Polish J. Chem., **76**, 581–588 (2002)

A Comparison of Basicities of Substituted Pyridines and Pyridine *N*-Oxides

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(Received July 11th, 2001; revised manuscript November 16th, 2001)

The basicity of pyridine and its derivatives, as representatives of monocyclic heterocyclic *N*-bases, has been compared with that of pyridine *N*-oxide and its derivatives representing the class of heterocyclic monocyclic oxygen-containing bases. The basicities have been compared both in the gas phase and in solution. To do this, correlated were both calculated (at RHF, MP2 levels and using SCRF and PCM methods) energy parameters, ΔE_{prot} and ΔG_{prot}, with experimental pK_a values for a particular class of the bases, as well as theoretical and experimental characteristics of the two classes of compounds studied. Results of the correlations paved the way to discussion of the effect of the medium on basicity of both classes of compounds, as well as enabled to compare the basicities of these very important classes of organic bases in a quantitative way.

Key words: substituted pyridines, substituted pyridine *N*-oxides, basicity in the gas phase and solution, thermodynamics

In polar non-aqueous solvents, in systems of heterocyclic bases, amines and heterocyclic amine *N*-oxides containing conjugate cationic acids, the dominating acid-base equilibria involve those of acid dissociation of the protonated bases. pK_a values of cationic acids conjugated with the organic bases studied determined in a variety of polar non-aqueous solvents [1–8] revealed that the bases are much stronger in the solvents specified than in water (with the exception of the substituted pyridines in the most basic dimethyl sulfoxide [4]). At the same time, the pyridines are at average by 2 – 3 orders of magnitude stronger bases than the corresponding *N*-oxides [6]. Further, it was demonstrated that pK_a's of the cationic acids conjugated with organic bases in polar solvents could be linearly correlated with their pK_a's in water [7]. Linear correlations could also be obtained between pK_a's of the protonated bases in two non-aqueous solvents [8]. The aforementioned experimental findings have been verified theoretically at the *ab initio* level using the RHF (Restricted Hartree-Fock) and MP2 (Møller-Plesset) methods, as well as using self-consistent reaction field (SCRF) method and the polarizable continuum model (PCM) [9,10]. The calculated energy parameters of protonation (both in the gas phase and in solution) of a number of substituted pyridine *N*-oxides [9] and parent pyridines [10] were correlated with pK_a of the protonated bases determined experimentally in non-aqueous media.

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The main purpose of this contribution is to compare the basicity of heterocyclic *N*-bases (pyridine and its derivatives) with that of heterocyclic *N*-oxides (pyridine *N*-oxide and its derivatives) both in the gas phase and in solution. To do this, supplemented were previously performed *ab initio* calculations, compiled the calculated protonation energy parameters and experimental pK_a's of the bases (substituted pyridines and their *N*-oxides) in both non-aqueous and aqueous solutions. Consequently, a comparison of these quantities and analysis of the established correlations between the calculated and experimental quantities served as basis for making generalizations, referring to the basicities of the substituted pyridines and their *N*-oxides in the gas phase and in solution.

METHODS

Closed-shell RHF calculations were carried out on pyridine, pyridine *N*-oxide, their derivatives and conjugated cationic acids using the GAMESS program [11] in the 6-31G* basis set. The starting geometry of the systems was constructed by the MOLDEN program [12]. All systems had optimized geometry down to a gradient standard not lower than 0.0001 a.u./bohr (0.1 kcal/mol·Å). The evaluation of the solvation contributions to the protonation energies was attempted using self-consistent reaction field (SCRF) [13,14] and polarizable continuum model (PCM) [15] methods. In both models the dielectric constant of acetonitrile was assigned a value of 35.94 [16]. Calculations were carried out for fixed geometries corresponding to the structures optimized *in vacuo*. The details of all *ab initio* calculations were described elsewhere [9,10].

RESULTS AND DISCUSSION

The calculated energies, ΔE_{prot} (RHF) and Gibbs free energies of protonation, ΔG_{prot} (RHF), at the RHF level, the protonation energies at the MP2 level, ΔE_{prot} (MP2), as well as the obtained using SCRF method, ΔE_{prot} (SCRF) and ΔG_{prot} (SCRF) energies and Gibbs free energies of protonation including the solvation energies for substituted pyridine *N*-oxides are collected in Table 1. For the sake of comparison in this table the experimental pK_a values in acetonitrile (pK_a^{AN}), as representative of polar non-aqueous and water pK_a^{W}, are collected. As it can be seen from the data in Table 1,

Table 1. Energies, ΔE_{prot} (RHF) and Gibbs free energies of protonation, ΔG_{prot} (RHF), at the RHF level, the protonation energies at the MP2 level, ΔE_{prot} (MP2), as well as the obtained using SCRF method, ΔE_{prot} (SCRF) and ΔG_{prot} (SCRF) energies and Gibbs free energies of protonation including the solvation energies for substituted pyridine *N*-oxides in kcal/mol. For comparison, the experimentally determined pK_a^{AN} and literature pK_a^{W} values are included.

N-oxide	ΔE_{prot} (RHF)	ΔG_{prot} (RHF)	ΔE_{prot} (MP2)	ΔE_{prot} (SCRF)	ΔG_{prot} (SCRF)	pK_a^{AN}	pK_a^{W}
$4NMe_2PyO$	–250	–251	–248	–128	–120	15.63[a]	3.88[b]
4MeOPyO	–241	–242	–236	–121	–111	12.28[a]	2.04[c]
4PicO	–237	–237	–231	–120	–112	11.00[a]	1.29[d]
3PicO	–235	–236	–230	–123	–115	10.31[a]	1.08[d]
2PicO	–235	–235	–229	–126	–118	10.23[a]	1.029[e]
PyO	–232	–233	–227	–117	–109	10.04[a]	0.79[d]
$4NO_2PyO$	–215	–215	–211	–114	–106	5.64[a]	–1.70[f]

N-oxide name abbreviations: 4-*N*′,*N*′-dimethylaminopyridine ($4NMe_2PyO$), 4-methoxypyridine (4MeOPyO), 4-methylpyridine (4PicO), 3-methylpyridine (3PicO), 2-methylpyridine (2PicO), pyridine (PyO) and 4-nitropyridine ($4NO_2PyO$) N-oxide.

[a] From ref. 6; [b] From ref. 17; [c] From ref. 18; [d] From ref. 6; [e] From ref. 20; [f] From ref. 21.

theoretical quantities change in the same direction, as do the experimental pK_a values. Therefore, the experimental pK_a^{AN} were previously [9] correlated with the calculated ΔE_{prot} and ΔG_{prot} at the RHF level, as well as the ΔE_{prot} at the MP2 level. In each case a linear correlation could be established. For instance, the following linear equation [9] can be obtained for the Gibbs free energy:

$$pK_a^{AN} = -0.273(0.016)\Delta G_{prot}\,(\mathrm{RHF}) - 54(4) \qquad R = -0.991 \tag{1}$$

In (1) and all subsequent equations the values of standard deviations are given in parentheses and R is the correlation coefficient. The calculated protonation energy parameters of pyridine *N*-oxide, ΔE_{prot} (RHF), ΔG_{prot} (RHF) and ΔE_{prot} (MP2) were also correlated with pK_a's in aqueous solution (pK_a^W) [17–21] as indicated by:

$$pK_a^{W} = -0.15(0.01)\Delta E_{prot}\,(\mathrm{RHF}) - 35(2) \qquad R = -0.992 \tag{2}$$

$$pK_a^{W} = -0.15(0.01)\Delta G_{prot}\,(\mathrm{RHF}) - 35(2) \qquad R = -0.994 \tag{3}$$

$$pK_a^{W} = -0.150(0.002)\Delta E_{prot}\,(\mathrm{MP2}) - 34(1) \qquad R = -0.999 \tag{4}$$

In Fig. 1 relationship of ΔE_{prot} (MP2) *vs*. pK_a^W in aqueous solutions for substituted pyridine N-oxides is shown. An attempt to estimate the solvent effects by employing the SCRF model was unsuccessful as far as an improvement in the correlations between the calculated energies (Gibbs free energies) of substituted pyridine *N*-oxides protonation and experimental pK_a values in acetonitrile is concerned. As a matter of fact, this procedure enabled to calculate the energies and Gibbs free energies of the cationic acids (*cf.* Table 1), but the calculated ΔE_{prot} (SCRF) and ΔG_{prot}

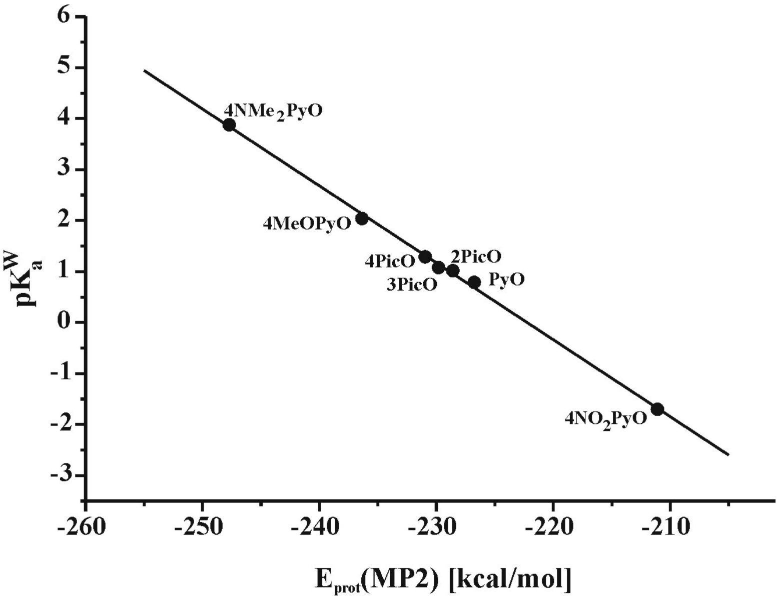

Figure 1. Relationship between calculated energy parameters of protonation of substituted pyridine *N*-oxides, ΔE_{prot} (MP2), and experimental pK_a values in water (pK_a^W).

(SCRF) quantities remain in a weaker correlation than analogous quantities calculated without consideration of solvation effects. For all the systems studied, the correlation coefficients for ΔG_{prot} (SCRF) and ΔG_{prot} (SCRF) were respectively 0.805 and 0.765 in correlations involving pK_a^{AN} in acetonitrile and 0.825 and 0.786 for those involving pK_a^{W} in water. After rejection of ortho-substituted compounds, the R values increased up to –0.925, –0.895, –0.933 and –0.904, respectively. However, the correlation coefficients were still considerably lower than those in equations (2)–(4), which do not account for the solvation effects. Consequently, it can be concluded that the SCRF model is too crude to be successfully adopted for such chemical species as studied here namely substituted pyridine *N*-oxides and their conjugated cations. An attempt to use a more sophisticated solvation model (PCM) to protonated substituted pyridine *N*-oxides turned out to be still less successful and for this reason corresponding quantities are not included in Table 1. These findings show that the mean-field solvation models are inadequate for protonated substituted pyridine *N*-oxides.

In Table 2 are collected the calculated energies, ΔE_{prot} (RHF) and Gibbs free energies of protonation, ΔG_{prot} (RHF), at the RHF level, the protonation energies at the MP2 level, ΔE_{prot} (MP2), and the obtained using PCM model, ΔE_{prot} (PCM) and ΔG_{prot} (PCM) energies and Gibbs free energies of protonation including the solvation energies, as well as for comparison, the experimental pK_a values in acetonitrile (pK_a^{AN}) and water pK_a^{W} for substituted pyridines. It has also been found that correlations involving basicities afford linear equations [10]:

$$pK_a^{AN} = -0.338(0.029)\Delta G_{prot}\,(\mathrm{RHF}) - 64(7) \qquad R = -0.966 \tag{5}$$

Table 2. Energies, ΔE_{prot} (RHF) and Gibbs free energies of protonation, ΔG_{prot} (RHF), at the RHF level, the protonation energies at the MP2 level, ΔE_{prot} (MP2), as well as the obtained using PCM method, ΔE_{prot} (PCM) and ΔG_{prot} (PCM) energies and Gibbs free energies of protonation including the solvation energies for substituted pyridines in kcal/mol. For comparison, the experimentally determined pK_a^{AN} and literature pK_a^{W} values are included.

Substituted pyridine	ΔE_{prot} (RHF)	ΔG_{prot} (RHF)	ΔE_{prot} (MP2)	ΔE_{prot} (PCM)	ΔG_{prot} (PCM)	pK_a^{AN}	pK_a^{W}
$4NH_2Py$	–239	–240	–243	–44	–45	18.38[a]	9.68[b]
$3NH_2Py$	–235	–236	–238	–37	–37	14.35[a]	6.34[b]
$2NH_2Py$	–232	–232	–238	–39	–39	14.66[a]	7.04[b]
2,4Lut	–234	–235	–237	–38	–38	15.00[a]	6.98[b]
4Pic	–230	–231	–233	–36	–37	14.52[a]	6.18[b]
3Pic	–229	–228	–233	–38	–36	13.66[a]	5.68[b]
2Pic	–229	–231	–234	–36	–37	13.88[a]	5.96[b]
Py	–226	–226	–229	–36	–36	12.60	4.94[b]
3AcOPy	–224	–224	–230	–32	–31	10.75[a]	3.26[b]
3BrPy	–219	–219	–225	–31	–30	9.49[a]	2.72[b]
2BrPy	–219	–219	–223	–26	–26	7.02[a]	0.71[b]
3ClPy	–218	–218	–223	–30	–30	10.01[a]	2.74[b]
2ClPy	–217	–216	–221	–26	–26	6.80[a]	0.60[b]
3CNPy	–211	–211	–216	–28	–28	8.04[a]	1.40[b]

Pyridine name abbreviations: 4-aminopyridine ($4NH_2Py$), 3-aminopyridine ($3NH_2Py$), 2-aminopyridine ($2NH_2Py$), 2,4-dimethylpyridine (2,4Lut), 4-methylpyridine (4Pic), 3-methylpyridine (3Pic), 2-methylpyridine (2Pic), pyridine (Py), 3-acetylpyridine (3AcOPy), 3-bromopyridine (3BrPy), 2-bromopyridine (2BrPy), 3-chloropyridine (3ClPy), 2-chloropyridine (2ClPy) and 3-cyanopyridine (3CNPy).

[a] From ref. 1; [b] From ref. 19.

To learn whether the protonation energy parameters are linearly related to the pK_a^W values [19], an attempt has been made to correlate them. The following relations were obtained:

$$pK_a^W = -0.31(0.03)\Delta E_{prot}\,(RHF) - 66(7) \qquad R = -0.943 \qquad (6)$$

$$pK_a^W = -0.31(0.03)\Delta G_{prot}\,(RHF) - 65(7) \qquad R = -0.947 \qquad (7)$$

$$pK_a^W = -0.33(0.03)E_{prot}\,(MP2) - 72(7) \qquad R = -0.949 \qquad (8)$$

In Fig. 2 relationship of ΔE_{prot} (MP2) *vs*. pK_a^W values in water for substituted pyridines is shown. The energies and Gibbs free energies of protonation of the substituted pyridines under consideration of solvation effects within the SCRF model are not presented in Table 2, because it became evident that the model is completely inadequate for the heterocyclic amines and conjugate cationic acids. On the other hand, it turned out that the polarizable continuum model (PCM) enabled to improve the agreement between the calculated energies (Gibbs free energies) and experimental pK_a^{AN} values in acetonitrile. Their values correlate very well with the experimental pK_a values in acetonitrile according to:

$$pK_a^{AN} = -0.63(0.03)\Delta E_{prot}\,(PCM) - 9(1) \qquad R = -0.986 \qquad (9)$$

$$pK_a^{AN} = -0.62(0.02)\Delta G_{prot}\,(PCM) - 9(1) \qquad R = -0.994 \qquad (10)$$

as well as aqueous pK_a^W values:

$$pK_a^W = -0.50(0.02)\Delta E_{prot}\,(PCM) - 12.3(0.7) \qquad R = -0.989 \qquad (11)$$

$$pK_a^W = -0.49(0.01)\Delta G_{prot}\,(PCM) - 12.2(0.4) \qquad R = -0.997 \qquad (12)$$

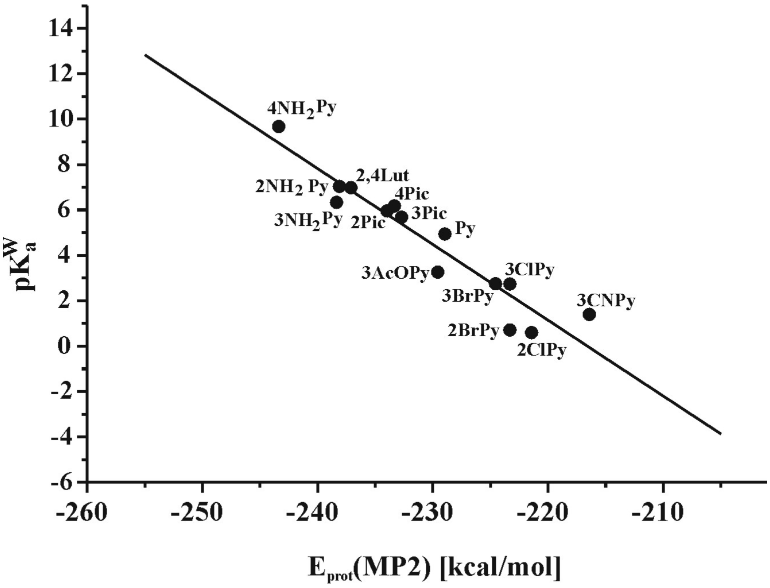

Figure 2. Relationship between calculated energy parameters of protonation of substituted pyridines, ΔE_{prot}(MP2), and experimental pK_a values in water (pK_a^W).

Data collected in Tables 3 and 4 enable comparison of basicities of monocyclic heterocyclic bases and their *N*-oxides taking as respective examples pyridine and its *N*-oxide. In order to facilitate the comparison, the data are summarized in Table 3, while in Table 4 are included pK_a's of protonated pyridine and its *N*-oxide in other than acetonitrile and water solvents – dimethyl sulfoxide, acetone, methanol, propylene carbonate and nitromethane. As far as the protonation energy parameters are concerned (Table 3), higher absolute values at the RHF level are characteristic of pyridine *N*-oxide, thus indicating a significantly stronger (the difference exceeds 6 kcal/mol for both the energy and Gibbs free energy) basicity of the *N*-oxide in the gas phase relative to that of pyridine. This finding is consistent with theoretical predictions, because the stronger basicity of the *N*-oxides can be explained in terms of a higher negative charge on the oxygen atom as compared to that on the amine nitrogen.

Table 3. Comparison of energies, ΔE_{prot} (RHF) and Gibbs free energies of protonation, ΔG_{prot} (RHF), at the RHF level, the protonation energies at the MP2 level, ΔE_{prot} (MP2), the obtained using SCRF and PCM methods, ΔG_{prot} (SCRF) and ΔG_{prot} (PCM) Gibbs free energies of protonation including the solvation energies in kcal/mol, as well as the experimentally determined pK_a^{AN} and literature pK_a^{W} values for substituted pyridines and pyridine *N*–oxides.[a]

Base	ΔE_{prot}(RHF)	ΔG_{prot}(RHF)	ΔE_{prot}(MP2)	ΔG_{prot}(SCRF)	ΔG_{prot}(PCM)	pK_a^{AN}	pK_a^{W}
Py	–226	–226	–229	–	–36	12.60[b]	4.94[c]
PyO	–232	–233	–227	–109	–	10.04[d]	0.79[e]
Δ	6	7	–2	–	–	2.56	4.15
a	0.79	1.03	1.08			1.63(1.85)	2.40(2.48)
b	4.3	14	17			3.32(5.75)	3.18(2.98)
R	0.909	0.940	0.991			0.858(0.953)	0.913(0.999)

[a]The values of correlation coefficients obtained after removing 2-substituted derivatives. [b] From ref. 1; [c] From ref. 20; [d] From ref. 6; [e] From ref. 19.

Table 4. Comparison of experimental pK_a values determined in non-aqueous solvents, as well as aqueous pK_a^{W} values for substituted pyridines (Py) and pyridine *N*-oxides (PyO).[a]

Base	DMSO	AC	MeOH	AN	PC	NM	W
Py	3.19[b]	7.23[c]	5.21[c]	12.60[d]	11.54[e]	12.23[f]	4.94[g]
PyO	1.63[h]	5.11[h]	2.69[h]	10.04[h]	8.59[h]	8.66[h]	0.79[i]
Δ	1.56	2.12	2.52	2.56	2.89	3.67	4.15
DN[j]	29.8	17.0	19.1	14.9	15.1	2.7	–
a	0.78	0.66	1.30	1.85	0.12	0.99	2.48
b	2.00	3.81	1.94	5.75	10.4	4.06	2.98
R	0.933	0.998	0.894	0.953	0.334	0.777	0.999

[a] The values of correlation coefficients obtained after removing 2-substituted derivatives. [b] From ref. 4; [c] From ref. 3; [d] From ref. 1; [e] From ref. 5; [f] From ref. 2; [g] From ref. 20; [h] From ref. 6; [i] From ref. 19; [j] From ref. 22.

Nevertheless, going to a higher level of the *ab initio* calculations (MP2), which accounts for dynamic correlation in the energies, enabled to revert the sequence of basicities of the two bases, the differences in energies at this level being quite small (*ca* 2 kcal/mol). It might be anticipated that the difference would be larger after inclusion of the solvent effect in the *ab initio* calculations. However, such a comparison turned out to be impossible, since the available energies for the two bases referred to different solvation models. Nonetheless, experimental data in Table 3 show that upon going from the gas phase to the acetonitrile solution, the basicity of pyridine becomes distinctly enhanced relative to that of its *N*-oxide (pK_a^{AN} values are 12.60 and 10.04 for pyridine [1] and its *N*-oxide [6], respectively) and further going to a strongly solvating medium (water) still enlarges this difference (pK_a^{W} values are respectively 5.25 [19] and 0.79 [19]). Another illustration of these variations in relative basicities of pyridine and its *N*-oxide is provided by differences in calculated energy parameters and experimental pK_a's (as listed in Tables 3 and 4 and marked with Δ). In particular, the influence of solvation can be seen when analysing pK_a's of protonated pyridine and its *N*-oxide in the non-aqueous solvents and water. It should be noted that Δ denotes the basicity difference in solution between the more basic pyridine and its *N*-oxide. It increases in the series of non-aqueous solvents with decreasing donicity numbers (DN), which serve as a measure of solvent basicity [22] and reaches a maximum for the strongly amphiprotic water.

In the next step, it seemed worthwhile to extend the comparison over full classes of the organic bases. To do this, correlations have been established both between the energy parameters of protonation of substituted pyridine *N*-oxides and the set of substituted pyridines, as well as experimental pK_a's of the both classes of bases. Such correlations carried out for calculated in the gas phase basicity parameters, ΔE_{prot}^{Py} (RHF), ΔG_{prot}^{Py} (RHF) and E_{prot}^{Py} (MP2) of substituted pyridines on the one hand, and those of ΔE_{prot}^{PyO} (RHF), ΔG_{prot}^{PyO} (RHF) and E_{prot}^{PyO} (MP2) for substituted pyridine *N*-oxides, on the other, revealed weak linear relationships (with R = 0.875, 0.796 and 0.759, respectively) when all compounds were included. Rejection of ortho-substituted derivatives afforded correlations with considerably higher correlation coefficients:

$$\Delta E_{prot}^{Py}\ (\mathrm{RHF}) = 0.79(0.36)\Delta E_{prot}^{PyO}\ (\mathrm{RHF}) - 43(85) \qquad R = 0.909 \tag{13}$$

$$\Delta G_{prot}^{Py}\ (\mathrm{RHF}) = 1.03(0.34)\Delta G_{prot}^{PyO}\ (\mathrm{RHF}) + 14(80) \qquad R = 0.949 \tag{14}$$

$$\Delta E_{prot}^{Py}\ (\mathrm{MP2}) = 1.08(0.19)\Delta E_{prot}^{PyO}\ (\mathrm{MP2}) + 17(34) \qquad R = 0.991 \tag{15}$$

the values of *a*, *b* and *R* being shown in Table 3. The exclusion was done on assumption of a negative influence of the derivatives on the quality of the correlations by virtue of the so-called *ortho*-effect [10]. Remarkable is the much better improvement of the correlation coefficients in calculations accomplished at the MP2 level. Correlational analyses have also been made for experimental pK_a's in non-aqueous solvents and in aqueous solutions to give the following equations for acetonitrile and water:

$$pK_a^{AN}\ (\mathrm{Py}) = 1.63(0.69)pK_a^{AN}\ (\mathrm{PyO}) - 3.32(7.21) \qquad R = 0.858 \tag{16}$$

$$pK_a^{W}\ (\mathrm{Py}) = 2.40(0.76)pK_a^{W}\ (\mathrm{PyO}) + 3.18(0.81) \qquad R = 0.913 \tag{17}$$

in which the correlation coefficients increase up to 0.953 and 0.984, respectively, after rejection of 2-substituted compounds (see Table 3). Correlations were also established for the remaining polar non-aqueous solvents. The obtained *b* and *R* coefficients are summarized in Table 4. The coefficient values after rejection of 2-substituted derivatives indicate that linear correlations exist in the majority of the solvents studied. Only in propylene carbonate, pK_a's of substituted pyridines are not linearly related to pK_a's of their *N*-oxide counterparts, whereas in nitromethane analogous correlation is very weak.

Acknowledgments

Financial support by the Polish State Committee for Scientific Research, under grants No. 7 T09A 035 20 and DS/8231-4-0097-1 is gratefully acknowledged.

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