Experimental and Theoretical Studies of Acid−Base Equilibria of Substituted 4-Nitropyridine *N*-Oxides

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By using the potentiometric titration method, acidity constants in the polar aprotic solvent acetonitrile (in the form of pK_a^{AN} values) of cations obtained by protonation of 13 substituted 4-nitropyridine *N*-oxides and cationic homoconjugation constants (K_{BHB^+}) of the cationic acids conjugated with the *N*-oxides studied have been determined. A correlation has been established between the tendency toward cationic homoconjugation (expressed as log K_{BHB^+}) and the basicity of the *N*-oxides in acetonitrile (pK_a^{AN}). Further, by using ab initio methods at the RHF and MP2 levels utilizing the Gaussian 6-31G* basis set, energies and Gibbs free energies have been determined of protonation and formation of homocomplexed cations stabilized by O···H···O bridges in the gas phase. The calculated protonation energies, ΔE_{prot}, and Gibbs free enthalpies, ΔG_{prot}, in vacuo have been found to correlate well with the acid dissociation constants (expressed as pK_a^{AN} values) of protonated *N*-oxides, whereas the calculated energies, ΔE_{BHB^+}, and Gibbs free energies, ΔG_{BHB^+}, of homoconjugation do not correlate with the cationic homoconjugation constant values determined in acetonitrile.

Introduction

This contribution is a continuation of investigations carried out in our laboratory, using both experimental and theoretical approaches, into acid−base equilibria present in systems involving organic bases. It is worth noting that a model of acid−base equilibria established between acids (both molecular and cationic) and organic bases in nonaqueous media is highly complex.[1−3] Nevertheless, this model can be both predicted and limited, under experimental conditions, to so-called fundamental equilibria only, namely those of dissociation of cationic acids (1), as well as cationic homoconjugation (2):

$$BH^+ \rightleftarrows B + H^+ \quad (1)$$

$$BH^+ + B \rightleftarrows BHB^+ \quad (2)$$

where B denotes the base molecule, BH^+ is a cation of the protonated base, and BHB^+ is a symmetric homocomplexed cation. These equilibria have been the main objects of our interest.

Our investigations were primarily focused on two series of heterocyclic bases, pyridine and its derivatives[4−7] and the derivatives of pyridine *N*-oxide.[8−10] The chemistry of heterocyclic amine *N*-oxides raised widespread interest due to the exceptionally high bioactivity of these compounds,[11] encompassing, among others, antibiotics, antibiotic antagonists, and compounds exhibiting cancerostatic, mutagenic, sedative, anticonvulsive, and fungistatic efficacy.[12] Referring to the substituted 4-nitropyridine *N*-oxides studied here, an important feature is[13] that the presence of the nitro group has been crucial for developing the antifungal efficacy of these compounds. In this respect, all studies concerned directly or indirectly with the electronic structure of the *N*-oxides of heterocyclic amines substituted with the nitro group and with their protonated forms are of particular importance, as they may contribute to understanding the mechanism of antifungal activity of these compounds.

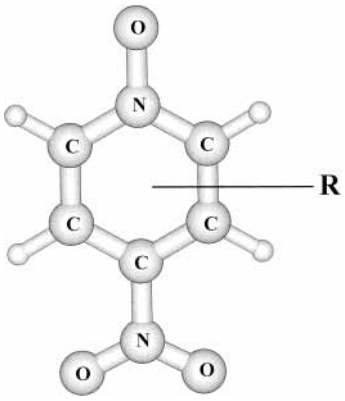

Figure 1. Structure of substituted 4-nitropyridine *N*-oxide. R denotes at least one substituent.

Recently, there has been a distinct upsurge of interest in 4-nitropyridine *N*-oxide and its derivatives owing to certain interesting features of the compounds themselves and their biochemical activities.[14−16] Specifically, the structure of these compounds is of interest as are inherent properties, in particular, electron−donor and electron−acceptor ones. The molecule of 4-nitropyridine *N*-oxide carries both the electron-attracting nitro group and an electron-donating *N*-oxide group (oxygen atom linked to the nitrogen atom of the pyridine ring; see Figure 1). Other electron-donating substituents, for instance, methyl, methylamino, and ethylamino groups, are likely to affect the

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acid−base properties of the *N*-oxides. Results of spectroscopic investigations revealed a strong charge-transfer band in the range 242−333 nm in the spectra of substituted 4-nitropyridine *N*-oxides.[17] Ehara and co-workers[18] have found that the tendency toward intramolecular charge-transfer declines with increasing electropositive character of the *N*-oxide oxygen. It has also been found that the so-called *ortho* effect of the methyl substituents in the ring of 4-nitropyridine results in the appearance of paramagnetism of the nitro group.[19]

All these interesting features of the family of organic bases prompted us to undertake investigations into their acid−base properties. First of all, the potentiometric titration method has been used to determine acidity constants (eq 1) of the protonated *N*-oxides and cationic homoconjugation constants of the free and protonated *N*-oxides (eq 2) for a representative group of 13 methyl-substituted 4-nitropyridine *N*-oxides. Then, by utilizing ab initio methods, energetic parameters (energies and Gibbs free energies) of protonation and formation of the homocomplexed cations were determined both in the gas phase at the restricted Hartree−Fock (RHF) and Møller−Plesset (MP2) levels. In the next step, an attempt has been made to correlate the calculated quantities with experimental values of acid dissociation constants, pK_a^{AN}, and cationic homoconjugation constants, $\log K_{BHB^+}$, in acetonitrile (AN) as a representative of polar nonaqueous solvents.

The following 4-nitropyridine *N*-oxides were investigated (their acronyms in parentheses): 2-methyl (2Me), 3-methyl (3Me), 2,3-dimethyl ($2,3Me_2$), 2,5-dimethyl ($2,5Me_2$), 2,6-dimethyl ($2,6Me_2$), 3,5-dimethyl ($3,5Me_2$), 2,3,6-trimethyl ($2,3,6Me_3$), 2-methylamino-3-methyl (2MeNH3Me), 2-methylamino-5-methyl (2MeNH5Me), 2-methylamino-6-methyl (2MeNH6Me), 2-(ethylamino)-3-methyl (2EtNH3Me), 2-(ethylamino)-5-methyl (2EtNH5Me), and 2-(ethylamino)-6-methyl (2EtNH6Me), which apart from the electron-accepting nitro group contain the electron-donating methyl substituent in their molecules, thus constituting a family of 4-nitropyridine *N*-oxides. To expand the range of acid−base properties, some of the compounds have additional methyl and/or other electron-donating substituents such as methylamino and ethylamino ones.

Experimental Section

Compounds. The syntheses of the methyl derivatives of 4-nitropyridine *N*-oxide were described previously.[20−24] However, these syntheses were modified. Accordingly, a solution of 10 g of methyl derivative of pyridine in 50 cm^3 of acetic anhydride was treated with portions of 30 cm^3 of 50% hydrogen peroxide. The reaction mixture was left standing at room temperature for 24 h and then heated for 5 h at 70−80 °C. Then, the excess of acetic acid was distilled off under reduced pressure, the residue was added in small portions to 30 cm^3 of concentrated sulfuric acid, and the resulting solution was poured into nitrating acid (50 cm^3 of HNO_3, $d = 1.52$ g/cm^3 + 30 cm^3 of concentrated H_2SO_4). The nitration reaction was carried out at 100 °C for 1.5 h. Then the reaction mixture was poured on ice, neutralized with solid ammonium carbonate, and finally neutralized with ammonia up to an alkaline reaction with lithmus. The methyl derivative of 4-nitropyridine *N*-oxide formed was filtered off. The filtrate was extracted with chloroform, and the extract was dried with anhydrous magnesium sulfate. In the next step chloroform was removed and the residue was combined with the previously filtered product. The obtained methyl derivative of 4-nitropyridine *N*-oxide was recrystallized from a mixture of water and ethanol. 2-Alkylamino-4-nitropicoline *N*-oxides were obtained according to refs 25 and 26. A sample of 5 g of 2-chloro-4-nitropicoline *N*-oxide and 20 cm^3 of 30% alkylamine solution in methanol was refluxed for 5 h. Then the reaction mixture was evaporated to dryness. After the methanol was distilled off and water was added, the precipitate was filtered off and recrystallized from water to give the proper 2-alkylamino-4-nitropicoline *N*-oxide.

The simple perchlorates of *N*-oxides under study were prepared by mixing together equivalent quantities of a 72% aqueous perchloric acid (Merck Co.) with *N*-oxide in methanol. The mixture was vacuum concentrated. The residue was filtered off, washed twice with chloroform, and dried in a vacuum over P_2O_5.

Picric acid (Fluka AG) was purified by triple crystallization from ethanol. Tetra-*n*-butylammonium picrate was obtained by mixing together equimolar quantities of the purified picric acid with 25% tetra-*n*-butylammonium hydroxide in methanol. Tetra-*n*-butylammonium perchlorate was obtained by mixing together equimolar quantities of 72% aqueous $HClO_4$ solution with 25% tetra-*n*-butylammonium hydroxide in methanol. Both salts were crystallized twice from ethanol. Tetra-*n*-butylammonium chloride (Serva Co.) was purified by triple crystallization from a 1:1 mixture of acetonitrile and ethyl acetate.

Acetonitrile (Serva Co.) was purified by the modified Coetzee method.[2] At first the solvent was dried with CaH_2 (10 g/dm^3) for 48 h. After decantation AN was distilled over P_2O_5 (3 g/dm^3). The distillate was dried again with CaH_2 and distilled after 48 h. The purified solvent had a specific conductivity of $4-10 \times 10^{-8}$ $S \cdot cm^{-1}$.

Experimental Procedures. The reversible potential difference (*E*) measurements of the cell (indicator glass electrode|system studied||modified calomel electrode) were run with an OP-208 digital potentiometer (Radelkis) with the accuracy ±0.1 mV. An OP-7183 (Radelkis) indicator glass electrode and an OP-08303 (Radelkis) reference calomel electrode were used. The reference calomel electrode, modified by replacing the aqueous KCl solution by a 0.1 mol/dm^3 solution of tetra-*n*-butylammonium chloride in nonaqueous solvent, was placed in a shortened salt bridge filled with 0.01 mol/dm^3 tetra-*n*-butylammonium perchlorate solution in the solvent under study. The reversible potential difference measurements of the *N*-oxide perchlorate−*N*-oxide systems were run at a constant ionic strength. The solution containing *N*-oxide perchlorate ($BHClO_4$) at a concentration of about 10^{-3} mol/dm^3 was titrated with the solution containing the *N*-oxide B at a concentration of about 10^{-2} mol/dm^3 and $BHClO_4$ at the same concentration as that of the titrand (to keep the formal ionic strength constant for all titration points). The reversible potential difference (*E*) was recorded for each titration point, after electrode relaxation (i.e. when the measured potential was stable). Each reversible potential difference measurement in the system studied was preceded by the determination of the characteristic of the glass electrode. The linearity of the response of the glass electrode versus the modified calomel electrode in acetonitrile was checked by means of the standardizing system: tetra-*n*-butylammonium picrate−picric acid ($pK_a^{AN} = 11.0$)[27] at a constant ionic strength. A 0.001 mol/dm^3 tetra-*n*-butylammonium picrate solution was titrated by the solution containing picric acid and tetra-*n*-butylammonium picrate at the concentrations 0.01 and 0.001 mol/dm^3, respectively, to keep the formal ionic strength constant. Solutions for potentiometric measurements were prepared on the volume basis. All potentiometric measurements were run at 298.1 ± 0.1 K.

Calculations. To calculate the acidic−basic constant values from potentiometric−titration data, the general nonlinear con-

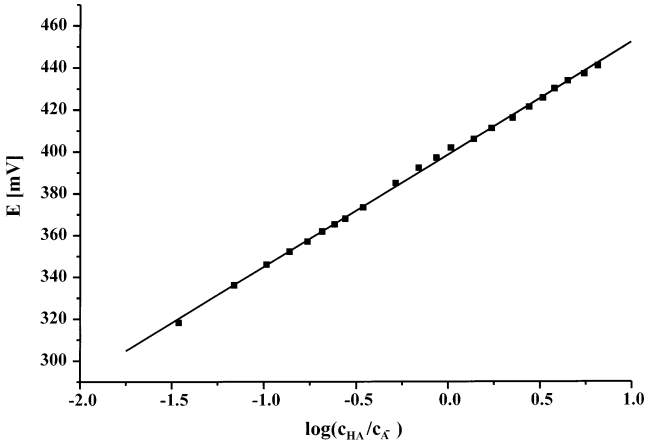

Figure 2. Calibration graph of the glass electrode for the (tetra-*n*-butylammonium picrate + picric acid) standardizing system in acetonitrile.

fluence analysis program STOICHIO based on the algorithm of Kostrowicki and Liwo[28−30] was used.

Theoretical Methods

All the systems were optimized by the ab initio methods at the RHF (restricted Hartree−Fock) level using the GAMESS[31] program. The optimization was performed to a gradient of 0.0001 au/bohr (approximately 0.1 kcal mol^{-1} Å^{-1}). In calculations, the 6-31G* basis set was used.

Equations 3 and 4 define the protonation and homoconjugation energies, respectively:

$$\Delta E_{\text{prot}} = E_{\text{BH}^+} - E_{\text{B}} \tag{3}$$

$$\Delta E_{\text{BHB}^+} = E_{\text{BHB}^+} - (E_{\text{BH}^+} + E_{\text{B}}) \tag{4}$$

where E_{BHB^+} is the energy of a homocomplexed cation, E_{BH^+}, is the energy of a proton donor, and E_{B} is the energy of proton acceptor.

After optimization, to gain a better insight into variations of the energy of the systems, translational, rotational, and vibrational contributions have been calculated. To do this, thermodynamic corrections were calculated. Their values enabled us to check whether the stationary point found was a true minimum and to compute zero-point energy contributions (eqs 5 and 6).

The Gibbs free energies of protonation, ΔG_{prot}, and homoconjugation, ΔG_{BHB^+}, were calculated from eqs 5 and 6, respectively:

$$\Delta G_{\text{prot}} = \Delta E_{\text{prot}} + \Delta E^{\circ}_{\text{vib,prot}} + p\Delta V_{\text{prot}} - T\left[(S_{\text{vib,BH}^+} + S_{\text{rot,BH}^+}) - (S_{\text{vib,B}} + S_{\text{rot,B}}) - \frac{3}{2}R\right] \tag{5}$$

$$\Delta G_{\text{BHB}^+} = \Delta E_{\text{BHB}^+} + \Delta E^{\circ}_{\text{vib,BHB}^+} + p\Delta V_{\text{BHB}^+} - T\left[(S_{\text{vib,BHB}^+} + S_{\text{rot,BHB}^+}) - (S_{\text{vib,BH}^+} + S_{\text{rot,BH}^+} + S_{\text{vib,B}} + S_{\text{rot,B}}) - \frac{3}{2}R\right] \tag{6}$$

where $\Delta E^{\circ}_{\text{vib;prot}}$ and $\Delta E^{\circ}_{\text{vib,BHB}^+}$ are the differences between the zero-point vibrational energies of the products and those of the substrates, respectively, p is the pressure, and V is the volume of a system under the assumption that it satisfies an ideal gas equation-of-state; S_{rot} and S_{vib} are the rotational and vibrational entropies, respectively, and the term $^3/_2R$ refers to the translational degrees of freedom of the system. A temperature of 298 K and a pressure of 1 atm were assumed in all calculations.

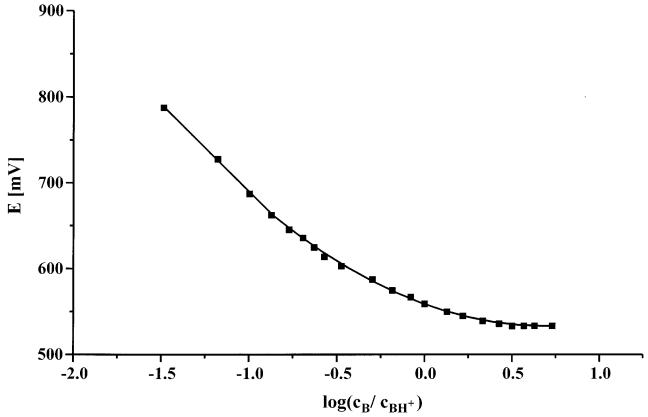

Figure 3. Reversible potential difference (E) vs log $c_{\text{B}}/c_{\text{BH}^+}$ in acetonitrile for the 2MeNH6Me system.

Subsequently, the perturbation theory was applied to further improve the calculated electronic energies[32] of protonation and formation of the homocomplexed cations at the MP2 (Møller−Plesset) level. The effect of the dynamic correlation was calculated within a single iteration procedure for structure optimized at the RHF level.[33] Such a procedure was used due to the complexity of the systems considered (large molecules and cations).

In systems consisting of at least two monomers, their energies[34] are replaced by basis functions of a single molecule (BSSE—basis superposition set error), which affect another molecule, and vice versa. To demonstrate this effect, the energy of the systems was estimated under consideration of the BSSE effect. The calculations were performed by using the following general scheme (they are analogous when calculating Gibbs free energies):

$$\Delta E_{\text{BSSE}} = \Delta E_{\text{complex}} + (E_{\text{A}} + E_{\text{B}}) - (E_{\text{complex}}(\text{A}) + E_{\text{complex}}(\text{B})) \tag{7}$$

where ΔE_{BSSE} is the energy of a system under consideration of the BSSE, $\Delta E_{\text{complex}}$ is the energy without consideration of the BSSE, E_{A} and E_{B} are the energies of the A and B monomers, respectively, and $E_{\text{complex}}(\text{A})$ and $E_{\text{complex}}(\text{B})$ are the energies of complexes A and B, respectively, on assumption that the orbitals of molecules A and B are the so-called "ghost" orbitals.[34]

Results and Discussion

Potentiometric Data. As mentioned in the Experimental Section, before running each series of measurements in substituted 4-nitropyridine *N*-oxide, the response of the glass electrode was checked in a (picric acid + tetra-*n*-butylammonium picrate) standardizing system. The characteristic of the glass electrode used for the standardizing system picrate ion (A^-)−picric acid (HA) in acetonitrile is shown in Figure 2. In all the standardizing titrations there were linear relationships between reversible potential difference (E) and log($c_{\text{HA}}/c_{\text{A}^-}$) over the range −1.5 to 1, and slopes, ranging from 59 to 61 mV, were close to the Nernst theoretical ones. On the basis of determined in the calibration procedure E° (standard reversible potential difference) and s (slope) values, as well as the reversible potential difference variations in the systems studied (an example system is shown in Figure 3), acid dissociation and cationic homoconjugation constant values were calculated. The acid−base equi-

TABLE 1: Acidity Constants, pK_a^{AN}, and log K_{BHB^+} of the Cationic Homoconjugation Constants of Substituted 4-Nitropyridine *N*-Oxides Determined Potentiometrically in Acetonitrile at 298.1 K

N-oxide[a]	log K_{BHB^+}	pK_a^{AN}	pK_a^{W} [b]
2Me	1.89	5.73	−1.52
3Me	2.02	6.38	−1.16
2,3Me$_2$	2.10	6.92	−0.87
2,5Me$_2$	2.56	6.47	−1.11
2,6Me$_2$	2.28	6.71	−0.98
3,5Me$_2$	2.49	7.32	−0.65
2,3,6Me$_3$	2.42	6.86	−0.90
2MeNH3Me	2.32	8.22	−0.16
2MeNH5Me	2.44	7.95	−0.31
2MeNH6Me	2.72	7.81	−0.38
2EtNH3Me	2.72	9.22	0.39
2EtNH5Me	2.91	8.49	−0.01
2EtNH6Me	2.68	8.18	−0.18

[a] *N*-oxide abbreviations: 2Me, 2-methyl-4-nitropyridine *N*-oxide; 3Me, 3-methyl-4-nitropyridine *N*-oxide; 2,3Me$_2$, 2,3-dimethyl-4-nitropyridine *N*-oxide; 2,5Me$_2$, 2,5-dimethyl-4-nitropyridine *N*-oxide; 2,6Me$_2$, 2,6-dimethyl-4-nitropyridine *N*-oxide; 3,5Me$_2$, 3,5-dimethyl-4-nitropyridine *N*-oxide; 2,3,6Me$_3$, 2,3,6-trimethyl-4-nitropyridine *N*-oxide; 2MeNH3Me, 2-methylammino-3-methyl-4-nitropyridine *N*-oxide; 2MeNH5Me, 2-methylammino-5-methyl-4-nitropyridine *N*-oxide; 2MeNH6Me, 2-methylammino-6-methyl-4-nitropyridine *N*-oxide; 2EtNH3Me, 2-ethylammino-3-methyl-4-nitropyridine *N*-oxide; 2EtNH5Me, 2-ethylammino-5-methyl-4-nitropyridine *N*-oxide; 2EtNH6Me, 2-ethylammino-6-methyl-4-nitropyridine *N*-oxide. [b] Acidity constants in aqueous solutions, obtained from eq 10.

librium constant values were calculated under the assumption that the acid dissociation and cationic homoconjugation equilibria are set up simultaneously in the systems studied using a general Kostrowicki and Liwo method.[28−30] The general algorithm of this method is based on a general description of chemical equilibria in ideal solutions and uses nonlinear confluence analysis to determine equilibrium parameters from physicochemical data. It can also take into account the errors in electrode-calibration parameters and composition of the stock solutions and reagents.

The acidity (expressed as pK_a^{AN} values) and cationic homoconjugation (as log K_{BHB^+}) constants determined in acetonitrile for 13 substituted 4-nitropyridine *N*-oxides are collected in Table 1. Inspection of the pK_a^{AN} values collected in the table shows that the sequence of changes of the acidity constants is consistent with that predicted on the basis of substituent effects. Thus, with increasing electron-donating strength of the substituent (the methyl−methylamino−ethylamino series), the basicity of the substituted 4-nitropyridine *N*-oxides also increases. On the other hand, the tendency toward cationic homoconjugation, expressed in terms of log K_{BHB^+}, also increases with increasing basicity, This finding is compatible with conclusions drawn from a relationship between the tendency toward homoconjugation and the basicities of monosubstituted pyridine *N*-oxides.[35] To verify this relationship, an attempt has been made to linearly correlate log K_{BHB^+} against pK_a^{AN}. Unfortunately, after taking into account all the *N*-oxides studied, the respective equation (standard deviation in parentheses; *R* correlation coefficient):

$$\log K_{BHB^+} = 0.24(0.06)pK_a^{AN} + 0.64(0.44) \quad R = 0.800 \quad (8)$$

had a too small coefficient *R* to justify linear correlation. However, after rejection of two outliers (2,5Me$_2$ and 2MeNH3Me), a much higher *R* was obtained:

$$\log K_{BHB^+} = 0.30(0.04)pK_a^{AN} + 0.22(0.29) \quad R = 0.933 \quad (9)$$

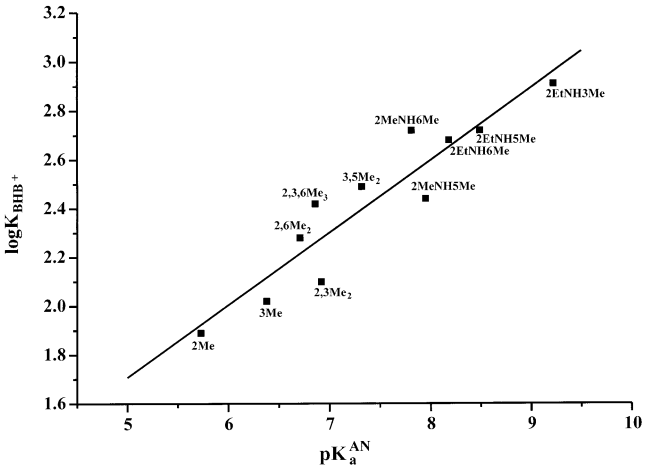

Figure 4. Plot of log K_{BHB^+} against pK_a^{AN} for the substituted 4-nitropyridine *N*-oxides under study. Abbreviations for *N*-oxides are given in the graph.

This means that a correlation between the tendency toward cationic homoconjugation and the basicity of the compounds does exist (Figure 4).

In view of the lack of pK_a values in aqueous solutions (pK_a^{W}) for the majority of the cationic acids investigated, these were estimated from linear relationships between pK_a's in acetonitrile, pK_a^{AN}, and those in water, pK_a^{W}, of the cationic acids conjugated with mono- and disubstituted pyridine *N*-oxides:

$$pK_a^{AN} = 1.83(0.05)pK_a^{W} + 8.51(0.08) \quad R = 0.998 \quad (10)$$

The above linear relationship was derived from a previously established[36] equation: $pK_a^{AN} = 1.83pK_a^{W} + 8.56$ after accounting for the literature[37,38] pK_a^{W} values for some trisubstituted pyridine *N*-oxides. The pK_a^{W} values obtained in this way are summarized in Table 1 together with those determined by the potentiometric method in acetonitrile, pK_a^{AN}. As seen, the pK_a^{W} values are all higher than the pK_a^{W} for 4-nitropyridine *N*-oxide. As the pK_a^{W} value of one of the *N*-oxides studied here was found in the literature, its comparison with that obtained from correlation (10) can provide a quality assessment of the whole procedure for estimation of the pK_a^{W} values based on those obtained in nonaqueous media, in this case, in acetonitrile (pK_a^{AN}). Thus, the literature pK_a^{W} for 2,6-dimethyl-4-nitropyridine *N*-oxide[38] is −0.861, while that calculated from eq 10 is −0.980 and falls in the range of error of the correlation.

Ab Initio Calculations. Selected geometric parameters of the substituted 4-nitropyridine *N*-oxides, their neutral forms (bases), their protonated forms (cationic acids), and systems stabilized by the O···H···O bridges (homocomplexed cations) are collected in Table 2. The N−O bond lengths of the N−O group of the bases range from 1.253 to 1.298 Å. They are generally longer than that calculated within the same functional base for the parent compound (4-nitropyridine *N*-oxide), which is[8] 1.25 Å, being only slightly shorter than the experimental value[39] of 1.30 Å. The elongation of the N−O bonds in the molecules of the substituted compounds as compared with the length in the parent *N*-oxide can be explained in terms of the presence of electron-donating substituents in various positions of the ring. As seen in Table 2, the highest value emerges in the presence of the strongest electron-donating group in the ring, the ethylamino group, especially in the case when the strong effect of this group is fortified by another electron donor, the methyl group. With cationic acids, the presence of the amino

TABLE 2: Selected Geometric Parameters of 4-Nitropyridine *N*-Oxide Derivatives,[a] Their Cationic Acids, and Their Homoconjugated Cations (Bond Lengths in Angstroms and Angles in Degrees) Calculated in the 6-31G* Basis Set

		cationic acid			homoconjugated cation					
N-oxide system	base d(N−O)	d(N−O)	d(O−H)	∠(N−O−H)	d(O−O)	d(N−O)[b]	d(N−O)[c]	d(O−H)[c]	∠(N−O−H)[c]	∠(N[b]−O[b]−O[c]−N[c])
2Me	1.261	1.354	0.957	108.16	2.550	1.309	1.347	0.997	106.33	160.39
3Me	1.253	1.353	0.957	108.03	2.552	1.307	1.344	0.995	106.86	−166.20
2,3Me$_2$	1.264	1.356	0.956	107.93	2.547	1.312	1.348	0.999	106.12	175.49
2,5Me$_2$	1.260	1.354	0.956	108.07	2.550	1.309	1.347	0.998	106.11	174.65
2,6Me$_2$	1.270	1.355	0.956	108.19	2.558	1.312	1.347	0.997	107.38	−149.24
3,5Me$_2$	1.258	1.354	0.957	107.91	2.549	1.311	1.345	0.997	107.11	−169.24
2,3,6Me$_3$	1.267	1.356	0.956	107.17	2.560	1.314	1.348	0.997	107.40	−150.67
2MeNH3Me	1.283	1.351	0.955	107.35	2.528	1.330	1.352	1.009	105.92	−173.25
2MeNH5Me	1.272	1.357	0.955	107.39	2.530	1.323	1.351	1.008	105.74	168.47
2MeNH6Me	1.297	1.358	0.956	107.74	2.541	1.329	1.351	1.006	106.90	145.18
2EtNH3Me	1.293	1.357	0.955	107.29	2.540	1.329	1.353	1.003	106.08	−158.06
2EtNH5Me	1.291	1.356	0.956	107.59	2.534	1.328	1.351	1.006	105.56	−173.15
2EtNH6Me	1.298	1.358	0.956	107.54	2.552	1.329	1.351	1.003	106.36	161.09

[a] *N*-oxide abbreviations: 2Me, 2-methyl-4-nitropyridine *N*-oxide; 3Me, 3-methyl-4-nitropyridine *N*-oxide; 2,3Me$_2$, 2,3-dimethyl-4-nitropyridine *N*-oxide; 2,5Me$_2$, 2,5-dimethyl-4-nitropyridine *N*-oxide; 2,6Me$_2$, 2,6-dimethyl-4-nitropyridine *N*-oxide; 3,5Me$_2$, 3,5-dimethyl-4-nitropyridine *N*-oxide; 2,3,6Me$_3$, 2,3,6-trimethyl-4-nitropyridine *N*-oxide; 2MeNH3Me, 2-methylammino-3-methyl-4-nitropyridine *N*-oxide; 2MeNH5Me, 2-methylammino-5-methyl-4-nitropyridine *N*-oxide; 2MeNH6Me, 2-methylammino-6-methyl-4-nitropyridine *N*-oxide; 2EtNH3Me, 2-ethylammino-3-methyl-4-nitropyridine *N*-oxide; 2EtNH5Me, 2-ethylammino-5-methyl-4-nitropyridine *N*-oxide; 2EtNH6Me, 2-ethylammino-6-methyl-4-nitropyridine N. [b] Proton acceptor. [c] Proton donor.

group in the ring has only insignificant influence on the lengths of the N−O bond, these varying only slightly between 1.351 and 1.358 Å, not showing any regularity in changes. It is remarkable that this bond length matches that previously calculated[8] (1.35 Å) for unsubstituted 4-nitropyridine *N*-oxide using the same computational technique. In the case of the homocomplexed cations, the situation resembles that of the cationic acids: the lengths of the N−O bond are only slightly affected by the nature of the substituents. They are shortened by 0.004−0.009 Å as compared to those in the corresponding cationic acids. On the other hand, the situation in proton acceptors resembles that in the molecules of the *N*-oxides; the bonds become longer with increasing electron-donating power of substituents. The extent of the variations is, however, slightly smaller than that for free *N*-oxides (1.307−1.330 Å).

The lengths of the O−H bonds in cationic acids (protonated 4-nitropyridine *N*-oxides) fall in the range 0.955−0.957 Å. The bonds are short, thus indicating that the proton is firmly bound to the oxygen atom of the N−O group. The angles between the N−O−H atoms in the cationic acids range from 107.17 to 108.19°, thus revealing sp^3 hybridization of the oxygen atom in the protonated *N*-oxide group. A slight deviation of the angles from that in a regular tetrahedron is due to the presence of substituents in the ring. The greater the number of the substituents, the larger the deviation from the ideal value of 109.5°.

The lengths of the O···O hydrogen bridges in the complexed cations vary between 2.528 and 2.560 Å, thus indicating a strong hydrogen bonding in the homoconjugated cations. These values match those previously calculated for substituted pyridine *N*-oxides that range from 2.51 to 2.55 Å. This shows that in the homocomplexed cations of 4-nitropyridine *N*-oxides, similar to the case of pyridine *N*-oxides, there is a strong symmetric hydrogen bonding, only slightly weaker than that in unsubstituted pyridine *N*-oxide. As predicted on the basis of the strong electron-donating power of the amino group, the shortest hydrogen bridges occur in the amino derivatives. In all cases, the N−O bonds in the homocomplexed cations are longer in proton acceptors by ∼0.03 Å relative to those in the molecules of the corresponding *N*-oxides. This is indicative of a strong affinity of the proton toward the oxygen of the *N*-oxide group. In the proton donors, the lengths of the N−O bond are only slightly shorter (by approximately 0.007 Å). Again, in this case

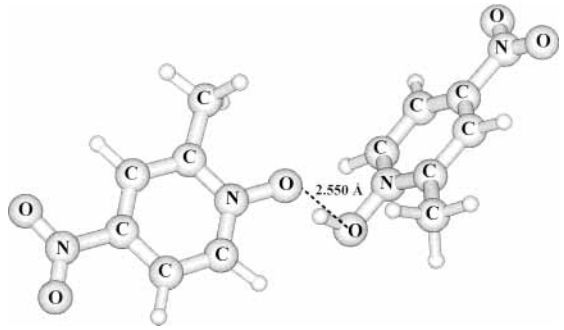

Figure 5. Example structure of the homoconjugated cation of 2-methyl-4-nitropyridine *N*-oxide (2MeH2Me)$^+$.

the O−H bonds are significantly longer than those in the corresponding cationic acids. In each case the difference oscillates around 0.045 Å. On this basis one can speculate that there is a possibility of free transfer (or through a low energy barrier) of the proton in the homocomplexed cation[8] from the proton donor to the proton acceptor. Moreover, the angle between the N−O−H atoms in the molecules of the proton donors undergoes deformation. In the homocomplexed cations it varies between 105.56 and 107.3°, whereas in the amino derivatives the deformation is still larger. Examination of dihedral angles between the N−O−O−N atoms, where the first N−O atoms belong to proton acceptors and the successive ones to proton donors, shows that the homocomplexed cations are not coplanar; that is, the proton donor and proton acceptor do not lie in one plane (see Figure 5). These angles range from 145.18 to 175.49°. It can also be seen that the more the angle deviates from linearity (180°), the longer is the O···O bridge and the weaker the hydrogen bonding. Accordingly, the formation energies of the homocomplexed cations formed by the substituted 4-nitropyridine *N*-oxides are likely to decline in the same direction.

Table 3 lists protonation energies, ΔE_{prot}, determined at the RHF and MP2 levels and Gibbs free energies, ΔG_{prot}, determined at the RHF level. For the sake of comparison, included also are pK_a^{AN} constants determined by potentiometric titration in acetonitrile representing polar nonaqueous solvents. For comparison with the calculated energetic protonation parameters, pK_a constants determined in one solvent only were taken,

TABLE 3: Calculated Energies, ΔE_{prot}(RHF), and Gibbs Free Energies, ΔG_{prot}(RHF), of Protonation at the RHF Level, as Well as MP2, ΔE_{prot}(MP2), Respectively, for 4-Nitropyridine *N*-Oxide Derivatives[a] (kcal/mol) with Experimental pK_a^{AN} Values in Acetonitrile Included for Comparison

N-oxide	ΔE_{prot}(RHF)	ΔG_{prot}(RHF)	ΔE_{prot}(MP2)	pK_a^{AN}
2Me	−217.86	−218.88	−213.26	5.73
3Me	−216.89	−219.02	−214.97	6.38
$2,3Me_2$	−222.14	−223.98	−218.94	6.92
$2,5Me_2$	−220.60	−220.29	−216.85	6.47
$2,6Me_2$	−222.22	−223.57	−217.65	6.71
$3,5Me_2$	−222.35	−224.28	−219.88	7.32
$2,3,6Me_3$	−224.30	−226.24	−219.58	6.86
2MeNH3Me	−232.25	−232.72	−226.23	8.22
2MeNH5Me	−231.23	−231.33	−224.39	7.95
2MeNH6Me	−227.43	−227.36	−222.66	7.81
2EtNH3Me	−235.51	−238.89	−232.84	9.22
2EtNH5Me	−229.61	−227.98	−224.11	8.49
2EtNH6Me	−226.96	−226.06	−221.95	8.18

[a] *N*-oxide abbreviations: 2Me, 2-methyl-4-nitropyridine *N*-oxide; 3Me, 3-methyl-4-nitropyridine *N*-oxide; $2,3Me_2$, 2,3-dimethyl-4-nitropyridine *N*-oxide; $2,5Me_2$, 2,5-dimethyl-4-nitropyridine *N*-oxide; $2,6Me_2$, 2,6-dimethyl-4-nitropyridine *N*-oxide; $3,5Me_2$, 3,5-dimethyl-4-nitropyridine *N*-oxide; $2,3,6Me_3$, 2,3,6-trimethyl-4-nitropyridine *N*-oxide; 2MeNH3Me, 2-methylammino-3-methyl-4-nitropyridine *N*-oxide; 2MeNH5Me, 2-methylammino-5-methyl-4-nitropyridine *N*-oxide; 2MeNH6Me, 2-methylammino-6-methyl-4-nitropyridine *N*-oxide; 2EtNH3Me, 2-ethylammino-3-methyl-4-nitropyridine *N*-oxide; 2EtNH5Me, 2-ethylammino-5-methyl-4-nitropyridine *N*-oxide; 2EtNH6Me, 2-ethylammino-6-methyl-4-nitropyridine *N*-oxide.

because, as it was previously demonstrated,[40] the acidity constants determined in different solvents can be intercorrelated. Again, acetonitrile was chosen as a representative solvent, because the acidity constants just in this solvent have been most accurately determined.[41] Another reason was that the solvent has consequently been used for such comparisons in our previous studies.[5,8,42] As seen, the amino derivatives display higher absolute values of the protonation energies than the methyl derivatives. This means that the amino-substituted 4-nitropyridine *N*-oxides are stronger bases than the methyl derivatives and, consequently, they should have higher pK_a values. Preliminary comparison of the calculated and experimental pK_a^{AN} values seems to support this hypothesis. The protonation energies of the methyl derivatives obtained by the MP2 method oscillate around −215 kcal mol^{-1} (range between −213.26 and −219.88), whereas those for the amino derivatives oscillate around −225 kcal mol^{-1} (range from −221.95 to −232.84), thus being 10 kcal mol^{-1} higher (taking into account their absolute values) on average. The pK_a^{AN} values display a similar trend. For methyl substituted 4-nitropyridine *N*-oxides they fall in the range 5.73−7.32, whereas for the amino compounds they are 1.5 pK_a units higher (7.81−9.22). For comparison, the pK_a^{AN} for 4-nitropyridine *N*-oxide is[43] 5.64, being lower than that for any of its derivatives studied here. Consequently, as predicted on the basis of electron-donating effects of substituents, all the substituted *N*-oxides under study are stronger bases than their parent compound, 4-nitropyridine *N*-oxide.

Further, a closer look at Table 3 shows that both the calculated and experimental values change in the same direction. On this basis an attempt has been made to establish linear correlations between the pK_a^{AN} and the calculated ΔE_{prot}(RHF), ΔG_{prot}(RHF), and ΔE_{prot}(MP2) values. The correlations can be represented as the following linear functions (where *R* is the correlation coefficient):

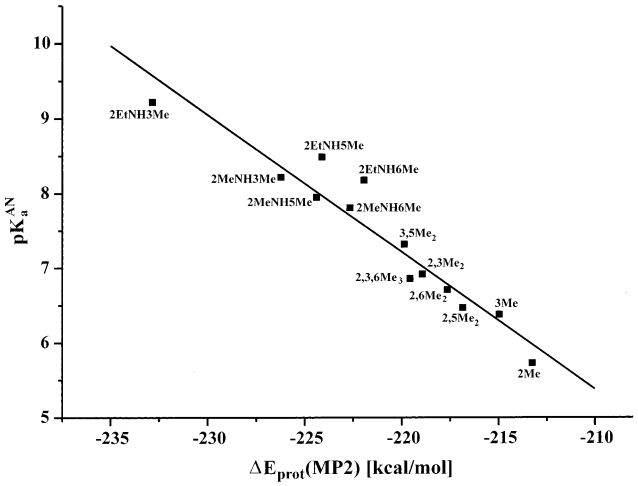

Figure 6. Plot of pK_a^{AN} against ΔE_{prot}(MP2) for the substituted 4-nitropyridine *N*-oxides under study. Abbreviations for *N*-oxides are given in the graph.

$$pK_a^{AN} = -0.16(0.02)\Delta E_{prot}(RHF) - 29.60(4.08) \qquad R = -0.939 \quad (11)$$

$$pK_a^{AN} = -0.16(0.02)\Delta G_{prot}(RHF) - 28.34(5.14) \qquad R = -0.903 \quad (12)$$

$$pK_a^{AN} = -0.18(0.03)\Delta E_{prot}(MP2) - 33.18(3.71) \qquad R = -0.957 \quad (13)$$

An exemplary graphical representation of these correlations is shown in Figure 6, where pK_a^{AN} is plotted against ΔE_{prot}(MP2). The relatively high *R* values reveal a strong correlation between the basicities of the *N*-oxides in vacuo and those determined in solution. Similar correlations were established previously for monosubstituted pyridine *N*-oxides[8] and pyridine derivatives.[5] It is worth noting that the quality of these correlations does not increase significantly upon going from the RHF to the MP2 level. This means that even the relatively cheap ab initio calculations accomplished at the RHF level enable prediction of the sequence of acidity constants of the protonated 4-nitropyridine *N*-oxide derivatives in polar nonaqueous solvents.

The energies of formation of the homocomplexed cations and Gibbs free energies calculated at both levels are collected in Table 4. Included also are values calculated at the RHF level under consideration of the base set superposition error (BSSE). The strongest impact of the BSSE on the energetic parameters is seen for the disubstituted and more greatly substituted compounds and for those with bulky substituents (methylamino and ethylamino groups). For the sake of comparison, included also are logarithms of the cationic homoconjugation constants of substituted 4-nitropyridine *N*-oxides (log K_{BHB^+}). Similar to the case of the protonation reactions, an attempt has been made to correlate the energetic parameters of the cationic homoconjugation with the experimental cationic homoconjugation constants in acetonitrile. After consideration of all the derivatives, the correlation coefficients were low, ranging between 0.5 and 0.6. Rejection of the two outliers did not improve the coefficients significantly. Much higher *R* values (in excess of 0.9) were obtained only after rejection of five systems, this resulting, however, in doubtful statistical significance. It can thus be concluded that there are no linear correlations for the substituted

TABLE 4: Calculated Cationic Homoconjugation Energies, ΔE_{BHB^+}(RHF), and Gibbs Free Energies, ΔG_{BHB^+}(RHF) (for Both ΔE_{BHB^+} and ΔG_{BHB^+}, BSSE Values Also Included), at the RHF Level, as Well as MP2, ΔE_{BHB^+}(MP2), Energies of Formation of Homocomplexed Cations and Gibbs Free Energies, Respectively, for 4-Nitropyridine *N*-Oxide Derivatives[a] (kcal/mol)[b]

N-oxide	ΔE_{BHB^+}(RHF)	ΔE_{BHB^+}(RHF) (BSSE)	ΔG_{BHB^+}(RHF)	ΔG_{BHB^+}(RHF) (BSSE)	ΔE_{BHB^+}(MP2)	log K_{BHB^+}
2Me	−25.68	−25.59	−13.98	−13.76	−28.20	1.89
3Me	−26.02	−26.51	−15.59	−13.97	−29.57	2.02
2,3Me$_2$	−26.39	−26.01	−15.83	−13.93	−30.30	2.10
2,5Me$_2$	−24.88	−24.96	−14.20	−15.22	−28.72	2.56
2,6Me$_2$	−25.36	−23.70	−15.90	−13.73	−30.49	2.28
3,5Me$_2$	−28.32	−28.31	−15.07	−14.96	−30.90	2.49
2,3,6Me$_3$	−25.99	−25.23	−15.40	−13.57	−30.23	2.42
2MeNH3Me	−30.04	−25.51	−15.03	−11.20	−33.94	2.32
2MeNH5Me	−40.33	−27.39	−24.57	−11.55	−41.11	2.44
2MeNH6Me	−25.02	−25.11	−12.04	−12.20	−30.06	2.72
2EtNH3Me	−31.20	−24.67	−20.21	−11.67	−40.00	2.72
2EtNH5Me	−26.19	−26.02	−16.17	−14.50	−29.66	2.91
2EtNH6Me	−26.41	−24.85	−14.59	−12.34	−32.00	2.68

[a] *N*-oxide abbreviations: 2Me, 2-methyl-4-nitropyridine *N*-oxide; 3Me, 3-methyl-4-nitropyridine *N*-oxide; 2,3Me$_2$, 2,3-dimethyl-4-nitropyridine *N*-oxide; 2,5Me$_2$, 2,5-dimethyl-4-nitropyridine *N*-oxide; 2,6Me$_2$, 2,6-dimethyl-4-nitropyridine *N*-oxide; 3,5Me$_2$, 3,5-dimethyl-4-nitropyridine *N*-oxide; 2,3,6Me$_3$, 2,3,6-trimethyl-4-nitropyridine *N*-oxide; 2MeNH3Me, 2-methylammino-3-methyl-4-nitropyridine *N*-oxide; 2MeNH5Me, 2-methylammino-5-methyl-4-nitropyridine *N*-oxide; 2MeNH6Me, 2-methylammino-6-methyl-4-nitropyridine *N*-oxide; 2EtNH3Me, 2-ethylammino-3-methyl-4-nitropyridine *N*-oxide; 2EtNH5Me, 2-ethylammino-5-methyl-4-nitropyridine *N*-oxide; 2EtNH6Me, 2-ethylammino-6-methyl-4-nitropyridine *N*-oxide. [b] Experimental log K_{BHB^+} values in acetonitrile are included for comparison.

4-nitropyridine *N*-oxides between the calculated, at both levels, energetic parameters of the cationic homoconjugation in the gas phase and experimentally derived constants of this equilibrium set up in acetonitrile. This situation is thus unlike that observed with monosubstituted pyridine *N*-oxides, where such correlations have been established,[8] but it is identical to that in the case of substituted pyridines.[5] This means that in systems with free and protonated 4-nitropyridine *N*-oxides the sequence of changes of the cationic homoconjugation constants in polar nonaqueous solvents cannot be predicted on the basis of the energies and Gibbs free energies of homoconjugation calculated by ab initio methods. In view of these findings, one of the plausible explanations of this situation may be the lack of correlation between calculated parameters (ΔE(RHF), ΔG(RHF), and ΔE(MP2)) of protonation and cationic homoconjugation of the 4-nitropyridine *N*-oxides in the gas phase. To verify this hypothesis, another effort to correlate these parameters was undertaken. Correlation coefficients in the derived correlations lead to the conclusion that the energies of protonation and cationic homoconjugation in the gas phase calculated by the ab initio methods at both the RHF and MP2 levels for the 4-nitropyridine *N*-oxides cannot be intercorrelated by a linear function. This finding may be explained by the high specificity of the systems owing to the presence of various substituents in the ring, including the electron-donating methyl, methylamino, and ethylamino groups adjacent to the electron-accepting nitro group which may interact. There may be, for instance, intramolecular charge transfer from the *N*-oxide group to the nitro group across the ring. The lack of correlations between calculated energetic protonation and cationic homoconjugation parameters in vacuo on one hand, and the existence of such correlations between experimental cationic homoconjugation constants and basicities in acetonitrile solutions on the other hand, shows that the interactions proceed more readily in the gas phase. Other reasons for the deviation of the systems from linearity may be both steric and *ortho* effects.[5,8,17]

Conclusions

The potentiometric measurements carried out in acetonitrile, together with calculations accomplished by using ab initio methods at the RHF and MP2 levels, for 13 derivatives of 4-nitropyridine *N*-oxide, have led to the following conclusions:

All the *N*-oxides studied are characterized by a distinct tendency toward cationic homoconjugation (with log K_{BHB^+} ranging between 1.89 and 2.91), determinable by the potentiometric titration method. Their basicities are stronger than that of the parent 4-nitropyridine *N*-oxide and fall within the pK_a^{AN} range 5.73−9.22.

The tendency toward cationic homoconjugation, as expressed by log K_{BHB^+}, is a linear function of the basicity of the compounds in acetonitrile (pK_a^{AN}).

The method of estimation of the dissociation constants in aqueous solution, pK_a^W, on the basis of the constants determined in nonaqueous solutions (for instance, in acetonitrile, pK_a^{AN}) can be applied to cationic acids obtained by protonation of substituted pyridine *N*-oxides. The pK_a^W values of the *N*-oxides studied estimated by this method fall in the range −1.51 to 0.40.

The 6-31G* basis set is sufficient to reliably predict the geometry of hydrogen bonded systems for substituted 4-nitropyridine *N*-oxides.

CPU-nonintensive ab initio calculations at the RHF level enable prediction of the sequence of acid dissociation constant values of protonated 4-nitropyridine *N*-oxide derivatives in polar nonaqueous solvents.

The variation of the cationic homoconjugation constant values in systems containing free and protonated substituted 4-nitropyridine *N*-oxides in the polar nonaqueous solvent acetonitrile cannot be predicted on the basis of energies and Gibbs free energies calculated by the ab initio methods applied.

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