxyethylpyridine	MNDO, AM1, PM3
2-(4′-Pyridylmethylene)-6-bromo-1-indanone	MNDO, AM1, PM3
2-*p*-Aminophenylpyridine	MNDO
3-*m*-Nitrophenylpyridine	MNDO
4-*p*-Nitrophenylpyridine	AM1, PM3
2,4-Diformylpyridine	AM1, PM3
3-Acetylpyridine	AM1
2,6-Diacetylpyridine	MNDO
1-(2′-Pyridyl)-3-phenyl-1-propenone	PM3
1-(2′-Pyridyl)-3-(4″-tolyl)-1-propenone	PM3
1-(2′-Pyridyl)-3-(4″-anisyl)-1-propenone	MNDO, AM1, PM3
1-(2′-Pyridyl)-3-(2″-thienyl)-1-propenone	PM3
3-Carboxypyridine (Nicotinic acid, Niacin)	MNDO
4-Carboxypyridine (Isonicotinic acid)	AM1, PM3
Hydrazide of isonicotinic acid	MNDO, PM3
4-*N*,*N*-Dimethylaminopyridine	MNDO
cis-2-*o*-Chlorophenylazopyridine	MNDO
cis-3-*o*-Chlorophenylazopyridine	AM1
2-Amino-3-nitropyridine	MNDO
2-Amino-5-nitropyridine	AM1
2-Nitro-5-chloropyridine	PM3
trans-2,2′-Azobipyridine	PM3
trans-3,3′-Azobipyridine	MNDO, AM1, PM3
cis-4,4′-Azobipyridine	MNDO, AM1, PM3
Bis(2-pyridyl)ketone	MNDO

chemical computations of proton affinities for 2,2′-bipyridine and a series of its 4-substituted derivatives for which the experimental basicity data do exist [2,62]. We computed proton affinities in accordance with the aforesaid formula ($\mathrm{PA} = \Delta\Delta H_\mathrm{f}$), as well as using free energies ($\mathrm{PA} = \Delta\Delta G_\mathrm{f}$) instead of enthalpies:

$$\mathrm{PA} = \Delta G_\mathrm{f}(\mathrm{B}) + \Delta G_\mathrm{f}(H^+) - \Delta G_\mathrm{f}(\mathrm{BH}^+)$$

The experimental quantities of heat ΔH_f $(\mathrm{H}^+) = 367.163$ kcal/mol and free energy ΔG_f $(\mathrm{H}^+) = 362.570$ kcal/mol of the proton formation [27] are used.

It has been taken into consideration that in contrast to 2,2′-bipyridine [2] having *trans* conformation in crystal and solutions, the cation of its conjugate acid exists in *cis* form, by the UV spectroscopy data [2,63]. The latter is reinforced by our quantum chemical computations (Table 7). Therefore, the indirect data of electron spectroscopy with respect to the conformation of protonated 2,2′-bipyridine find a quantum chemical evidence.

Introducing the substituent into one of the aromatic cycles of the 2,2′-bipyridine molecule makes both the rings and nitrogen atoms, the centres of electrophilic attack by hydronium ion, nonequivalent chemically. Because of that, a demand arose for computing the proton affinities of substituted 2,2′-bipyridines on protonation by each nonequivalent nitrogen atoms. The results are given in Table 8.

As is seen, in the majority of cases 2,2′-bipyridines molecules are protonated more likely by a nonsubstituted aromatic ring. That is most pronounced for 4-nitro-2,2′-bipyridine: according to the various quantum chemical methods, the differences in heats and free energies of isomeric cations formation consist of 4.0–5.6 kcal/mol. The differences in energies between the conjugate acids of other 2,2′-bipyridines is relatively small regardless of the proton affinity value of the isomeric cation.

In line with the aforesaid, analyzing the quantitative relations of $\mathrm{p}K_\mathrm{a}$ vs PA we have considered enthalpies and free energies of proton affinity on 2,2′-dipyridyls protonation by a nonsubstituted ring.

Provided that the differences in 2,2′-bipyridines basicity are owing to intramolecular factors, and medium makes a constant contribution, the $\mathrm{p}K_\mathrm{a}$ vs PA dependences must be linear. However, for the whole set of considered substances, the linear dependences $\mathrm{p}K_\mathrm{a}$ vs $\Delta\Delta H_\mathrm{f}$ and $\mathrm{p}K_\mathrm{a}$ vs $\Delta\Delta G_\mathrm{f}$ are not observed. Obvious is differentiating effect of medium upon the protolytic properties of the 2,2′-bipyridine series.

The $\mathrm{p}K_\mathrm{a}$ and PA values of 4-X-2,2′-bipyridines with X = H, $\mathrm{CONH_2}$, $\mathrm{NO_2}$, $\mathrm{OCH_2C_6H_5}$, Cl, and Br satisfy the linearity condition of the interrelation between the above quantities (Table 8), which probably corresponds to the permanent medium contribution to the substances' basicity. Only the PM3 method

TABLE 7 Heats of Formation (ΔH_f), Entropies (S) and Free Energies of Formation (ΔG_f) for *cis* and *trans* Conformers of Protonated 2,2′-Bipyridine

	*ΔH*f *(kcal/mol)*			*S (cal/(mol K))*			*ΔG*f *(kcal/mol)*		
Conformer	*MNDO*	*AM1*	*PM3*	*MNDO*	*AM1*	*PM3*	*MNDO*	*AM1*	*PM3*
Cis	213.32	215.99	209.86	91.75	91.15	91.48	245.54	248.40	242.16
Trans	217.47	219.90	214.59	90.58	90.81	91.86	250.04	252.41	246.78

TABLE 8 pK_a Values [2,62] Measured in Water by Spectrophotometric Technique and PM3-Computed Proton Affinities (PA) for 4-Substituted 2,2′-Bipyridines

			PA (kcal/mol)					
			$\Delta\Delta H_f$			$\Delta\Delta G_f$		
Substituent	pK_a	*Aromatic Ring*	*MNDO*	*AM1*	*PM3*	*MNDO*	*AM1*	*PM3*
H	4.27	–	212.68	223.07	219.97	203.13	213.48	210.24
$CONH_2$	4.00	Substituted	208.95	218.71	215.01	199.73	209.62	205.93
		Unsubstituted	210.34	220.31	216.66	201.31	211.22	207.39
$NHCOCH_3$	4.17	Substituted	214.09	224.56	224.57	204.76	215.40	214.24
		Unsubstituted	215.01	227.30	224.59	205.36	218.61	213.71
NO_2	3.24	Substituted	198.64	208.62	206.18	189.35	199.59	196.72
		Unsubstituted	204.20	213.39	210.22	193.71	204.40	201.02
OCH_3	4.91	Substituted	211.73	222.80	221.76	200.66	213.54	212.18
		Unsubstituted	214.81	224.99	221.84	204.08	215.60	212.15
OC_2H_5	5.00	Substituted	212.26	223.67	222.47	202.46	213.80	214.06
		Unsubstituted	214.29	226.16	222.31	204.42	215.86	213.91
$OCH_2C_6H_5$	4.36	Substituted	214.53	224.73	223.10	202.61	218.26	210.77
		Unsubstituted	215.78	225.70	220.80	203.71	216.80	208.80
Cl	3.83	Substituted	208.10	218.86	218.29	198.99	209.77	208.82
		Unsubstituted	210.41	220.96	218.89	201.28	211.86	209.34
Br	3.80	Substituted	209.57	218.69	217.35	200.41	209.61	207.77
		Unsubstituted	211.08	220.34	217.98	201.99	211.30	208.62

data for PA = $\Delta\Delta G_f$ demonstrate a tendency to disperse, that is reflected in a relatively low value of correlation coefficient.

On the MNDO, AM1, and PM3 methods computations results, for PA = $\Delta\Delta H_f$, $\Delta\Delta G_f$ positive deviations from the trend line in the case of methoxy and ethoxy substituted 2,2′-bipyridines, and negative deviations with reference to the compound with the $NHCOCH_3$ substituent turn attention on itself.

As Table 9 shows, the data for both the compounds with obviously hydrophilic ($CONH_2$, NO_2), as well as with relatively hydrophobic ($OCH_2C_6H_5$, Cl, Br) atomic groups are put in dependences pK_a vs PA. Deviations from the trend take place for sufficiently bulky substituents, in which the hydrophilic–hydrophobic balance has been more or less kept.

TABLE 9 Correlation Coefficients **r** for Linear Dependencies pK_a vs PA Attributed to 4-X-2,2′-Bipyridines with X = H, $CONH_2$, NO_2, $OCH_2C_6H_5$, Cl, and Br Substituents

PA	*Method*	***r***
$\Delta\Delta H_f$	MNDO	0.9558
$\Delta\Delta H_f$	AM1	0.9679
$\Delta\Delta H_f$	PM3	0.9150
$\Delta\Delta G_f$	MNDO	0.9274
$\Delta\Delta G_f$	AM1	0.9575
$\Delta\Delta G_f$	PM3	0.8436

CONCLUSION

As Table 5 shows, the quality of quantum chemical evaluations is good, and the semiempirical models used would be successful for the predictions of thermodynamic and molecular characteristics for the pyridine series. Possible reasons for the deviations of theoretical values from the experimental ones, as well as for the estimation failures, have been discussed, and the properties' unfit reproductions occur but are not due to the quantum chemical methods drawbacks.

An a priori evaluation of the thermodynamic and molecular parameters by quantum chemical methods is important for molecular design of compounds with given properties, and may serve as a base for expert decision on reasonableness of synthesis that is sometimes labor- and time-consuming, requiring complicated devices, rigid conditions, expensive and toxic chemicals.

Our computational results indicate that the basicity of 2,2′-bipyridines depends not only upon the molecules electronic structure, but also on the medium. In order to enhance the predicting abilities of quantitative relations of pK_a vs PA, it is necessary to measure the pK_a values for more extensive series of 2,2′-bipyridines with different modes of electron-donor and electron-acceptor substitution in aromatic ring. Therewith the groups of various steric sizes differing also in hydrophilicity (hydrophobicity) must be involved.

ACKNOWLEDGMENTS

The author thank Dr. Olga M. Tsivileva and Leading Engineer Eugeny V. Kalmykov for technical assistance.

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