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Ab Initio Study of the Energetics of Protonation and Homocomplexed Cation Formation in Systems with Pyridine and Its Derivatives

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The energetics of protonation of pyridine and a series of its derivatives, as well as the energetics of formation of hydrogen-bonded N...H...N homocomplexed cations in systems involving substituted pyridines and conjugate cationic acids were investigated by means of restricted Hartree−Fock (RHF) and Møller−Plesset (MP2) ab initio calculations. The Gaussian functional basis set 6-31G* was employed to calculate energy and Gibbs free energy of protonation and cationic homoconjugation in the gas phase. The proton potential of a homocomplexed pyridine cation exhibits a double minimum with a 5.7 kcal/mol energy barrier, which could be reduced to 2.7 kcal/mol by accounting for a thermodynamic correction factor. The calculated protonation energies, ΔE_{prot}, and Gibbs free energies, ΔG_{prot}, have been found to correlate well with the acid dissociation constants (expressed as pK_a values) in acetonitrile. On the contrary, the calculated energies, $\Delta E_{\mathrm{BHB^+}}$, and Gibbs free energies, $\Delta G_{\mathrm{BHB^+}}$, of formation of the homocomplexes do not correlate with the cationic homoconjugation constant values (expressed as $\log_{10} K_{\mathrm{BHB^+}}$) determined in acetonitrile.

Introduction

Acid−base equilibria set up in nonaqueous media in systems containing heterocyclic bases such as amines[1−5] (pyridine and substituted pyridines) and amine *N*-oxides[4,6−17] (pyridine *N*-oxide and its derivatives) have been systematically studied in our laboratory. Our interest was focused not only on acid dissociation[1−13]

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

of protonated pyridine and pyridine *N*-oxide, as well as their derivatives, but also on consecutive acid−base reactions[18] occurring in media of limited capability to exchange proton (polar aprotic and medium polar amphiprotic solvents), referred to as cationic homoconjugation:[1−13]

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

In the preliminary step, the above equilibria were systematically surveyed in the BH^+/B systems of substituted pyridine *N*-oxides in nonaqueous media, as well as by ab initio methods[19] in the gas phase. The calculations accomplished at the RHF and MP2 levels revealed that the experimental quantities were well related to the theoretical ones.[19]

In the next step, the BH^+/B systems containing substituted pyridines were investigated. All preceding studies of these systems were only fragmentary, involved various types of amines, and were carried out using various instrumental techniques.[20−30] Consequently, the results could not provide a sound basis for any generalizations in relation to acid−base properties of substituted pyridines in solutions. For this reason, the studies of acid−base equilibria in substituted pyridines systems have been planned to encompass a series of compounds of as large as possible basicity range. Further, polar solvents of a broad range of donor−acceptor properties were used, encompassing aprotic protophobic nitromethane,[2] acetonitrile,[1] propylene carbonate,[4] and acetone[3] over aprotic protophilic dimethyl sulfoxide[5] to amphiprotic methanol.[3]

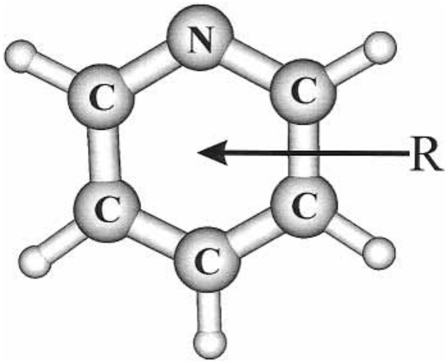

Figure 1. Molecular structure of pyridine derivatives.

The objective of the present study was to compare the experimental data obtained for pyridine and its derivatives (Figure 1 shows a molecular structure of this class of compounds) with theoretical ones and the correlation of experimental and calculated values. To do this, the energies, ΔE_{prot}(RHF,MP2), and the Gibbs free energies, ΔG_{prot}(RHF), of protonation as well as the energies, $\Delta E_{\mathrm{BHB^+}}$(RHF,MP2), and the Gibbs free energies, $\Delta G_{\mathrm{BHB^+}}$(RHF), for the formation of homocomplexed ions in the gas phase were first calculated by the ab initio method for the substituted pyridines under study. In the second step, an attempt has been made to correlate the calculated quantities with experimental values of acid dissociation constants, pK_a, and cationic homoconjugation constants, $\log_{10} K_{\mathrm{BHB^+}}$, in acetonitrile (AN) as a representative of polar nonaqueous solvents. In addition, estimation of the solvent effects has been attempted by using the self-consistent reaction field (SCRF) and more elaborate polarizable continuum (PCM) models. Apart from pyridine (Py), the following substituted pyridines were selected for theoretical considerations: 2-me-

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thylpyridine (2Pic), 3-methylpyridine (3Pic), 4-methylpyridine (4Pic), 2-aminopyridine ($2NH_2Py$), 3-aminopyridine ($3NH_2Py$), 4-aminopyridine ($4NH_2Py$), 2,4-dimethylpyridine (2,4Lut), 3-acetylpyridine (3AcOPy), 2-bromopyridine (2BrPy), 3-bromopyridine (3BrPy), 2-chloropyridine (2ClPy), 3-chloropyridine (3ClPy), and 3-cyanopyridine (3CNPy). The selected derivatives ensured representativeness of this class of compounds (a total of 14 derivatives) and were characterized by a wide range of pK_a values.

Methods

Closed-shell RHF calculations were carried out on pyridine and its derivatives, conjugate cationic acids, and homocomplexed cations using the GAMESS program[31] in the 6-31G* basis set. The starting geometry of the systems was constructed by the MOLMOL program.[32] All systems had an optimized geometry down to a gradient standard not lower than 0.0001 au/bohr (0.12 kcal/(mol·Å)).

The protonation and homoconjugation energies are defined by eqs 3 and 4, respectively:

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

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

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

Because in the optimization procedure a molecule is regarded as a rigid solid, after optimization has been completed, a thermodynamic correction was derived to account for the translational, rotational, and vibrational modes of the molecule. To do this, an energy Hessian matrix was computed[33] to check if the stationary point found was an actual minimum and to compute contributions of harmonic entropy and zero-point energy of the system (eqs 5 and 6).

Also, the perturbation theory[34] was applied to the calculation of protonation and homoconjugation energies at the MP2 level (Møller−Plesset). A dynamic correlation effect was computed for a single iteration for the structures optimized at the RHF level.[35]

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

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

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

where $\Delta E^{\circ}_{\mathrm{vib,prot}}$ and $\Delta E^{\circ}_{\mathrm{vib,BHB^+}}$ are the differences between the zero-point vibrational energies of the products and those of the substrates, respectively (these quantities can be calculated from eqs 5 and 6), p is the pressure, and V is the volume of a system under assumption that it satisfies the ideal gas equation-of-state; S_{rot} and S_{vib} are the rotational and vibrational entropies, respectively, and the term $^3/_2R$ refers to translational degrees of freedom of the system. A temperature of 298 K and a pressure of 1 atm were assumed in all calculations.

To estimate solvation contributions to the protonation and homoconjugation energies, self-consistent reaction field (SCRF) and polarizable continuum (PCM) models were applied. In the SCRF model the solvent is represented as a continuous dielectric and the solute as a spherical cavity of a given radius immersed in a dielectric of fixed dielectric constant corresponding to a particular solvent.[36−39] The PCM model[40−43] employs a van der Waals surface type cavity and parametrizes the cavity/dispersion contributions on the basis of the surface area. In this model, the free energy of a solvated system is described by two terms where the first term represents the solute Hamiltonian, which is modified by the electric field of the solvent. The second term includes both the solvent−solute stabilization energy, as well as the reversible work needed to polarize the solvent. The second term is evaluated from the induced charges on the reaction field cavity surface. In both models the dielectric constant of acetonitrile was assigned a value of 35.94.[44] Calculations were carried out for fixed geometries corresponding to the structures optimized in vacuo.

A proton potential in the PyH^+...Py homocomplex was calculated by accomplishing a series of constrained energy minimizations with fixed N...H distances and optimizing the remaining degrees of freedom.

Results and Discussion

The C−N−C angles calculated at the RHF level with a 6-31G* basis set for optimized neutral bases,[45−47] simple cations,[48] and complexed cations[49,50] match those experimentally determined, being by almost 1° larger than the latter. Their values oscillate around 120° and increase upon moving from the free bases (116.08−118.68°) over complexed cations (120.45−123.53°) to simple cations (121.22−124.41°). Very similar relations are retained within the homocomplexed cations between pyridine molecules acting as proton donors and proton acceptors. This finding is compatible with a conclusion reached from measurements carried out by using the neutron diffraction method,[49] which showed that in a homocomplexed cation one molecule of substituted pyridine can be regarded as the protonated one, a cation (proton donor), while the other (proton acceptor) is a neutral molecule.

Table 1 summarizes some selected bond lengths calculated for optimized pyridine bases, their conjugated acids and homocomplexed cations. Their values are in good agreement with those determined experimentally,[46−51] being shorter by only 0.01−0.02 Å. A closer inspection of the calculated C−N bond lengths shows that within the homocomplexed cation there is a shortening of the bond in the acceptor molecule relative to its length in the cationic acid, while in the donor molecule there is an increase in bond length. Nevertheless, experimentally determined bond lengths are usually different,[45] this way revealing the asymmetry of the NHN bond. Further, in non-protonated bases in the case of 2-substituted derivatives, remarkable is a shortening (up to 0.02 Å) of the bond C−N at the carbon atom carrying a substituent relative to the length of a bond on the opposite side of the ring (unsubstituted carbon atom). A similar effect, but somewhat less pronounced, is observed in the proton acceptor molecule within the complexed cation. This effect was observed experimentally during hydrogen bond formation between 2-aminopyridine and 5,5-diethylbarbituric acid.[51]

The N−H bond length in the cationic acids studied varies only slightly (between 0.998 and 1.003 Å), exhibiting a weak tendency toward shortening with decreasing basicity of substituted pyridines. There is, however, a distinct increase in the

TABLE 1: Selected Geometric Parameters of Substituted Pyridines,[a] Their Cationic Acids, and Homoconjugated Cations (Bond Lengths in Å) Calculated in the 6-31G* Basis Set

	base[b]	cationic acid		homoconjugated cation[b]			
	d(NC)	*d*(NC)	*d*(N−H)	*d*(N−N)	*d*(N−H)	*d*(NC)[c]	*d*(NC)[d]
$4NH_2Py$	1.323	1.337	0.998	2.878	1.029	1.330	1.339
$3NH_2Py$	1.327	1.333	1.002	2.887	1.031	1.324	1.327
$2NH_2Py$	1.325(1.321)	1.338	0.999	3.680	1.031	1.328(1.318)	1.338
2.4Lut	1.326(1.318)	1.337	1.001	2.878	1.029	1.332(1.326)	1.335
4Pic	1.318	1.338	1.001	2.884	1.031	1.328	1.331
3Pic	1.317	1.333	1.002	2.878	1.031	1.324	1.335
2Pic	1.324(1.321)	1.337	1.001	2.874	1.031	1.332(1.326)	1.336
Py	1.320	1.337	1.002	2.878	1.032	1.326	1.332
3AcOPy	1.319	1.333	1.002	2.868	1.031	1.324	1.331
3BrPy	1.321	1.336	1.003	2.889	1.031	1.326	1.331
2BrPy	1.325(1.303)	1.337	1.002	2.997	1.024	1.331(1.312)	1.337
3ClPy	1.320	1.335	1.003	2.889	1.031	1.324	1.331
2ClPy	1.325(1.304)	1.337	1.003	2.996	1.026	1.330(1.312)	1.333
3CNPy	1.321	1.333	1.003	2.897	1.031	1.324	1.331

[a] Substituted pyridine 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; 3-cyanopyridine, 3CNPy. [b] Two quantities are given for the 2-substituted derivatives (neutral molecules and homoconjugated cations). The first, standing before parentheses, refers to the bond length between the nitrogen atom and the unsubstituted carbon atom of the ring. The other quantity (in parentheses) refers to the bond length between the nitrogen atom and the substituted carbon atom of the ring. [c] Proton acceptor. [d] Proton donor.

N−H bond length (1.024−1.032 Å; in most cases 1.031 Å) upon going from a simple cation to the homocomplexed one due to hydrogen bond formation with the nitrogen atom of the proton acceptor. In this case there is no relation between the bond length and basicity of the substituted pyridine. Generally, the lengths are in good agreement with the experimental ones, which are 1.004 and 1.086 Å for protonated 2-aminopyridine[52] and the homocomplexed pyridine cation,[50] respectively.

The N...N distances between the proton donor (cationic acid−protonated substituted pyridine) and proton acceptor (conjugate substituted pyridine) range from 2.868 to 2.997 Å for all pyridine derivatives with the exception of $2NH_2Py$. These values differ by 0.01−0.02 Å from the experimental ones, amounting to 2.744 and 2.698 Å for the complexed pyridine cation[50] and the 4-aminopyridine cation,[49] respectively. The disagreement between the experimental and calculated N...N distances can be attributed to the classical treatment of the vibrational degrees of freedom of the NHN moiety and absence of the crystal field effects.[53] It should be noted that the values close to the lower limit are characteristic for the 3- and 4-substituted derivatives while the ortho-substituted (2-substituted) ones display the greatest distances. This finding is supported by experiments where the N...N distances in complexed cations formed by 2-substituted pyridines are markedly greater than those of both unsubstituted and 4-substituted derivatives, amounting[47] to 2.85 Å. As seen in Table 1, the homocomplexed cation of 2-aminopyridine exhibits a still greater N...N distance of 3.04 Å. This can be explained in terms of the possibility of formation of a structure consisting of a double hydrogen bonding between the nitrogen atoms of the ring and those of the NH_2 substituents (Figure 2; the MOLMOL program[32] has been employed for deriving the structure).

Bearing in mind the calculated N...N distances on one hand and the N−H bond lengths in the homocomplexed cation on the other, a conclusion reached from experimental data[49,50] stating that the N−H...N bonds in cations formed by pyridines are weak asymmetric hydrogen bondings can unambiguously be confirmed. An energetically optimized structure of the homocomplexed pyridine cation is shown in Figure 3. The hydrogen bonding in it is asymmetric. The angles of both pyridine rings relative to the axis determined by two nitrogen atoms are not tied with symmetry elements. Moreover, the calculations show that the pyridine rings in the homocomplex are even not coplanar. Similar conclusions were reached from the ab initio study of homocomplexed cations formed by pyridine *N*-oxide.[19,54] The calculated structures of the homocomplexed cations formed by substituted pyridines are all similar with the exception of the cation formed by NH_2Py (Figure 2).

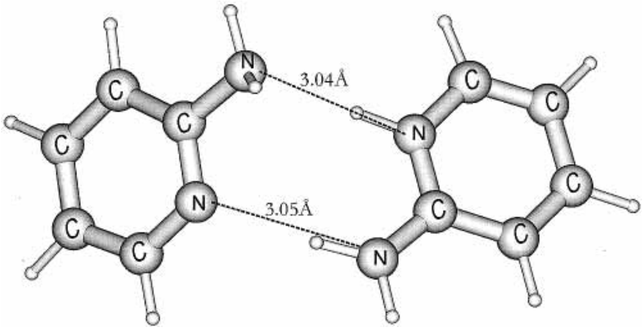

Figure 2. Equilibrium structure of the $2NH_2PyHPy2NH_2^+$ cation calculated with the 6-31G* basis set.

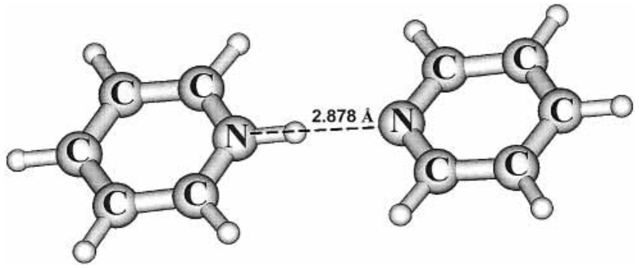

Figure 3. Equilibrium structure of the $PyHPy^+$ cation calculated with the 6-31G* basis set.

The foregoing consideration of the geometric parameters leads to a general conclusion that the bond lengths and angles calculated by the ab initio method are compatible with experimental data and that they change upon going from bases over simple cations to the complexed cations in the same sequence as do those of pyridine *N*-oxide and substituted pyridine *N*-oxide cations.[19] Furthermore, for pyridine, the parameters are in very good agreement with those previously calculated by ab initio methods. For instance, the C−N bond length and the CNC angle calculated by Lane et al.[55] are respectively 1.321 Å and 117.7°.

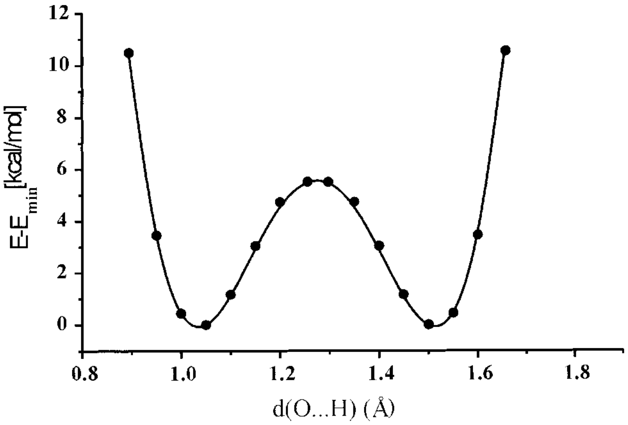

Figure 4. Energy variation on proton potential in the N−H···N bridges of the pyridine homoconjugated cation. Filled circles represent points where 6-31G* energies have been calculated.

TABLE 2: Energies, ΔE_{prot}(RHF), and Gibbs Free Energies, ΔG_{prot}(RHF), of Protonation Calculated at the RHF Level, as Well as MP2, ΔE_{prot}(MP2), and PCM, ΔG_{prot}(PCM), Protonation Energies and Gibbs Free Energies for Pyridine Derivatives[a] (kcal/mol) (pK_a Values[1] in Acetonitrile Included for Comparison)

compd	ΔE_{prot}(RHF)	ΔG_{prot}(RHF)	ΔE_{prot} (MP2)	ΔG_{prot} (PCM)	pK_a
4NH$_2$Py	−239.30	−239.59	−243.38	−44.57	18.38
3NH$_2$Py	−235.34	−235.76	−238.36	−37.43	14.35
2NH$_2$Py	−231.74	−232.29	−238.11	−39.09	14.66
2,4Lut	−234.16	−234.56	−237.11	−38.47	15.00
4Pic	−229.50	−230.75	−233.34	−37.31	14.52
3Pic	−229.35	−227.52	−232.72	−36.22	13.66
2Pic	−229.40	−230.90	−233.97	−37.13	13.88
Py	−225.97	−226.10	−228.95	−35.95	12.60
3AcOPy	−224.33	−223.92	−229.58	−31.22	10.75
3BrPy	−218.98	−219.10	−224.56	−30.93	9.49
2BrPy	−218.77	−218.90	−223.31	−26.45	7.02
3ClPy	−218.22	−218.33	−223.31	−30.27	10.01
2ClPy	−217.21	−216.33	−221.43	−25.65	6.80
3CNPy	−210.97	−211.14	−216.41	−27.84	8.04

[a] Substituted pyridine abbreviations: 4-aminopyridine, 4NH$_2$Py; 3-aminopyridine, 3NH$_2$Py; 2-aminopyridine, 2NH$_2$Py; 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; 3-cyanopyridine, 3CNPy.

In summary it can be stated that the 6-31G* basis set is sufficient to reliably predict the geometry of hydrogen-bonded systems for substituted pyridines. A similar conclusion concerning this type of basis set was reached as regards the possibility of estimation of spectroscopic features of hydrogen bonds formed by pyridine.[56]

The proton potential in the N...H...N bridge of the pyridine homocomplexed cation shown in Figure 4 exhibits a potential barrier of 5.7 kcal/mol, this being ca. 2.5 times as high as that of the pyridine *N*-oxide homocomplexed cation.[19] After accounting for a thermodynamic correction, the barrier has been suppressed to a still relatively high level of 2.7 kcal/mol. More precise simulation[57] of the proton-transfer reaction in solution and, consequently, the accurate value of potential barrier needs mixed quantum/classical molecular dynamics methods, e.g., the mean field[58,59] or the surface hopping approaches[60,61] to be applied. Nevertheless, the calculated barrier can be treated as indicative of a restriction of the proton movement within the hydrogen-bonded bridge and the inherent asymmetry of the hydrogen bond. This finding is in accord with the previously drawn conclusions and with experimental evidence[49] referring to structural and spectroscopic features of similar systems.

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 experimental pK_a values in acetonitrile[1] are collected in Table 2. For comparison with theoretical quantities, those determined only in one nonaqueous solvent were taken, because, as was demonstrated previously,[62] the dissociation constant values (expressed as pK_a) in various polar solvents can be linearly intercorrelated. Acetonitrile was chosen as a representative of nonaqueous solvents because it belongs to a small class of those solvents in which the acid−base constants were determined with the greatest precision.[63]

As seen in Table 2, theoretical quantities change in the same direction, as do the experimental pK_a values. This prompted us to make an attempt at finding linear correlations between the pK_a's and ΔE_{prot} and ΔG_{prot} values at the RHF level and the ΔE_{prot} at the MP2 level (ΔE_{prot}^{MP2}). The following linear functions can be written for the found correlations:

$$\mathrm{p}K_a = -0.344(0.030)\Delta E_{prot} - 65(7) \qquad R = -0.964 \quad (7)$$

$$\mathrm{p}K_a = -0.338(0.029)\Delta G_{prot} - 64(7) \qquad R = -0.966 \quad (8)$$

$$\mathrm{p}K_a = -0.367(0.034)\Delta E_{prot}^{MP2} - 72(8) \qquad R = -0.960 \quad (9)$$

in which R is the correlation coefficient. A closer inspection of these equations shows that parameters a and b, as well as coefficient R, in individual equations are very close to one another, the R values being relatively high. The latter was still higher when 2-substituted pyridines were excluded from the correlations. 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. Namely, the ortho substituent (position 2 or 6) has been claimed to shield the nitrogen atom thus making difficult attachment of the hydrogen atom. A significant influence of this effect on the quality of the correlations has been reported for substituted pyridine *N*-oxides.[19] After exclusion of the 2-substituted compounds, the following equations were obtained:

$$\mathrm{p}K_a = -0.360(0.026)\Delta E_{prot} - 69(6) \qquad R = -0.984 \quad (10)$$

$$\mathrm{p}K_a = -0.359(0.025)\Delta G_{prot} - 68(6) \qquad R = -0.984 \quad (11)$$

$$\mathrm{p}K_a = -0.393(0.028)\Delta E_{prot}^{MP2} - 78(6) \qquad R = -0.985 \quad (12)$$

The high correlation coefficient values in these equations lead to the conclusion that the experimental pK_a values of the protonated substituted pyridines can be represented as linear functions of theoretical energetic parameters of protonation of these compounds in the gas phase. Similar correlations were also found for substituted pyridine *N*-oxides.[19] It should be emphasized that the quality of the correlations does not improve significantly upon moving from the RHF level to the MP2 level. This means that even CPU nonintensive ab initio calculations at the RHF level enable prediction of the sequence of acid dissociation constants of protonated pyridines in polar solvents. For the sake of comparison, relationships of pK_a in acetonitrile vs ΔG_{prot} are shown in Figure 5 with inclusion of all the substituted pyridines studied (solid line) and of those after rejection of the 2-substituted derivatives (broken line), eqs 8 and 11, respectively.

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 Gibbs free energies and

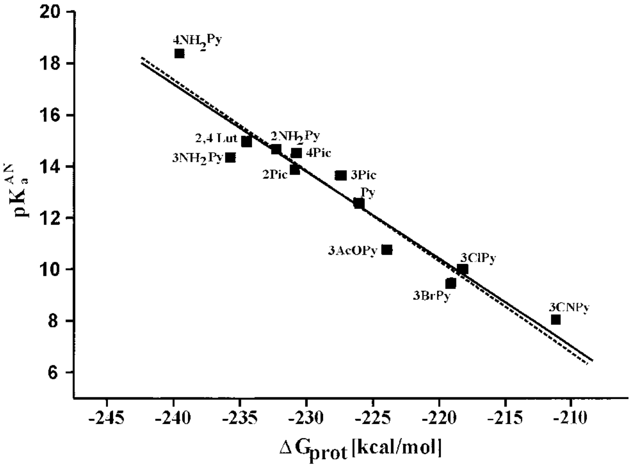

Figure 5. Relationships of pK_a in acetonitrile vs ΔG_{prot} in vacuo. The solid line denotes inclusion of all the substituted pyridines studied, and the broken line denotes the relationship after rejection of the 2-substituted derivatives. Abbreviations for pyridine derivatives are given in the graph.

experimental pK_a values in acetonitrile is concerned. On the contrary, a ranking of the SCRF ΔE_{prot} and ΔG_{prot} values has a weaker bearing (in relation to RHF ΔE_{prot} and ΔG_{prot} values) on the ranking of experimental pK_a values. Therefore, these results are not included in Table 2. Consequently, it can be concluded that the SCRF model is too crude to be successfully adopted for such chemical species as studied here, substituted pyridines and their conjugated cations. Similar conclusions regarding the use of the SCRF model have been reached previously[19] in our studies of the substituted pyridine *N*-oxide systems, as well as by other authors.[64,65]

In the next step the polarizable continuum model[40-43] (PCM) in which the solute cavity is represented as a union of spheres was used to improve the agreement between the calculated Gibbs free energies and experimental pK_a values in acetonitrile. The values obtained using the PCM model Gibbs free energies of protonation, ΔG_{prot}(PCM), including the solvation effect, are collected in Table 2. It turned out that their values correlate very well with the experimental pK_a values in acetonitrile according to the following relationship:

$$\mathrm{p}K_a = -0.622(0.020)\Delta G_{prot}(\mathrm{PCM}) - 9.2(0.7) \qquad R = -0.994 \quad (13)$$

The high value of correlation coefficient *R* in the above equation enables us to conclude that the introduction of solvation in the PCM model improves the agreement between the calculated Gibbs free energies and experimental pK_a values in nonaqueous media. To check whether the so-called ortho effect is able to influence the quality of the above correlations between PCM energies Gibbs free energies and acetonitrile pK_a values, the 2-substituted derivatives were excluded from correlation (13). After exclusion of the 2-substituted compounds, the following equation was obtained:

$$\mathrm{p}K_a = -0.623(0.030)\Delta G_{prot}(\mathrm{PCM}) - 9.1(1.0) \qquad R = -0.991 \quad (14)$$

which means that the ortho effect has no influence on the PCM Gibbs free energy values. This is illustrated in Figure 6 where the relationships of pK_a in acetonitrile vs ΔG_{prot}(PCM) are shown with inclusion of all the substituted pyridines studied (solid line) and of those after rejection of the 2-substituted derivatives (broken line), eqs 13 and 14, respectively.

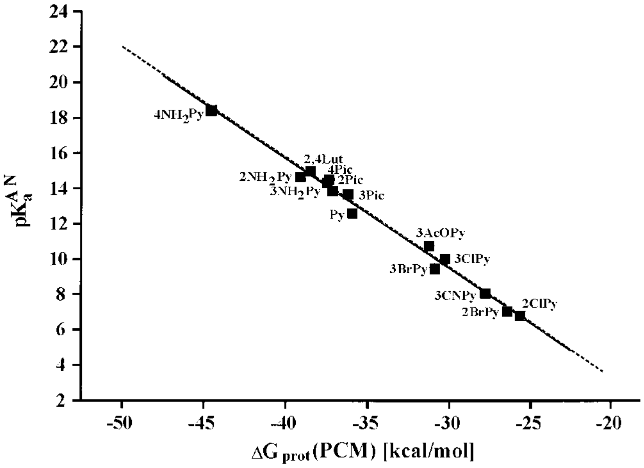

Figure 6. Relationships of pK_a in acetonitrile vs ΔG_{prot} in acetonitrile solution calculated using the PCM model of solvation. The solid line denotes inclusion of all the substituted pyridines studied, and the broken line denotes the relationship after rejection of the 2-substituted derivatives. Abbreviations for pyridine derivatives are given in the graph.

Table 3 summarizes the calculated energies, ΔE_{BHB^+}(RHF), and Gibbs free energies, ΔG_{BHB^+}(RHF), as well as the ΔE_{BHB^+}(MP2) energies of formation of the homocomplexed cations together with experimental cationic homoconjugation constant values (in logarithmic form) of the free and protonated pyridines in acetonitrile.[1] The constant values determined in one solvent only have been included, because the logarithms of cationic homoconjugation constants determined in various solvents can be correlated linearly.[66] Moreover, the number of pK_a and $\log_{10} K_{BHB^+}$ values of substituted pyridines determined in this solvent was greatest[1] as compared with that determined in other solvents.[2-4]

Similar to the protonation reactions, an attempt has been made to establish a correlation between calculated values and experimental data for the cationic homoconjugation. The very low correlation coefficient values in relationships between the $\log_{10} K_{BHB^+}$ values in acetonitrile and ΔE_{BHB^+}($R = 0.054$), as well as ΔG_{BHB^+}($R = -0.036$) values at the RHF level and between ΔE_{BHB^+} one at the MP2 level ($R = 0.473$) show that there are no linear correlations between the energy parameters of the cationic homoconjugation in the gas phase calculated at both levels and experimental constant values in acetonitrile. In this situation, an attempt has been made to establish a correlation between theoretical (ΔE_{BHB^+}, ΔG_{BHB^+}, $\Delta E^{MP2}_{BHB^+}$) energy parameters and homoconjugation constant values determined in other polar solvents studied. However, also in this case there was no correlation between theoretical and experimental quantities characterizing cationic homoconjugation in substituted pyridine systems. This means that the sequence of changes of the cationic homoconjugation constants in systems containing free and protonated pyridines in polar solvents cannot be predicted on the basis of energies and Gibbs free energies calculated by ab initio methods at the RHF and MP2 levels.

In the next step, an attempt to estimate the solvent effects by employing the SCRF and PCM models was done. The results of calculations confirmed that the SCRF model is definitely too crude to be successfully adopted for such intricate chemical species as the homocomplexed cations studied here, as far as the linear correlations between the calculated homoconjugation energies and experimental cationic homoconjugation constant values are concerned. In the case of PCM approach some improvement in these correlations was observed. The correlation

TABLE 3: Calculated Cationic Homoconjugation Energies, ΔE_{BHB^+}(RHF), and Gibbs Free Energies, ΔG_{BHB^+}(RHF), at the RHF Level, as Well as MP2, ΔE_{BHB^+}(MP2), and PCM, ΔG_{BHB^+}, Cationic Homoconjugation Gibbs Free Energies for Pyridine Derivatives[a] (kcal/mol) ($\log_{10} K_{BHB^+}$ Values[1] in Acetonitrile Included for Comparison)

compd	ΔE_{BHB^+}(RHF)	ΔG_{BHB^+}(RHF)	ΔE_{BHB^+}(MP2)	ΔG_{BHB^+}(PCM)	$\log_{10} K_{BHB^+}$
4NH$_2$Py	−19.79	−9.42	−6.11	−4.51	1.76
3NH$_2$Py	−14.27	−3.99	−11.39	−6.43	[b]
2NH$_2$Py	−19.25	−9.57	−11.79	−6.93	[b]
2,4Lut	−18.15	−8.2	−6.79	−4.64	1.19
4Pic	−18.85	−8.35	−6.20	−4.06	1.77
3Pic	−18.52	−6.71	−6.09	−4.15	1.48
2Pic	−19.68	−6.55	−6.93	−5.51	1.47
Py	−18.31	−7.88	−7.46	−4.18	[b]
3AcOPy	−22.00	−6.24	−6.20	−2.54	1.34
3BrPy	−15.99	−5.22	−5.97	−3.66	1.25
2BrPy	−19.99	−8.14	−7.57	−5.85	0.94
3ClPy	−16.01	−5.33	−6.44	−3.47	1.44
2ClPy	−17.83	−5.52	−6.73	−2.65	1.85
3CNPy	−12.83	−4.32	−6.66	−2.82	[b]

[a] Substituted pyridine abbreviations: 4-aminopyridine, 4NH$_2$Py; 3-aminopyridine, 3NH$_2$Py; 2-aminopyridine, 2NH$_2$Py; 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; 3-cyanopyridine, 3CNPy. [b] The cationic homoconjugation constant could not be determined from potentiometric measurements.

coefficient R in the relationship between the $\log_{10} K_{BHB^+}$ values in acetonitrile and calculated ΔG_{BHB^+} values was increased from 0.054 to 0.429 when the solvation effect was taken into account. Nevertheless, this value is still too low to claim the existence of the linear correlation between the experimental and calculated quantities. The calculated values of ΔG_{BHB^+}(PCM) are summarized in Table 3.

This lack of correlation between quantities describing cationic homoconjugation in systems involving substituted pyridines in the gas phase (calculated by ab initio methods ΔE_{BHB^+}, ΔG_{BHB^+}, and $\Delta E^{MP2}_{BHB^+}$ values) and the cationic homoconjugation constants, K_{BHB^+}, determined in polar solvents, was not surprising in view of a conclusion drawn from previous experiments. Namely, the studies of acid dissociation and cationic homoconjugation in a variety of polar solvents[1−3] have shown the lack of linear correlations between experimental cationic homoconjugation, $\log_{10} K_{BHB^+}$, and acid dissociation, pK_a, constant values in the acid−base systems considered. A preliminary hypothesis based on purely experimental grounds interpreted the lack of the discussed correlations in terms of a weak tendency of substituted pyridines to enter into cationic homoconjugation reactions in nonaqueous media. Consequently, cationic homoconjugation constant values could not be determined in almost all the substituted pyridine systems surveyed, while in those where they could be established, they were relatively low (of the order of approximately 2, as expressed by $\log_{10} K_{BHB^+}$) and burdened with relatively high values of standard deviation. In view of these findings on one hand and the lack of correlations between quantities describing cationic homoconjugation in systems involving substituted pyridines in the gas phase and in polar nonaqueous solvents on the other, one of the reasonable explanations of this situation would be the lack of correlation between the calculated ΔE(RHF), ΔG(RHF), and ΔE(MP2) parameters of the protonation and homoconjugation reactions in the gas phase. To check the reliability of this hypothesis, an attempt has been made to correlate these quantities. The following relationships were thus obtained:

$$\Delta E_{prot} = 0.176(0.054)\Delta E_{BHB^+} + 22(12) \qquad R = 0.714 \quad (15)$$

$$\Delta G_{prot} = 0.185(0.027)\Delta G_{BHB^+} + 35(6) \qquad R = 0.905 \quad (16)$$

$$\Delta E^{MP2}_{prot} = 0.170(0.073)\Delta E^{MP2}_{BHB^+} + 31(17) \qquad R = 0.589 \quad (17)$$

An inspection of the correlation coefficient values in these equations shows that the protonation and cationic homoconjugation energies in the gas phase calculated by the ab initio method at the RHF and MP2 levels for the substituted pyridine systems cannot be linearly correlated. As far as the Gibbs free energy is concerned (eq 16), it can be stated that there is only a weak correlation (correlation coefficient almost exactly equal to 0.9) between the quantities describing the protonation and cationic homoconjugation processes. This situation thus differs from that reported for substituted pyridine *N*-oxides where such a correlation has been established.[19] This difference can be explained in terms of the influence of various factors in the O−H···O and N−H···N systems on the tendency toward cationic homoconjugation. Namely, in the O−H···O systems the electrostatic interactions play a main role, whereas in the N−H···N systems other factors have to be also taken into account. A plausible explanation is the fact that nitrogen in amine groups has a greater polarizability than oxygen in *N*-oxides and, therefore, the polarizability and charge-transfer contribution to the hydrogen bonding energy is lower in the $[N-H\cdots N]^+$ than in the $[O-H\cdots O]^+$ bridges. This lack of correlation in the case of quantities calculated by ab initio methods manifests itself in the lack of correlation between experimental quantities. The low probability of a theoretically predictable (in the case of Gibbs free energy) weak linear correlation between the quantities describing the energetics of protonation and homoconjugation processes in polar solvents is suppressed by low homoconjugation constant values, burdened, in addition, by large standard deviation values. As a consequence, there is the observed[1−3] lack of correlation in the nonaqueous media between cationic homoconjugation constant values and the basicity of the pyridine derivatives.

Conclusions

The calculations accomplished for pyridine and 13 substituted pyridine systems (neutral bases, protonated bases—simple cations and homocomplexed cations) lead to the following conclusions.

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

CPU nonintensive ab initio calculations at the RHF level enable prediction of the sequence of acid dissociation constant values of protonated pyridine derivatives in polar nonaqueous solvents. Corrections made by inclusion of the MP2 perturbation corrections do not improve correlations between the calculated protonation energies (Gibbs free energies) and experimental acid dissociation constant values in nonaqueous solvents. On the other hand, the introduction of solvation in the PCM model improves the agreement between the calculated energies (Gibbs free energies) and experimental pK_a values in nonaqueous media.

The variation of the cationic homoconjugation constant values in systems containing free and protonated pyridines in polar nonaqueous solvents cannot be predicted on the basis of energies and Gibbs free energies calculated by ab initio methods at the RHF and MP2 levels.

The proton potential of a homocomplexed pyridine cation exhibits a relatively high energy barrier even when the thermodynamic correction is included. The existence of such a barrier is indicative of a restriction of the proton movement within the hydrogen-bonded bridge and that the homoconjugated cation is effectively asymmetric.

The self-consistent reaction field (SCRF) model is not suitable for calculation of solvation effects in complicated systems devoid of spherical shape.

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