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Experimental and theoretical studies of solvent effects on the hydrogen bonds in homoconjugated cations of substituted 4-halo (Cl, Br) pyridine N-oxide derivatives

Łukasz Gurzyński a, Aniela Puszko b, Mariusz Makowski a, Lech Chmurzyński a,*

a Department of General and Inorganic Chemistry, University of Gdańsk, Sobieskiego 18, 80-952 Gdańsk, Poland
b Department of Organic Chemistry, School of Economics, Wrocław, Poland

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Abstract

Hydrogen bond OHO-type bridges formed between six substituted 4-halo (Cl, Br) pyridine N-oxide systems and their simple cations have been investigated by using the potentiometric titration method. The formation constants of these complexes (expressed as \( \lg K_{BBH^+} \)) have been determined in two non-aqueous aprotic solvents with different polarity, i.e., acetone (AC) and acetonitrile (AN). It has been observed that tri- and tetra-substituted pyridine N-oxides [B] and their cationic acids [BH+] form stable homocomplexed cations [BHB+] stabilized by O-C1/C1/C1/C1 bridges in both solvents used. It has been found that the most stable homocomplexed system is formed by 3,5-dimethyl-4-chloropyridine N-oxide (3,5Me24ClPyO). The \( \lg K_{BBH^+} \) values for this compound in acetone and acetonitrile are 3.15 and 2.82, respectively. Furthermore, by using \textit{ab initio} methods at the RHF and MP2 levels utilizing the Gaussian 6-31++G** basis set, the energies of formation of the homocomplexed cations and Gibbs free energies have been determined \textit{in vacuo}. The calculated energy parameters \textit{in vacuo} have been compared with the cationic homoconjugation constants determined potentiometrically in acetone and acetonitrile to establish a correlation between these magnitudes. Additionally, the results of potentiometric measurements have been used to determine the acidity constants of the conjugate acids of N-oxides.

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1. Introduction

The hydrogen bond belongs to the most significant concepts in supra-molecular chemistry, with important implication in molecular biology and materials science. Although, the term “hydrogen bond” has emerged in 1930 [1], the basic idea of a weak and specific interaction involving the atoms of hydrogen is much older [2,3]. This relatively weak chemical force, only about 10% as strong as covalent bonds, has a very important effect on the chemical and physical properties of water. It is responsible for the tertiary structure of proteins, and also plays an important role in biological systems, involving DNA [4–6]. Nowadays, over 70 years later after Huggins’ publication [1], the nature of the hydrogen bonding (H-bonding) in the solution and the solid phase is not fully understood.

For the last several years, considerable advances have been made in understanding the nature of the hydrogen bonding in the liquid phase. A large number of experimental data on the H-bonding between the N-oxide group and mineral acids, phenols, carboxylic acids, and water are available in the literature [7–12], but only few on the hydrogen bonds in non-aqueous solutions.

On the other hand, substituted heterocyclic amines with the N → O group are worth studying due to their interesting physicochemical properties [13–15] and bioactivity [16,17]. For instance, it has been observed that pyridine
N-oxide (PyO) and 4-morpholino pyridine N-oxide are able to enhance the solubilization of silica in water, that is very important for the plant silicon content and pest resistance of the edible plants [13,14]. Moreover, Zięba et al. [16] investigated substituted pyridine N-oxides as a novel generation of the radio-sensitizers as a drug that makes tumour cells more sensitive to radiation therapy. The search for new hypoxic cell-specific radio-sensitizers has shown that amine N-oxides are better compounds in radiotherapy of cancer than the most promising nitroimida-zoles. Furthermore, experiments carried out by Balzarini et al. revealed that pyridine N-oxide derivatives have inhibitory activity against the human SARS-CoV [17].

The interactions between halo-substituted N-oxides and cationic forms of these compounds in solution are very complex. In polar aprotic solvents containing amine N-oxides and their protonated forms, not only the simple species can be found but also complexes stabilized by the H-bonding; for example homoconjugated cations. Consequently, the following equilibria of acid dissociation (1) and cationic homoconjugation (2) can be observed [18]:

\[ \text{BH}^+ \rightleftharpoons \text{B} + \text{H}^+ \quad K_a \]  
\[ \text{BH}^+ + \text{B} \rightleftharpoons \text{BHB}^+ \quad K_{\text{BHB}^+} \]

where B denotes amine N-oxide and BH⁺ is a cationic acid of an N-oxide. The cationic homoconjugation reaction (2) creates symmetric complex ions, \([\text{BHB}^+]\) stabilized by hydrogen bonding of the \(\text{O} \cdots \text{H} \cdots \text{O}\) type. The equilibrium structure of the homoconjugated cation of 3,5-dimethyl-4-bromopyridine N-oxide \((3,5\text{Me}_2\text{4BrPyO})\) calculated with the 6-31++G** basis set is presented in figure 1.

In this aspect, the principal purpose of the present studies is to show the results of experimental investigations of homocondensed cations with symmetric hydrogen bond bridges \(\text{O} \cdots \text{H} \cdots \text{O}\), resulting from the reaction of 4-halo (Cl, Br) pyridine N-oxides with a conjugate cationic acids in non-aqueous solvents, i.e., acetone (AC) and acetonitrile (AN). Two non-aqueous aprotic solvents with different polarity, i.e., acetone (donor number, \(\text{DN} = 17.0\) [19]), and acetonitrile (\(\text{DN} = 14.9\) [19]) were chosen in our experimental studies because of their strong differentiating capacity and weak acid-base properties, which enable to observe specific, subtle properties of solutions, i.e., homo-conjugation equilibria.

Consequently, homoconjugation equilibria have been investigated in systems formed by six halo pyridine N-oxide derivatives (their acronyms in parentheses): 2,5-dimethyl-4-chloropyridine N-oxide (2,5Me₂₄ClPyO), 2,5-dimethyl-4-bromopyridine N-oxide (2,5Me₂₄BrPyO), 3,5-dimethyl-4-chloropyridine N-oxide (3,5Me₂₄ClPyO), 3,5-dimethyl-4-bromopyridine N-oxide (3,5Me₂₄BrPyO), 2,3,6-trimethyl-4-chloropyridine N-oxide (2,3,6Me₃₄ClPyO), and 2,3,6-trimethyl-4-bromopyridine N-oxide (2,3,6Me₃₄BrPyO). Three of them contain a chlorine atom at position 4 and three others a bromine atom at that position. In addition to characterize these complexes, we use two approaches, i.e., the potentiometric titration method and \(ab\) \(initio\) methods at the RHF and MP2 levels. Furthermore, the calculated energy parameters of formation of these cations obtained \(in\) \(vacuo\) were compared with the experimental results (expressed as \(\text{lg} \ K_{\text{BHB}^+}\)) obtained in acetonitrile and acetone.

2. Experimental

2.1. Compounds

All the pyridine N-oxide derivatives were obtained by the Talik and Puszko procedure [20]. The purified amine N-oxides were stored in evacuated desiccator over \(\text{P}_2\text{O}_5\).

The salts of the N-oxides (perchlorates) and auxiliary compounds for potentiometric measurements were obtained and purified by using procedures described in the proceeding papers [21,22]. The purity of the perchlorates of N-oxides was checked by the elemental analysis. Results obtained by elemental analyses for all species studied are shown in table 1.

2.2. Solvents

Acetone (AC). Acetone was purified by the Vogel method [23]. To 1 dm³ of acetone (Aldrich, mass fraction purity 0.999 HPLC), boiling under reflux, small portions of crystalline \(\text{KMnO}_4\) were added until attaining a violet tinge of solution. After cooling and decantation from a precipitate of manganese oxides, the solvent was dried over CaSO₄, filtered and distilled over a Vigreaux column protected with a glass tube packed with a freshly calcined CaCl₂. A fraction boiling at \(T = 329.45\) K was collected.

Acetonitrile (AN). Acetonitrile was purified by a modified Coetzees procedure [24]. In the first step, acetonitrile (Aldrich, mass fraction purity 0.9993 HPLC) was dried with CaH₂ (10 g · dm⁻³) for 48 h. After decantation solvent was then distilled over \(\text{P}_2\text{O}_5\) (3 g · dm⁻³). The distillate was dried again with CaH₂ and distilled after 48 h. A fraction boiling at \(T = 354.75\) K was collected.

The determination of water content in acetone (AC) and acetonitrile (AN) was carried out by Karl–Fischer method.

![Figure 1](image-url)
TABLE 1
Experimental compositions of the perchlorates of N-oxides studied checked by the elemental analysis

| N-oxide | Experimental | Calculated |
|---------|--------------|------------|
| 2,5Me₄ClPyO | 32.51%C, 5.34%N, 3.50%H | 32.58%C, 5.42%N, 3.51%H |
| 3,5Me₂ClPyO | 32.55%C, 5.26%N, 3.48%H | 32.58%C, 5.24%N, 3.49%H |
| 2,3,6Me₃ClPyO | 35.29%C, 5.29%N, 4.07%H | 35.31%C, 5.14%N, 4.07%H |
| 2,5Me₄BrPyO | 27.79%C, 4.59%N, 3.18%H | 27.79%C, 4.63%N, 2.99%H |
| 3,5Me₂BrPyO | 27.57%C, 4.52%N, 3.04%H | 27.79%C, 4.63%N, 2.99%H |
| 2,3,6Me₃BrPyO | 30.60%C, 4.43%N, 3.51%H | 30.35%C, 4.42%N, 3.50%H |

For comparison calculated values are included.

* N-oxide abbreviations 2,5Me₄ClPyO-2,5-dimethyl-4-chloropyridine N-oxide; 3,5Me₂ClPyO-3,5-dimethyl-4-chloropyridine N-oxide; 3,5Me₂BrPyO-3,5-dimethyl-4-bromopyridine N-oxide; 2,3,6Me₃ClPyO-2,3,6-trimethyl-4-chloropyridine N-oxide; 2,3,6Me₃BrPyO-2,3,6-trimethyl-4-bromopyridine N-oxide.

In both cases residual water content was less than 0.05%.

2.3. Experimental procedures

The titration method utilized the cell of the type: indicator glass electrode | the system studied || modified calomel electrode.

The potential difference ($E$) was measured with a precision of ±0.01 mV by using a potentiometric microtitration unit equipped with a computer-aided microtitrator system and a millivoltmeter. An ESH 10-00 (Metron) indicator glass microelectrode and an EK10-00 (Metron) reference calomel microelectrode were used. A reference calomel microelectrode was filled with 0.1 mol · dm⁻³ tetra-n-butylammonium chloride in non-aqueous solvent. All the $E$ measurements were conducted at a constant ionic strength equal to 0.001 mol · dm⁻³. This was kept stable by addition to the titrant of a salt solution in such a quantity as to equalize concentrations of both solutions. The titration cell initially contained 3 cm³ of N-oxide perchlorate and was thermostatted (Lauda E 100). Concentrations of the titrant N-oxides were $10^{-2}$ mol · dm⁻³ and those of the perchlorate N-oxides were $10^{-3}$ mol · dm⁻³. The titrant was added dropwise using a 2.5 cm³ Hamilton syringe with an accuracy of 0.01 cm³. The potential difference ($E$) was recorded for each titration point, when the measured potential was stable (no potential changes were observed for 150 s). The same potentiometric-titration procedure was implemented in the electrode calibration, with tetra-n-butylammonium picrate in the titrant and mixture of this salt and picric acid in the titrand, respectively.

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2.4. Calculations

The results of potentiometric titrations were processed by using a CVEQUID computer programme based on Kostrowicki and Liwo’s general method [28–30]. This programme can handle any model of chemical equilibria and determines the equilibrium constants as parameters of the function to be minimized by Marquardt’s method [31]. Thus, this method can be applied to systems of any degree of complexity [28–30]. The details of the calculations of equilibrium constants have been described previously [32].

3. Theoretical methods

The structures of all the systems studied were optimised using the ab initio methods at the RHF (Restricted Hartree Fock) and MP2 (Møller–Plesset) levels using the GAMESS program [33]. The optimisation was performed to a gradient of 0.0001 a.u. · bohr⁻¹ (approx. 0.42 kJ · mol⁻¹ · Å⁻¹). In the calculations, the 6-31++G** basis set was used. Equation (3) defines the homocoupling energy:

$$\Delta E_{BB}^- = E_{BB}^- - (E_{BH}^- + E_B^+),$$

where $E_{BB}^-$ is the energy of a homocomplexed cation, $E_{BH}^-$ is the energy of proton donor and $E_B^+$ is the energy of proton acceptor. The energy of proton in vacuo equals to zero from the definition [34].

After optimisation, vibrational frequencies were computed and, based on their values, it was verified that the calculated structures were minima in the corresponding potential-energy surfaces. The translational, rotational, and vibrational contributions to the thermodynamic corrections to energies and to the Gibbs free energies were also computed. The energy of cationic homocoupling, $\Delta G_{BB}^-$, was calculated based on the following equation:

$$\Delta G_{BB}^- = \Delta E_{BB}^- + \Delta E_{BB}^{\text{vib}} + p\Delta V_{BB}^- = T \left( S_{\text{vib}}(T) + S_{\text{rot}}(T) + \frac{3}{2} R \right) \left[ (S_{\text{vib}}(T) + S_{\text{rot}}(T)) - \left( S_{\text{vib}}(T) + S_{\text{rot}}(T) - \frac{3}{2} R \right) \right],$$

where $\Delta E_{BB}^{\text{vib}}$ is a difference between the zero-point vibrational energy of the products and those of the substrates, respectively, $p$ is the pressure, and $V$ is the volume of a system under assumption that it satisfies ideal gas equation-of-state; $S_{\text{rot}}$ and $S_{\text{vib}}$ are the rotational and vibrational entropies, respectively, and the term $3R/2$ 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.

In systems consisting of at least two monomers, the BSSE (Basis Superposition Set Error) has to be taken into account. To do this, the energy of each monomer should be computed in the basis set of the dimer to minimize the basis set superposition error (the well-known Boys–Bernardi counterpoise approach) [35]. The calculations were performed by using the following general scheme (they are analogous when calculating Gibbs free energies):

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

where $\Delta E_{\text{BSSE}}$ is the energy of a system under consideration of BSSE, $\Delta E_{\text{complex}}$ is the energy without consideration of BSSE, and $E_A$ and $E_B$ are the energies of the A and B monomers, respectively.

The $E_{\text{complex}}(A)$ and $E_{\text{complex}}(B)$ 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 [35]. The separate BSSE calculations in the RHF and a separate one in the MP2 scheme were done.

To estimate solvation contributions to homoconjugation energies, the polarizable continuum model (PCM) was applied. The PCM model [36] employs a van der Waals surface type cavity and sets the parameters for the cavity/dispersion contributions based on 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 this model the dielectric permittivity of acetonitrile was assigned a value [37] of 35.94. Calculations were carried out for fixed geometries corresponding to the structures optimized in vacuo.

4. Results and discussion

Prior to each series of potentiometric titrations, the glass microelectrode was calibrated by using an appropriate standardizing system (tetra-$n$-butylammonium picrate + picric acid) in both solvents studied. In acetone (AC) and acetonitrile (AN), plots of the potential difference $E$ vs. $\lg c(A)/c(A^-)$ were almost straight lines over the $-1.0$ to $1.0$ interval on the logarithmic scale, and slopes of the glass electrode response ($s$) were found to be dependent on the nature of the solvent, ranging from (58 to 61) mV (close to the Nernst theoretical values). A graph of the calibration of the glass electrode in acetonitrile (squares) and acetone (circles) is presented in figure 2.

The characteristics of the glass electrode for these plots can be described by the following equations:

$$E = 1073.7(21.8) + 59.35(1.92) \cdot \lg c_B/c_{BH^+}$$

$$E = 757.0(41.7) + 58.55(5.52) \cdot \lg c_B/c_{BH^+}$$

where ($E'$) is a standard potential difference and ($s$) a slope of the glass electrode response, with their standard deviations in parentheses, respectively. It is worth noting that (tetra-$n$-butylammonium picrate + picric acid) buffer was employed in all our measurements due to its relatively short stabilization time of the potential difference values in solvents studied. The parameters, $s$ and $E'$ calculated from the calibration measurements of the glass electrode together with the experimentally established relationships $E = f(\lg c_B/c_{BH^+})$ in both solvents, served to determine the values of stability constants of the homocomplexed cations with symmetric hydrogen bond bridges $O\cdot\cdot\cdotH\cdot\cdot\cdotO$, as well as the acid dissociation constants. These numerical values were determined by means of a computer programme based on the general method of Kostrowicki and Liwo. A graphical representation of the potentiometric titration is shown in figure 3, where potential difference ($E$) is plotted against $\lg c_B/c_{BH^+}$ in acetonitrile for the 3,5-dimethyl-4-chloropyridine N-oxide system.

As seen, the titration curve has a typical sigmoid shape. This confirms the existence of the stable cationic homocomplexed cation (PyOH$\cdot\cdot\cdot$OPy)$^+$. It is worth mentioning that similar shapes of the potentiometric titration curves have also been observed in the experiments carried out by Van der Heijde [38] and Harlow [39,40], who investigated the homoconjugation equilibria in acetonitrile, acetone, pyridine, benzene, toluene, and sulfolanes.

The values of homoconjugation constants (expressed as $\lg K_{BH^+}$) for symmetric cations resulting from the reaction of 4-halo (Cl, Br) pyridine N-oxides with conjugate cationic acids in acetone (AC) and acetonitrile (AN) are listed in table 2. These constants reveal that cationic homoconjugation equilibria are present for all BH$^+/B$ systems in AC and AN. Furthermore, analysis of the homoconjugation
constants shows that these values are charged with small standard deviations (0.02 to 0.19) for all 4-halopyridine N-oxide derivatives in both solvents studied. The homoconjugation constants obtained in acetonitrile are by a factor of about (0.06 to 0.63) greater (on average 0.32) than values determined in other aprotic solvents (acetonitrile) with a greater donor number. This confirms the general tendency that the range of homoconjugation involving N-oxides increases with the decreasing donor properties of the solvent. The smaller values of homoconjugation constants in acetonitrile in relation to acetonitrile can be interpreted as being due to a stronger solvation of cationic acids (BH⁺) constituents of the hydrogen-bonded complexes by the more basic acetonitrile, thus weakening the hydrogen bonding. Consequently, based on the results of our previous [41] and present studies, the sequence of non-aqueous solvents classified according to the increasing strength of cationic homoconjugation of organic N-bases with conjugate cationic acids, can be arranged as follows: nitromethane > benzonitrile > acetonitrile > propylene carbonate > acetone > methanol > N,N-dimethylformamide > dimethyl sulfoxide.

Moreover, detailed potentiometric studies indicated that the values of stability constants of the homocomplexed cations formed by oxygen-containing N-oxides studied (expressed as lg $K_{\text{HBB}}$) in acetonitrile are of the same order of magnitude as those determined in acetonitrile. The logarithms of the constants range from 2.46 to 3.15 and 2.18 to 2.82 in acetonitrile and acetone, respectively. Based on this, the correlation analysis was made between the lg $K_{\text{HBB}}$ values of the 4-halopyridine N-oxides in both solvents studied. As a result, after rejection of the most aberrant data points (2.5Me₂₅ClPyO) the following relationship was obtained:

$$\lg K_{\text{HBB}}^{AN} = 0.935(0.204)\lg K_{\text{HBB}}^{AC} + 0.419(0.518) \quad R = 0.935$$

(8)

where standard deviations are given in parentheses and R denotes the correlation coefficient. This means that a correlation between the values of the logarithms of the homoconjugation constants in AN and AC does exist.

The energies of formation of the homocomplexed cations and Gibbs free energies calculated at the RHF and MP2 levels and by using the PCM model of solvation are also collected in table 2 together with the values of lg $K_{\text{HBB}}$ in both solvents studied. Inspection of these data shows that all the calculated energetic parameters fall within a narrow range. Cationic homoconjugation energies ($\Delta E_{\text{HBB}}$) calculated at the RHF and MP2 level oscillate around $-121.3$ kJ·mol⁻¹ (from $-109.3$ to $-129.1$), the values of the Gibbs free energies $\Delta G_{\text{HBB}}$ (RHF) oscillate around $-71.1$ kJ·mol⁻¹ (from $-60.7$ to $-78.2$), and those calculated within the polarizable continuum model (PCM) accounting for solvation effects around $-41.8$ kJ·mol⁻¹ (from $-37.7$ to $-47.1$). The results of theoretical calculations confirm with the experimental data because both the logarithms of the homoconjugation constants and the theoretically calculated energies and Gibbs free energies of homoconjugation are contained within a narrow range of values.

In a continuation of this study, based on these experimental and theoretical data, an attempt has been made to establish a correlation between these approaches. After consideration of all the systems, the correlation coefficients were low, ranging from 0.76 to 0.87 in acetonitrile, and 0.60 to 0.92 in acetonitrile. Eliminating one point that is most distant from the correlation line (2,5Me₂₅ClPyO in

![FIGURE 3. Plot of potential difference $E$ against $\lg c_{BHB}^+/c_{AN}$ in acetonitrile for the 3,5-dimethyl-4-chloropyridine N-oxide system.](image)

TABLE 2

| N-oxide       | $\lg K_{\text{HBB}}^{AC}$ | $\lg K_{\text{HBB}}^{AN}$ | $\Delta E_{\text{HBB}}$ (RHF) | $\Delta G_{\text{HBB}}$ (RHF) | $\Delta E_{\text{HBB}}$ (MP2) | $\Delta G_{\text{HBB}}$ (PCM) |
|---------------|---------------------------|---------------------------|-----------------------------|----------------------------|-----------------------------|-----------------------------|
| 2,5Me₂₅ClPyO  | 2.90(0.02)                | 2.27(0.05)                | -120.0                      | -73.42                     | -123.5                      | -42.59                      |
| 3,5Me₂₅ClPyO  | 3.15(0.05)                | 2.82(0.10)                | -125.4                      | -78.24                     | -124.1                      | -42.84                      |
| 2,3,6Me₂₅ClPyO| 2.48(0.06)                | 2.18(0.19)                | -109.3                      | -60.67                     | -119.5                      | -37.70                      |
| 2,5Me₂₅BrPyO  | 3.02(0.08)                | 2.70(0.11)                | -121.8                      | -76.11                     | -123.9                      | -43.60                      |
| 3,5Me₂₅BrPyO  | 2.78(0.07)                | 2.72(0.07)                | -129.1                      | -76.61                     | -124.7                      | -47.07                      |
| 2,3,6Me₂₅BrPyO| 2.46(0.04)                | 2.19(0.07)                | -114.7                      | -61.13                     | -118.5                      | -39.59                      |

Calculated cationic homoconjugation energies, $\Delta E_{\text{HBB}}$ (RHF), and Gibbs free energies, $\Delta G_{\text{HBB}}$ (RHF) (for both $\Delta E_{\text{HBB}}$ and $\Delta G_{\text{HBB}}$ values after inclusion of the BSSE), at the RHF level, as well as MP2, $\Delta E_{\text{HBB}}$ (MP2) (values after inclusion of the BSSE), and PCM, $\Delta G_{\text{HBB}}$ (PCM), energies and Gibbs free energies of formation of homocomplexed cations, respectively, for 4-halopyridine N-oxide derivatives (kJ·mol⁻¹) are also listed. N-oxide abbreviations: 2,5Me₂₅ClPyO-2,5-dimethyl-4-chloropyridine N-oxide; 2,5Me₂₅BrPyO-2,5-dimethyl-4-bromopyridine N-oxide; 3,5Me₂₅ClPyO-3,5-dimethyl-4-chloropyridine N-oxide; 3,5Me₂₅BrPyO-3,5-dimethyl-4-bromopyridine N-oxide; 2,3,6Me₂₅ClPyO-2,3,6-trimethyl-4-chloropyridine N-oxide; 2,3,6Me₂₅BrPyO-2,3,6-trimethyl-4-bromopyridine N-oxide.
AC and 3,5Me2BrPyO in AN, respectively) improved the correlated coefficients. The following relationships were obtained ($R$ denotes the correlation coefficients):

$$\text{lg } K_{\text{BHB}}^\text{AC} = -0.15(0.038)\Delta E_{\text{BHB}}^\text{AC} (\text{RHF}) - 1.75(1.08) \ R = -0.916$$

(9)

$$\text{lg } K_{\text{BHB}}^\text{AN} = -0.15(0.005)\Delta G_{\text{BHB}} (\text{RHF}) + 0.047(0.084) \ R = -0.998$$

(10)

$$\text{lg } K_{\text{BHB}}^\text{AC} = -0.45(0.062)\Delta E_{\text{BHB}}^\text{AC} (\text{MP2}) - 10.46(1.82) \ R = -0.972$$

(11)

$$\text{lg } K_{\text{BHB}}^\text{AN} = -0.20(0.04)\Delta E_{\text{BHB}}^\text{AN} (\text{RHF}) - 2.80(1.12) \ R = -0.945$$

(12)

$$\text{lg } K_{\text{BHB}}^\text{AN} = -0.16(0.008)\Delta G_{\text{BHB}} (\text{RHF}) + 0.19(0.14) \ R = -0.996$$

(13)

$$\text{lg } K_{\text{BHB}}^\text{AN} = -0.49(0.07)\Delta E_{\text{BHB}}^\text{AN} (\text{MP2}) - 11.52(2.03) \ R = -0.972$$

(14)

$$\text{lg } K_{\text{BHB}}^\text{AN} = -0.48(0.12)\Delta G_{\text{BHB}}^\text{AN} (\text{PCM}) - 1.96(1.19) \ R = -0.918$$

(15)

This relatively high correlational coefficients $R$ revealed an existence of linear relationships between the values of stability of homocomplexed cations of the multisubstituted pyridine N-oxides determined in solution and those calculated in vacuo. Moreover, these findings show that the sequence of changes of the stability constants of the homocomplexed cations $[\text{BHB}]^+$ in polar non-aqueous solvents can be predicted on the basis of the cationic homoconjugation energies calculated by $ab \ initio$ methods.

An additional aim of this work is to determine the acid dissociation constants for cationic acids conjugated with 4-halopyridine N-oxides in both solvents studied. These values (expressed as $pK_a$ values) are listed in Table 3. It can be observed that they are characterized by relatively small standard deviations. The $pK_a$ values in acetone are relatively low, of order of 5 (the highest value 5.86 being for the 3,5Me2BrPyO) and lower. This finding can be explained in terms of the presence of strong electron-accepting substituent (a halogen atom) at position 4. Furthermore, it is noteworthy that values of $pK_a$ in acetonitrile for the conjugate acids of N-bases are by more than ten orders of magnitude lower than those of carboxylic acids $pK_a^\text{AN}$ values falling in the range 17 to 21 [42], phenols $pK_a^\text{AN}$ values are of the order of 16 to 27 [43] and only 1 to 2 orders of magnitude higher than those of mineral acids [44], including sulphuric acid ($pK_a^\text{AN} = 7.9$), nitric and hydrochloric acid ($pK_a^\text{AN} = 8.9$ for both). In addition, the $pK_a$ values of the N-oxides studied in acetone (DN = 17) are by four orders of magnitude lower than those determined in acetonitrile (DN = 14.9), and two orders of magnitude higher than those in polar amphiprotic methanol (DN = 19.1) [19]. This means that the strength of the cationic acids conjugated with the substituted pyridine N-oxides increases in the following series of solvents: AN < AC < MeOH, which is in agreement with the basicity of these solvents.

Table 3 also shows the values of acidity constants for the N-oxides in aqueous solutions, $pK_a^\text{W}$. In view of missing experimental data in water, these constants were estimated from a linear relationship previously derived [45] for other pyridine N-oxides: $pK_a^\text{AC} = 1.33pK_a^\text{W} + 4.32$, taking into consideration the $pK_a$ values determined experimentally in acetone.

5. Conclusions

The results of potentiometric measurements carried out in acetonitrile and acetone, together with the calculations by using $ab \ initio$ methods at the RHF, MP2 levels and within the PCM model of solvation, for the six derivatives of pyridine N-oxide, allow us to reach the following conclusions.

All the N-oxides studied are characterized by a tendency toward cationic homoconjugation (the logarithms of the constants, expressed as $\text{lg } K_{\text{BHB}}^\text{AN}$ range from 2.46 to 3.15 and 2.18 to 2.82 in AN and AC, respectively), determinable by the potentiometric titration method.

The values of stability constants of the homocomplexed cations $[\text{BHB}]^+$ held together by hydrogen bonding $\text{O} \cdots \text{H} \cdots \text{O}$ in acetonitrile are of the same order of magnitude as those determined in acetone. This tendency is expressed as a linear function of the values $\text{lg } K_{\text{BHB}}^\text{AN}$ of the compounds in both solvents studied.

The calculations of the energies of formation of the homocomplexed cations and Gibbs free energies determined in vacuo by using $ab \ initio$ methods at the RHF and MP2 levels, as well as within the PCM model utilizing the Gaussian 6-31++G** basis set indicated that all the calculated energy parameters values fall within a narrow range.

The 6-31++G** basis set is sufficient to predict reliably the sequence of changes of the stability constants of the homocomplexed cations $[\text{BHB}]^+$ stabilized by symmetric
hydrogen bond bridges O···H···O in polar non-aqueous solvents.

The acidity constants of cationic acids conjugated with the substituted pyridine N-oxides in the acetonitrile and acetone can be determined for all the systems studied (they are charged with relatively small standard deviations).

The values of acidity constants (expressed as pK\text{\text{AN}}_a) of the N-oxides studied in acetone are by four orders of magnitude lower than those determined in acetonitrile (expressed as pK\text{\text{AN}}_a).

The method of estimation of the dissociation constants in aqueous solution (expressed as pK\text{\text{W}}_a) on the basis of the values determined in non-aqueous solutions (for instance acetone) can be employed for cationic acids obtained by protonation of substituted 4-halopyridine N-oxides. The values of experimental acidity constants of the N-oxides studied estimated by this method fall in the range 0.59 to 1.14.

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