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Ab Initio Study of the Energetics of Protonation and Cationic Homoconjugation of Trimethylamine and Its *N*-Oxide[*]

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Ab initio methods at the RHF (Restricted Hartree Fock) and MP2 (Møller-Plesset) levels were used to study the energetics of protonation of trimethylamine and its derivative trimethylamine N-oxide, as well as the energetics of formation of hydrogen bonded $(N\cdots H\cdots N)^+$ and $(O\cdots H\cdots O)^+$ type, respectively, homocomplexed cations. The Gaussian functional basis sets 3-21G, 6-31G, 6-311G, 6-31G* and 6-31+G* were employed to calculate energy and Gibbs free energy of protonation and cationic homoconjugation in the gas phase and with the inclusion of solvation effects (using PCM method). The calculated energetic parameters in the gas phase and in solution, as well as experimental values of equilibrium constants of the acid dissociation and cationic homoconjugation reaction for trimethylamine and trimethylamine N-oxide systems provided a basis for a comparison of the basicity and tendency towards cationic homoconjugation of both compounds under study. Consequently, the acid-base properties of aliphatic bases have been compared with those of heterocyclic bases containing both oxygen and nitrogen.

Key words*:* trimethylamine and its N-oxide, protonation and cationic homoconjugation energies, proton potential, *ab initio* methods

A model of acid-base equilibria established between acids (both molecular and cationic) and organic bases in non-aqueous media is highly complex [1–3]. Nevertheless, the model of acid-base equilibria established in such media can be limited, under experimental conditions, to so-called fundamental equilibria only, namely these of dissociation of cationic acids (1), as well as cationic homoconjugation (2):

$$BH^+ \rightleftarrows B + H^+ \tag{1}$$

$$BH^+ + B \rightleftarrows BHB^+ \tag{2}$$

where B denotes the base molecule, BH^+ is a cation of protonated base and BHB^+ a symmetric homocomplex cation.

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[*] Dedicated to Prof. M. Szafran on the occasion of his 70th birthday.

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Acid dissociation of cationic acids, as well as cationic conjugation phenomenon is less extensively studied than anionic [4,5]. Consequently, a relatively limited number of papers refer to the cationic homoconjugation equilibria [6–8]. For this reason, acid-base equilibria, especially acid dissociation, as well as cationic homo-, and heteroconjugation, present in non-aqueous media in systems containing heterocyclic bases such as pyridine and substituted pyridines or pyridine *N*-oxide and its derivatives have been systematically studied in our laboratory [4,9,10].

After collecting a vast experimental data on the acidic-basic properties of heterocyclic bases in non-aqueous media, it seemed expedient to compare those properties with acidic-basic properties of aliphatic bases. Data referring to the aliphatic amines, especially to trimethylamine as the parent compound, are readily accessible in the chemical literature [2]. Trimethylamine (Me_3N) belongs to the class of the strongest organic bases, *e.g.* in acetonitrile being by more than five pK_a units stronger than pyridine (respective pK_a's being 17.61 [2] and 12.33 [2]). Despite the strong basicity, its tendency to cationic homoconjugation is only slightly greater than that of pyridine (respective logarithms of the cationic homoconjugation constants are 0.8 and 0.6 after Coetzee [2]). These quantities reveal a very weak tendency of both bases towards cationic homoconjugation. On the other hand, trimethylamine *N*-oxide (Me_3NO) exhibits very interesting acid-base properties. Being a base of the strength comparable to that of the parent trimethylamine, with pK_a of 16.93 [11] in acetonitrile, it shows a considerably stronger tendency to cationic homoconjugation. The logarithm of the homoconjugation constant in acetonitrile is 5.95 [11], while in other polar non-aqueous solvents it attains a value as high as 7.44 [12]. Moreover, trimethylamine *N*-oxide is known to form very strong hydrogen-bonded homoconjugated cation also in the solid state [13]. To explain the differences in tendency towards homoconjugation of trimethylamine and its *N*-oxide it seemed worthwhile to carry out calculations of the energetics of protonation and cationic homoconjugation of the bases by *ab initio* methods. This goal was compatible with similar calculations accomplished by us for heterocyclic amines (pyridine and its derivatives [14]) and their *N*-oxides [15]. Results of the calculations together with a full experimental evidence for their acid-base properties in solution should provide a basis for comparison of the properties of aliphatic and heterocyclic amines, as well as their *N*-oxides.

To reach the research goals, energy parameters of the protonation and cationic homoconjugation, *i.e.* the protonation energies, ΔE_{prot} (RHF, MP2) and the Gibbs free energies, ΔG_{prot} (RHF, MP2), the energies, ΔE_{BHB^+} (RHF, MP2), and the Gibbs free energies, ΔG_{BHB^+} (RHF, MP2), for the formation of homocomplexed cations without and under consideration of the BSSE (Basis Set Superposition Error) effect, ΔE_{BHB^+} (BSSE) and ΔG_{BHB^+} (BSSE), respectively, in the gas phase were calculated by means of Restricted Hartree-Fock (RHF) and Møller-Plesset (MP2) *ab initio* methods In the second step, estimation of the solvent effects has been attempted by using the polarizable continuum model (PCM) for such model solvents as acetonitrile (AN) and water (W).

METHODS

The structures of all the systems were optimized by the *ab initio* methods at the RHF (Restricted Hartree Fock) and MP2 (Møller-Plesset) levels using the GAMESS [16] program. The optimization was performed to a gradient of 0.0001 a.u./bohr (approx. 0.1 kcal mol^{-1} Å^{-1}). In calculations, the 3-21G, 6-31G, 6-311G, 6-31G* and 6-31+G* basis sets were used. Equations (3) and (4) define the protonation (understood as reverse process to acidic dissociation – eg. 1) and homoconjugation energies, respectively:

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

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

where E_{BHB^+} 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 equals to zero from the definition [17].

After optimization, to gain a better insight into variations of energy of the systems, translational, rotational and vibrational contributions have been calculated. To do this, thermodynamic corrections, *i.e.* the energy Hessian matrixes were calculated for stationary and excited states. Their values enabled to check whether the stationary point found was a true minimum and to calculate the zero-point energy contributions (equations (5) and (6)).

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

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

$$\begin{aligned}\Delta G_{BHB^+} = {} & \Delta E_{BHB^+} + \Delta E^{o}_{vib,\,BHB^+} + p\Delta V_{BHB^+} - T[(S_{vib,\,BHB^+} + S_{rot,\,BHB^+}) - \\ & - (S_{vib,\,BH^+} + S_{rot,\,BH^+} + S_{vib,B} + S_{rot,B}) - \frac{3}{2}R]\end{aligned} \tag{6}$$

where $\Delta E^{o}_{vib,\,prot}$ and $\Delta E^{o}_{vib,\,BHB^+}$ 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 assumption that it satisfies 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.

In systems consisting of at least two monomers (dimer or higher complex) the calculated interaction energy is decreased due to the fact that the basis set of complex formed is artificially enlarged with respect to basis sets of the monomers. This causes an error called Basis Set Superposition Error (BSSE). BSSE is estimated as the difference between the monomer energy values calculated in their basis sets and energy values of monomers calculated in the basis set of complex [18]. The calculations were performed by using the following general scheme (Eqs. 7) (they are analogous when calculating Gibbs free energies):

$$\Delta E_{BSSE} = \Delta E_{complex} - [E_{complex}(A) + E_{complex}(B)] + (E_A + E_B) \tag{7}$$

where: ΔE_{BSSE} denotes the interaction energy under consideration of BSSE; $\Delta E_{complex}$ is the interaction energy value without consideration of BSSE (calculated as the difference between the energy of the complex and the sum of energies of the isolated subunits A and B); $E_{complex}(A)$ and $E_{complex}(B)$ are the energy values of complexes on assumption that the orbitals of molecules A and B are the so-called "ghost" orbitals [18], E_A and E_B are the energy values of the A and B monomers, respectively.

To estimate solvation contributions to the protonation and homoconjugation energies polarizable continuum model (PCM) was applied. The PCM model [19] employs a van der Waals surface type cavity and parameterises 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 represent 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 of 35.94 [20]. Calculations were carried out for fixed geometries corresponding to the structures optimized *in vacuo*.

The proton-potentials in the $Me_3NH^+ \cdots Me_3N$ and $Me_3NOH^+ \cdots Me_3NO$ bridges were calculated by accomplishing a series of constrained energy minimization's with fixed N···H and O···H distances, respectively, and optimizing the remaining degrees of freedom (subject to BSSE [21,22]).

RESULTS AND DISCUSSION

The lengths of the $(N \cdots H \cdots N)^+$ and $(O \cdots H \cdots O)^+$ hydrogen bridges determined in the gas phase at the RHF and MP2 levels in the Gaussian 3-21G, 6-31G, 6-311G, 6-31G* and 6-31+G* functional basis sets are compiled in Table 1. The N···N spacing between the proton donor (protonated trimethylamine) and proton acceptor (trimethylamine) determined in these bases at RHF level varies in the range of 2.708–2.933 Å, being similar to the arithmetic mean calculated for all substituted pyridines [14], which fall within a narrow range of 2.868–2.997 Å (with the exception of $2NH_2Py$). This finding supports the previous conclusion based on experiments [23,24] that the N···H···N bonds in homocomplexed cations formed by amines are weak asymmetric hydrogen bonds. (An optimized structure of homocomplexed cation of trimethylamine is shown in Fig. 1). The data of Table 1 show that the lengths of the hydrogen bonds increase with increasing number of the basis functions in the functional basis. Inclusion in the calculations of both the polarization and diffusion functions results in a considerable elongation of the hydrogen bridges as compared to the smallest 3-21G basis used in the calculations. In contrast, inclusion of the electronic correlation at the MP2 level results in shortening of the hydrogen bond.

Table 1. Hydrogen bond lengths [Å] calculated using *ab initio* methods on RHF and MP2 levels.

Base	$(Me_3NOHONMe_3)^+$	$(Me_3NHNMe_3)^+$
	RHF	
3-21G	2.457	2.708
6-31G	2.517	2.815
6-311G	2.532	2.844
6-31G*	2.568	2.915
6-31+G*	2.582	2.933
	MP2	
3-21G	2.471	2.653
6-31G	2.526	2.718
6-311G	2.528	2.707
6-31G*	2.507	2.750
6-31+G*	2.529	2.751

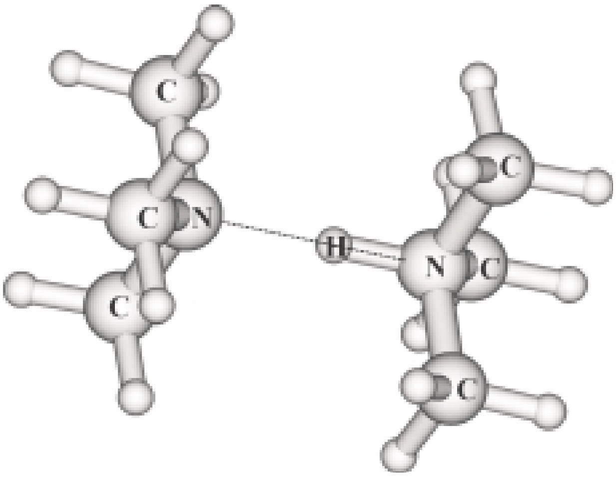

Figure 1. Equilibrium structure of the $(Me_3NHNMe_3)^+$ cation calculated in the gas phase.

In the calculations at this level, the bond lengths range between 2.653 and 2.751 Å, the length of the hydrogen bond is increasing in the same direction as it is in the case of the results obtained at the RHF level. A comparison of the N···H···N with O···H···O bond lengths shows that in each of the basis sets used, either at the RHF or MP2 levels, a markedly shorter hydrogen bond occurs in the $(Me_3NOHONMe_3)^+$ homocomplexed cation. This finding is compatible with experimental results, where in the crystalline compounds the O···O distances are *ca* 2.45 Å [25,26] and 2.54–2.57 Å [27] for the 2:1 and 3:2 salts, respectively. This means that the hydrogen bond in the homocomplexed trimethylamine N-oxide is stronger and more symmetric [26,28] than that in its trimethylamine counterpart. The structure of the homocomplexed trimethylamine N-oxide ion optimized in the gas phase is presented in Fig. 2.

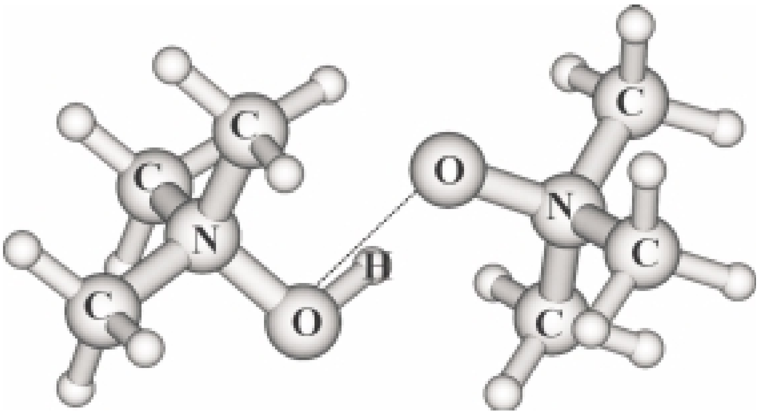

Figure 2. Equilibrium structure of the $(Me_3NOHONMe_3)^+$ cation calculated in the gas phase.

Fig. 3 represents a proton potential within the (N···H···N) bridge of the homocomplexed trimethylamine ion as determined at the RHF level in the 6-31+G* basis set. The curve has two minima at 1.05 and 1.88 Å corresponding to a distance between the proton and the proton donor. A maximum emerges at a N–H bond length of 1.47 Å, which corresponds to a half of the distance in the hydrogen bridge determined at the RHF level for the homocomplexed trimethylamine ion (2.933 Å), thus suggesting that the bond is symmetric. The potential barrier that must be overcome by the proton to move from the donor to the acceptor is 7.52 kcal mol^{-1}. After inclusion of the thermodynamic correction factor the barrier is lowered down to 4.36 kcal mol^{-1}. This high barrier supports the hypothesis that the hydrogen bond in the homocomplexed cation is weak. For the sake of comparison, in Table 2 are included the positions of the minima and maxima, as well as the potential barriers in the proton potentials for $(Me_3NHNMe_3)^+$ as determined in all the basis sets employed. As seen, the height of the energy barrier increases with increasing number of functions in the basis set.

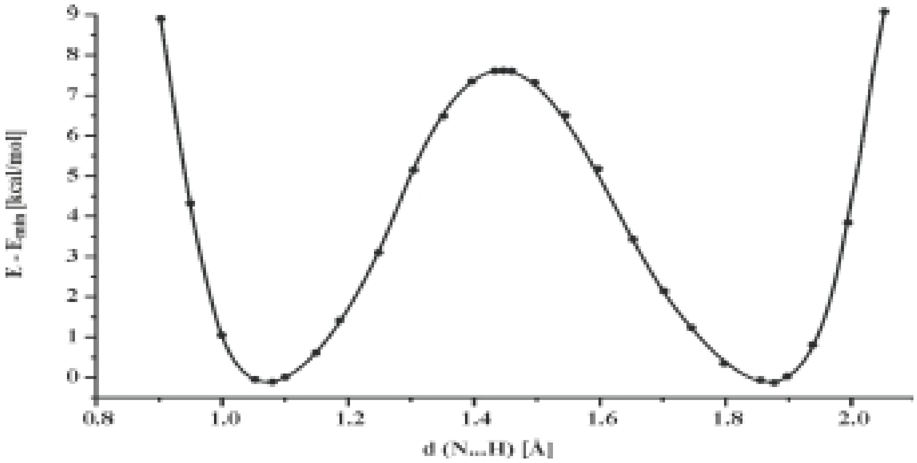

Figure 3. Energy variations on proton transfer curve in the N···H···N bridge formation of the trimethylamine homoconjugated cation. Filled circles represent points, where 6-31+G* energies heve been calculated.

The calculated barrier can be treated as indicative of a restriction of the proton movement within the hydrogen-bonded bridge. This finding is in accord with the previously drawn conclusions concerning substituted pyridine [14] systems, as well as with experimental evidence [29] referring to structural and spectroscopic features of amine systems.

Table 2. Positions of the minima and maxima, as well as the heights of the potential barriers in the proton transfer curves within different bases for homocomplexed cations of Me_3N and Me_3NO calculated using *ab initio* method on RHF level. In parentheses, the magnitude of the second minimum in the proton potential is provided, as well as the height of the potential barrier in the proton potential after inclusion of the thermodynamic correction factor.

	$(Me_3NHNMe_3)^+$			$(Me_3NOHONMe_3)^+$		
Base	Minimum [Å]	Maximum [Å]	Barrier [kcal/mol]	Minimum [Å]	Maximum [Å]	Barrier [kcal/mol]
3-21G	1.08	1.35	+ 1.40	1.07	1.23	+ 0.36
	(1.63)		(–0.38)	(1.40)		(–2.44)
6-31G	1.05	1.40	+ 3.77	1.01	1.26	+ 2.08
	(1.77)		(+ 1.22)	(1.50)		(–1.37)
6-311G	1.04	1.42	+ 4.98	1.00	1.27	+ 2.75
	(1.80)		(+ 1.05)	(1.55)		(–0.19)
6-31G*	1.03	1.46	+ 7.27	0.99	1.28	+ 3.09
	(1.88)		(+ 3.17)	(1.57)		(–0.27)
6-31+G*	1.05	1.47	+ 7.52	0.99	1.29	+ 3.69
	(1.88)		(+ 4.36)	(1.59)		(–0.12)

In Fig. 4 a curve is shown for the proton potential in the case of the trimethylamine N-oxide homocomplexed cation as determined at the RHF level in the $6\text{-}31{+}G^*$ basis set. Two energetic minima occur at the O–H distances of 0.99 and 1.59 Å, and the maximum at 1.29 Å, the O···O distance being 2.57 Å. The potential barrier for the proton transfer is 3.69 kcal mol^{-1}, and after inclusion of the thermodynamic correction factor, it passes through a deep minimum by 0.12 kcal mol^{-1} lower compared with the values at minima calculated without inclusion of the thermodynamic factor. This suggests that the hydrogen bond in the homocomplexed trimethylamine N-oxide ion is short, strong and symmetric.

Positions of the minima, maxima and the values of the energetic barriers in the proton potentials determined in all the basis sets for the homocomplexed trimethylamine N-oxide ion are collected in Table 2. Similar to the trimethylamine homocomplexed cation, also in this case an increase in the number of functions in the basis set is accompanied by an increase in the energetic barrier in the proton potential. However, unlike the situation with the N···H···N bridge, inclusion of the thermodynamic correction factor in each functional basis set results in disappearance of the potential barrier in the proton potential and emergence of one broad and deep minimum with an energy lower than that occurring in the proton transfer curve without inclusion of the factor. Hence, a conclusion can be drawn that there is a strong hydrogen bond in this ion and a high probability of the proton position at a half distance between the proton donor and acceptor occurs. This suggests that the movement of the proton in the hydrogen bond bridge is unrestricted and that this bond is effectively symmetric. These findings are in agreement with the facts that O···H···O bridge is crystallographically symmetric [26,28] and that in the IR spectra of N-oxide basic salts [30,31] the very broad O···H bands are observed, as well with our findings regarding cationic homoconjugating systems of substituted pyridine N-oxides [15].

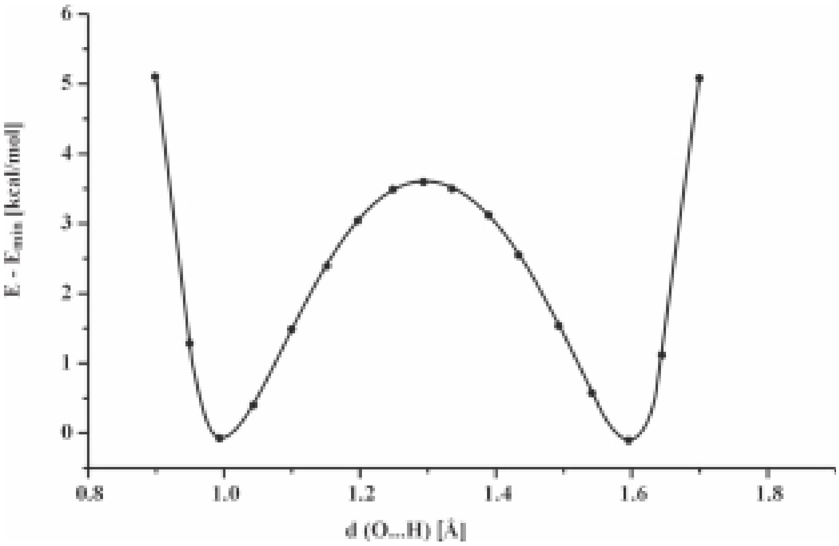

Figure 4. Energy variations on proton transfer curve in the O···H···O bridge formation of the trimethylamine N-oxide homoconjugated cation. Filled circles represent points, where 6-31+G* energies heve been calculated.

Table 3 lists energies and Gibbs free energies of protonation at the RHF level, ΔE_{prot}(RHF) and ΔG_{prot}(RHF), protonation energies and Gibbs free energies at the MP2 level, ΔE_{prot}(MP2) and ΔG_{prot}(MP2), as well as Gibbs free energies of protonation with inclusion of the solvation effects within the PCM model for acetonitrile, ΔG_{prot}(AN) and water, ΔG_{prot}(W) determined for trimethylamine and its N-oxide. The protonation energies calculated at all computational levels (RHF, MP2 and PCM) decline in absolute values with increasing number of functions in the basis sets accounted for in calculations. The results of calculations at the RHF level unequivocally differentiate the basicities of trimethylamine and its N-oxide. On the other hand, inclusion of electronic correlation in the calculations using the MP2 method unambiguously points to a stronger basicity of trimethylamine. This is compatible with experimental results. In aqueous solutions the difference in basicities of the two bases is also large, their pK_a's being 4.65 [26] and 9.76 [2]. In the solvation model (PCM), the basicity of trimethylamine is also stronger than that of its N-oxide, in particular in aqueous solutions. However, it should be stressed that PCM solvation energies may suffer quite substantial errors. The serious drawbacks of continuum electrostatic solvation models were described in literature [32–34].

Table 3. Protonation energies (ΔE_{prot}) and Gibbs free energies (ΔG_{prot}) of trimethylamine (Me_3N) and trimethylamine N-oxide (Me_3NO) calculated using *ab initio* methods on RHF and MP2 levels. The energy values are in [kcal/mol] and were carried out in the gas phase. ΔG_{prot}(PCM) were calculated for acetonitrile and water models.

			Me_3N			
Base	RHF		MP2		PCM	
	ΔE_{prot}	ΔG_{prot}	ΔE_{prot}	ΔG_{prot}	ΔG_{prot}(AN)	ΔG_{prot}(W)
3-21G	–240.21	–239.37	–245.83	–245.19	–59.09	–57.61
6-31G	–236.56	–236.03	–238.81	–238.24	–52.67	–51.28
6-311G	–236.10	–235.51	–237.27	–236.67	–52.87	–51.44
6-31G*	–236.62	–236.07	–236.17	–235.53	–53.12	–51.76
6-31+G*	–234.74	–234.02	–232.52	–231.78	–51.62	–50.17
			Me_3NO			
3-21G	–245.45	–245.73	–253.52	–254.03	–47.33	–45.85
6-31G	–233.91	–234.29	–237.30	–237.92	–34.38	–32.91
6-311G	–233.01	–233.39	–233.29	–233.85	–33.58	–32.15
6-31G*	–239.73	–240.12	–237.71	–238.41	–40.45	–38.99
6-31+G*	–234.33	–234.70	–227.98	–228.63	–34.53	–33.01

In Table 4 are collected formation energies of the homocomplexed cations in the gas phase, ΔE_{BHB^+} and ΔG_{BHB^+}, at the RHF and MP2 levels, the energies after inclusion of the basis superposition error, ΔE_{BHB^+}(BSSE) and ΔG_{BHB^+}(BSSE) in the gas phase at both levels, and Gibbs free energies of formation of the homocomplexed ions within the PCM model for acetonitrile, ΔG_{BHB^+}(AN) and water, ΔG_{BHB^+}(W). A stronger impact of BSSE on the energetic parameters is seen with trimethylamine. In some cases, in particular at the MP2 level, inclusion of BSSE changes the magnitude of the energy by *ca* 10 kcal mol^{-1}. This is probably due to a facilitated flow of the electron pair at the nitrogen atom in the case of trimethylamine. Energies of the formation of the homocomplexed cations increase (become less negative) with increasing the number of functions of the basis sets used in calculations. A scrutiny of the figures in both Tables shows a markedly stronger tendency towards formation of the homocomplexes in the gas phase by trimethylamine N-oxide both at the RHF and MP2 levels. Similar conclusions have been drawn from the inspection of the proton transfer curves. Moreover, the energies of cationic homoconjugation in the gas phase change in line with changes of the cationic homoconjugation constants in non-aqueous solutions, *e.g.* the logarithms of the constants in acetonitrile for the *N*-oxide and the parent amine are 5.51 [11] and 0.8 [2], respectively.

Table 4. Uncorrected homoconjugation (ΔE_{BHB^+}) and Gibbs free (ΔG_{BHB^+}) energies, as well as their corrected values, ΔE_{BHB^+}(BSSE), ΔG_{BHB^+}(BSSE) of trimethylamine (Me_3N) and trimethylamine N-oxide (Me_3NO) calculated using *ab initio* methods on RHF and MP2 levels. The energy values are in [kcal/mol] and were carried out in the gas phase. ΔG_{BHB^+}(PCM) were calculated for acetonitrile (AN) and water (W) models.

					Me_3N					
	RHF				MP2				PCM	
	ΔE_{BHB^+}	ΔE_{BHB^+} (BSSE)	ΔG_{BHB^+}	ΔG_{BHB^+} (BSSE)	ΔE_{BHB^+}	ΔE_{BHB^+} (BSSE)	ΔG_{BHB^+}	ΔG_{BHB^+} (BSSE)	ΔG_{BHB^+} (AN)	ΔG_{BHB^+} (W)
3-21G	–27.55	–24.80	–16.53	–14.57	–41.86	–33.98	–31.16	–24.00	–20.16	–19.30
6-31G	–22.72	–18.44	–12.57	–8.74	–33.88	–27.21	–23.74	–17.65	–12.45	–12.60
6-311G	–23.10	–18.03	–11.10	–6.35	–34.68	–27.68	–22.88	–16.22	–12.20	–12.55
6-31G*	–22.85	–15.35	–12.70	–6.21	–35.01	–25.49	–22.93	–14.08	–13.51	–13.80
6-31+G*	–22.34	–14.60	–10.47	–3.59	–35.11	–24.85	–22.99	–13.45	–12.35	–12.76
					Me_3NO					
3-21G	–50.65	–50.74	–39.97	–40.02	–62.92	–63.19	–49.90	–50.27	–29.00	–27.04
6-31G	–40.23	–40.26	–29.91	–29.97	–48.77	–49.01	–37.26	–37.64	–16.64	–14.44
6-311G	–39.64	–39.56	–27.88	–27.82	–46.96	–46.96	–36.72	–36.73	–15.31	–13.10
6-31G*	–38.08	–37.90	–28.41	–28.20	–46.59	–46.70	–36.51	–36.59	–14.69	–12.55
6-31+G*	–34.82	–34.61	–24.80	–24.56	–42.52	–42.74	–33.18	–33.57	–11.43	–9.26

In Table 5 both the selected energy parameters and experimental equilibrium constants of protonation and cationic homoconjugation for trimethylamine and its N-oxide are compared with those previously determined for pyridine and its N-oxide. The first pair of compounds is represented by trimethylamine and the aromatic heterocyclic amine, pyridine, while the other by their *N*-oxides. Such a listing provided a basis for drawing conclusions concerning the comparison of basicities and the tendency to homoconjugation of aliphatic amines, heterocyclic amines and their *N*-oxides. As far as the protonation is concerned, data of Table 5 show that the calculated basicity of trimethylamine, both in the gas phase and under consideration of solvation with acetonitrile molecules, is stronger than that of pyridine. This conclusion is consistent with experiments. The pK_a values in acetonitrile (pK_a^{AN}) for protonated trimethylamine and pyridine are respectively 17.61 [2] and 12.60 [10], the difference being almost exactly five pK_a units. In aqueous solution, the relation is similar, respective pK_a^{W}'s being 9.76 [2] and 5.25 [34], this giving a comparable difference in basicity of around 4.5 pK_a units. As far as the comparison of the tendency to cationic homoconjugation is concerned, both the calculations and experiments reveal a comparable, yet still weak tendency of both *N*-bases to homoconjugation. Experimental logarithms of the constants in acetonitrile for trimethylamine and pyridine are respectively 0.8 and 0.6 [2].

Table 5. A comparison of selected calculated energy parameters [kcal/mol] of protonation, ΔE_{prot}(RHF), ΔG_{prot}(PCM) and cationic homoconjugation, ΔE_{BHB^+}(RHF), ΔG_{BHB^+}(PCM), in the gas phase, as well as of experimental pK_a's in acetonitrile (pK_a^{AN}) and water (pK_a^{W}) and of logarithms of cationic homoconjugation constants in acetonitrile ($\log K_{BHB^+}$) for trimethylamine (Me_3N) and its *N*-oxide (Me_3NO) with those previously determined for pyridine (Py) and its *N*-oxide (PyO). All calculations were carried out using 6-31G* basis.

	Basicity			
	ΔE_{prot}(RHF)	ΔG_{prot}(PCM)	pK_a^{AN}	pK_a^{W}
Me_3N	–236.62	–53.12	17.61[a]	9.76[a]
Py	–225.97	–35.95	12.60[b]	5.25[c]
Me_3NO	–239.72	–40.45	16.93[d]	4.65[c]
PyO	–232.15	–[e]	10.04[b]	0.79[c]

	Tendency towards homoconjugation			
	ΔE_{BHB^+}(RHF)	ΔG_{BHB^+}(PCM)	$\log K_{BHB^+}^{AN}$	–[f]
Me_3N	–22.85	–13.51	0.8[a]	
Py	–18.31	–4.18	0.6[a]	
Me_3NO	–38.08	–14.69	5.51[d]	
PyO	–32.08	–[e]	3.22[b]	

[a] From [2]; [b] From [10]; [c] From [30]; [d] From [11]; [e] Reliable solvation energy parameters could not be obtained within the PCM model for the pyridine *N*-oxide derivatives [15]; [f] The cationic homoconjugation equilibrium is not present in aqueous solutions.

A comparison of basicities of the aliphatic trimethylamine *N*-oxide and the heterocyclic pyridine *N*-oxide shows that both the calculated energy parameters of protonation and experimental data reveal the stronger basicity of trimethylamine *N*-oxide, the difference being as high as approximately 7 pK_a units in acetonitrile. The pK_a^{AN}'s for protonated trimethylamine and pyridine *N*-oxides are respectively 16.93 [2] and 10.04 [10]. In aqueous solution, owing to the strongly expressed levelling effect of water relative to cationic acids conjugated with the *N*-oxides than to the parent amines, the difference does not exceed 4 pK_a units, respective pK_a^{W}'s being 4.65 and 0.79 [35]. It is worth noting that the difference between pK_a's in acetonitrile and water is around 7.5 pK_a units for amines, whereas for the *N*-oxides it is larger and more differentiated, exceeding 9 pK_a units for pyridine *N*-oxide and as many as 12 pK_a units for Me_3NO. As far as the cationic homoconjugation is concerned, both the calculated energy parameters and the experimental homoconjugation constants in non-aqueous solvents unambiguously indicate the stronger tendency of Me_3NO than that of pyridine *N*-oxide towards homoconjugation. Respective logarithms of the constants are 5.51 [11] and 3.22 [10]. Data of Table 5 offer the possibility of further comparisons. For instance a comparison of basicities and the tendency to cationic homoconjugation of pyridine and its *N*-oxide. As seen, although both the calculated energy parameters and the experimental evidence unambiguously indicate the much stronger basicity of pyridine as compared to that of its *N*-oxide, the same data indicate much stronger tendency of the *N*-oxide towards cationic homoconjugation. This means that the principal parameter responsible for the stability of the symmetric hydrogen bond formed is the nature of the hydrogen bridge, the O···H···O bridges being much more stable than the N···H···N ones.

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