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Basicity of Amines in the Gas Phase – Analysis of the Base-Strengthening Effect of an *N*-Trityl Group by Use of a Triadic Formula

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An ab initio theoretical method based on a triadic formula has been employed to calculate changes in proton affinities (*PA*s) after sequential substitution of C–H by C–phenyl in methylamine and in the *N*-methyl component of *N*-methylacetamide. The overall objective was to investigate the cause of the recently reported unexpected basicity-enhancing effect of the *N*-trityl group in several amines and in acetamide. The triadic method indicates that the increase in *PA* from NH_3 to CH_3NH_2 is principally due to destabilisation of the lone pair, compensated to some degree by a smaller bond energy term. The increasing *PA*s along the series CH_3NH_2, $PhCH_2NH_2$, Ph_2CHNH_2 and Ph_3CNH_2 are mainly due to an increasing relaxation energy effect following increasing phenyl substitution, supported by increasing bond energy terms. Introduction of *para*-methoxy substituents in tritylamine would be calculated to result in small incremental increases in *PA*, in agreement with experimental findings. The *PA* of tricyclohexylmethylamine (233.6 kcal·mol^{-1}) is calculated to be similar to that of trimethoxytritylamine (233.5 kcal·mol^{-1}), a consequence of the destabilisation of the lone pair on nitrogen by the three bulky cyclohexyl groups. Results for acetamide indicate that protonation on oxygen is more favourable than on nitrogen, which supports the intuitive argument that conventional π-electron resonance stabilisation of the *O*-protonated cation should be appreciably greater than hyperconjugative stabilisation of the *N*-protonated isomer. The increase in *PA* along the series $MeCONHCH_3$, $MeCONHCH_2Ph$, $MeCONHCHPh_2$ and $MeCONHCPh_3$ parallels the increase from CH_3NH_2 to Ph_3CNH_2 and is again principally a consequence of the increasing relaxation energies, which dominate the negative bond energy term contributions. Prior to protonation, the nitrogen atom of MeNHAc is perfectly planar, consistently with resonance delocalisation of the nitrogen lone pair into the carbonyl group. In contrast, there is a 6.5 % degree of pyramidalisation at the nitrogen in TrNHAc [calculated at the B3LYP/6-31G(d) level], indicating a reduced resonance interaction due to steric crowding, in support of a previous suggestion. Finally, the computed *PA*s and predicted first adiabatic ionisation energies are in satisfactory agreement with experimental results where these are available.

Introduction

Substituted trityl (triphenylmethyl) moieties have been widely used in organic synthesis as protecting groups,[1] and the mechanism of deprotection of tritylamines has been intensively studied.[2] Acidic detritylation in aqueous solution liberates trityl carbenium ions, and the equilibrium between trityl alcohols and trityl carbenium ions in aqueous acid has also been extensively investigated;[3] it is the basis of the well known H_R acidity function scale.[4]

In addition to kinetics aspects, we have also reported base strengths and crystal structure determinations of several *N*-trityl,*N*-alkylamines.[5] Remarkably, *N*-tritylarylamines (ArNHTr) are strong bases like alkylamines (pK_{BH^+} ca. 9–10), and substituents in the Ar part of ArNHTr have very little effect upon base strength. We also established that *N*-tritylacetamides are much stronger bases than simpler amides: pK_{BH^+} = 3.81 for TrNHAc (Scheme 1), for example, compared with –0.56 for MeNHAc. As is well known, amides are protonated on oxygen rather than nitrogen, which makes TrNHAc one of the strongest carbonyl bases known. Similarly, but to a smaller degree, *N*-trityl groups enhance the base strengths of hydroxylamines.[6] The unifying feature of our measurements is that a (substituted) *N*-trityl group increases the base strengths of weakly basic amines, hydroxylamines and amides in solution, and the effect is greater when the original base-weakening structural feature exerts its effect through resonance (the arylamines and amides) than by induction (hydroxylamines). It was unclear at the time whether the anomalously high base strengths of these *N*-trityl compounds were due to intrinsic steric or electronic molecular effects, or to peculiarities arising out of aqueous solvation phenomena.[7]

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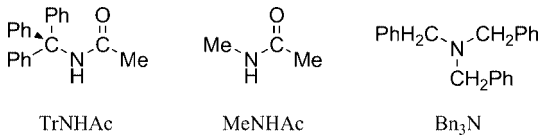

Scheme 1.

There have been contrasting previous reports concerning steric effects upon base strength in solution. Carboxylate and phenolate anions are made *more* basic by alkyl substitution,[8] whereas increased steric bulk generally makes ketones and some types of amines *less* basic,[9] although in our cases *N*-trityl has been shown to *increase* the base strengths of amines, hydroxylamines and amides. There has also been speculation over the years about whether resonance (delocalisation through the π-system) can be inhibited by steric effects.[10]

Comparison of reactions in solution and in the gas phase is a well established strategy for investigation of solvent effects, solvation phenomena and molecular structural effects upon reactivity, and we applied this to the peculiarities described above.[11] Base strengths in aqueous solution are expressed by Equation (1) and those in the gas phase by Equation (2), where *GB* is the gas-phase base strength (a free energy term) and *PA* the proton affinity (an enthalpy term). A possible complication in comparisons between the solution and gas phase is that different standard states apply – activities of 1 mol·dm^{-3} in solution and 1 standard atm in the gas phase.[11,12]

$$BH^+ + H_2O \rightleftharpoons B + H_3O^+;\ \Delta G^\circ,\ \Delta H^\circ,\ \Delta S^\circ;\ \Delta G^\circ = 2.303\ RT \cdot pK_a(BH^+) \quad (1)$$

$$BH^+ \rightleftharpoons B + H^+;\ \Delta G^\circ = GB,\ \Delta H^\circ = PA \quad (2)$$

By conventional ICR mass spectrometry[13] we observed that the increase in base strength from PhNHMe to PhNHTr in the gas phase (δGB = 8.7 kcal·mol^{-1}) is virtually identical to that between $MeNH_2$ and $TrNH_2$ (9.0 kcal·mol^{-1}), which can only be due to the increase in polarisability between Me and Tr. Consequently, there is no base strengthening in *N*-tritylamines through steric inhibition of resonance in the gas phase, and we attributed the enhanced base strengths of RNHTr in solution to steric effects upon solvation. Such solvation effects are not peculiar to single large bulky groups such as trityl, nor are they invariably base strength enhancements. The gas-phase base strength of tribenzylamine (Bn_3N; Scheme 1) has been shown to be unexceptional (*GB* = 230.7 kcal·mol^{-1}), so its anomalously low base strength in solution (pK_{BH^+} = 4.90) must also be a solvation effect.[11]

Following the same strategy to investigate whether the much higher solution base strength of TrNHAc (pK_{BH^+} = 3.81) in relation to MeNHAc (pK_{BH^+} = –0.56) is a solvation effect, we measured their base strengths in the gas phase. By a combination of conventional ICR mass spectrometry[13] and B3LYP/6-31G(d) calculations with the aid of the Gaussian 98 program,[14] *GB* values for MeNHAc (191.1 kcal·mol^{-1}) and TrNHAc (211.1 kcal·mol^{-1}) for protonation on nitrogen were obtained (i.e., TrNHAc is the stronger base by 20.0 kcal·mol^{-1}). On the assumption once again that the increase in *GB* values from $MeNH_2$ to $TrNH_2$ by 9.0 kcal·mol^{-1} is due to the increased polarisability of the alkyl residue on the nitrogen that becomes protonated, and that this may be transferred to other pairs of compounds bearing identical structural features, the higher *GB* value of TrNHAc in relation to MeNHAc for *N*-protonation, which is not attributable to the increased alkyl polarisability, drops to 11.0 kcal·mol^{-1}. We suggest that this, or an appreciable proportion of it, corresponds to the difference in gas-phase base strength (for *N*-protonation) between TrNHAc and MeNHAc due to reduced resonance interaction between the lone pair on nitrogen and the acetyl group in TrNHAc. We were unable to be so precise in our estimate of the extent of the base-strengthening effect for *O*-protonation of the *N*-trityl group above the contribution attributable to its polarisability, but it lies between 3 and 12 kcal·mol^{-1},[11] and almost certainly contributes towards the enhanced base strength of TrNHAc in aqueous solution.

Because proton transfer reactions are of such pivotal importance in a wide range of chemical and biochemical transformations, we believed that a more fundamental theoretical study of the effect of the trityl group on gas-phase base strengths of amines was warranted. The model we have adopted, which has been successfully applied to other neutral nitrogen bases,[15,16] involved resolution of the overall proton transfer process of Equation (2) into three distinct stages, as described below. Our starting point was ammonia, and the effect of replacing a single hydrogen atom by Me was investigated. Next, the effect of successively replacing the hydrogens of the methyl in CH_3NH_2 by Ph groups (which led through **3** and **4** up to **5** in Figure 1) was considered. The same protocol was then followed starting from acetamide ($AcNH_2$): the effect of replacing one hydrogen

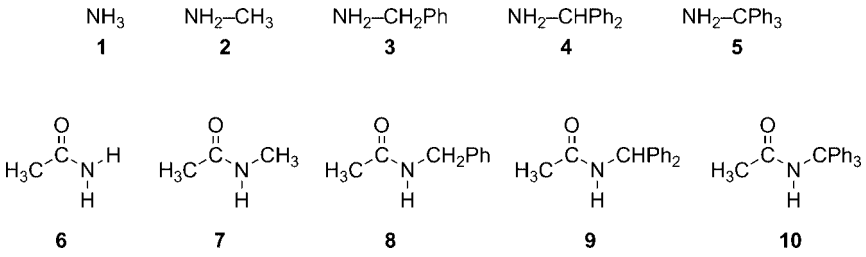

Figure 1. Schematic representation of substituted amines and acetamides investigated in this work.

on nitrogen by methyl (to give AcNHMe) was investigated, followed by consideration of the effect of successively replacing each of the hydrogens of the *N*–CH_3 by Ph (to give **8**, **9** and **10**).

Theoretical Framework

For current purposes, the base strength of a compound in the gas phase will be measured by its proton affinity (*PA*). It is obtained in the standard way as an enthalpy change of the reaction shown in Equation (2) and is calculated according to Equation (3)

$$PA(\mathrm{B}) = \Delta E + \Delta(pV) \quad (3)$$

where ΔE is the change in the total energy of the reaction in Equation (2), which includes the zero-point energy and the finite temperature (298.15 K) correction, and $\Delta(pV)$ stands for the pressure-volume work term.

A recently proposed novel triadic formula, Equation (4), enables estimation of the initial and final states' effects, as well as their interplay, on Brønsted basicities[15] and acidities[17] of organic compounds in the gas phase.

$$PA(\mathrm{B}) = -IE(\mathrm{B})_n^{\mathrm{Koop}} + E(\mathrm{ei})_{\mathrm{rex}}^{(n)} + (BDE)^{\cdot+} + 313.6\ \mathrm{kcal{\cdot}mol^{-1}} \quad (4)$$

The physical picture behind this approach is the separation of the protonation of a neutral organic base (Brønsted basicity) or a conjugate base anion (reverse process governing Brønsted acidity) into the three sequential steps: *i*) removal of an electron from the base/anion in question to give a radical, *ii*) attachment of the ejected electron to the incoming proton to form the hydrogen atom, and *iii*) creation of the chemical bond between the newly formed radical and the hydrogen atom. It has been demonstrated that this approach has certain advantages over some other models aiming to interpret Brønsted acidities and basicities, as discussed in great detail recently by Deakyne.[18] Triadic analysis also proved useful in explaining substituent effects in carboxylic acids[19a] and phenols[19b] as well as Lewis acidity of borane (BH_3) derivatives towards hydride ion H^-.[20] This resolution of the protonation process into three consecutive steps has a high cognitive value, enabling classification of studied molecules into three categories depending on whether the initial, intermediate or final state effect is predominant, as described below. Initial state effects on gas-phase basicities of neutral bases are reflected in Koopmans' ionisation energies,[21] $IE(\mathrm{B})_n^{\mathrm{Koop}}$, calculated in the frozen electron density and clamped atomic nuclei approximation (i.e., ionisation from the *n*th molecular orbital, counting the HOMO as the 1st). The $IE(\mathrm{B})_n^{\mathrm{Koop}}$ values reflect the price to be paid for taking an electron from the neutral molecule in a bond association process with the incoming proton, assuming that the ionisation is a sudden process. Since Koopmans' ionisation energies depend exclusively on the electron distribution of the neutral base under scrutiny, they reflect genuine properties of the initial state. The geometric and electronic reorganisation effects following electron ejection are given by the relaxation energy $E(\mathrm{ei})_{\mathrm{rex}}^{(n)}$, defined by Equation (5),

$$E(\mathrm{ei})_{\mathrm{rex}}^{(n)} = IE(\mathrm{B})_n^{\mathrm{Koop}} - IE(\mathrm{B})_1^{\mathrm{ad}} \quad (5)$$

where $IE(\mathrm{B})_1^{\mathrm{ad}}$ is the first adiabatic ionisation energy of the base. This is the intermediate phase of the protonation process. Finally, the electron affinity of the proton is experimentally determined to be exactly 313.6 kcal·mol^{-1},[22] whereas the bond dissociation energy describing homolytic bond formation between created radicals is given by the $(BDE)^{\cdot+}$ term and will be used in connection with the properties of the final state – in other words, with the protonated molecule. Although the formation of a new X–H bond is essentially a two-body interaction between the atoms X and H, or (rather) between their almost localised valence electrons, there is some additional relaxation of the rest of the molecule. For the sake of simplicity, this final relaxation is included in the $(BDE)^{\cdot+}$ term.

Although the above procedure is a simple extension of the well known thermodynamic cycle, where the sum of $IE(\mathrm{B})_n^{\mathrm{Koop}}$ and $E(\mathrm{ei})_{\mathrm{rex}}^{(n)}$ is replaced by a single term $IE(\mathrm{B})_1^{\mathrm{ad}}$, inclusion of the Koopmans' ionisation energies offers large interpretative advantages. The $IE(\mathrm{B})_n^{\mathrm{Koop}}$ corresponds to the *n*th ionisation energy, which is related to the specific MO affected most by the protonation. As such, it does not always have to relate to the HOMO; it could be one of the lower-lying molecular orbitals (vide infra), which is a very important feature of the triadic analysis.

We used a theoretical model that provides a very good compromise between reliability (accuracy) and practicability (feasibility): the MP2(fc)/6-311+G(d,p)//B3LYP/6-31G(d) approach, denoted hereafter as MP2. This gives basicities that compare reasonably well with experimental results.[15] It implies that all molecular geometries have been optimised and vibrational frequencies calculated at the B3LYP/6-31G(d) level of theory, which is the simplest approach taking into account the electron correlation effects. No scaling factor has been applied to the derived frequencies in the calculation of the thermodynamic parameters. For final single-point energy computations, we employed a more flexible 6-311+G(d,p) basis set within the MP2(fc) formalism, where (fc) denotes that the inner-core electrons of heavy atoms are kept frozen during the second-order Møller–Plesset perturbation calculations. The Koopmans' ionisation energies $(IE)_n^{\mathrm{Koop}}$ were computed by use of the HF/6-311+G(d,p)//B3LYP/6-31G(d) level of theory. Other entities were calculated with the restricted open-shell ROMP2(fc)/6-311+G(d,p)//B3LYP/6-31G(d) model. All calculations were performed with the aid of the GAUSSIAN 98 suite of programs.[14]

Results and Discussion

The proton affinities (*PA*s) of the studied compounds **1**–**10**, their contributions emerging from the triadic formula of Equation (4) and comparisons with existing experimentally determined values are presented in Table 1. The calculated

Table 1. Triadic analysis of the proton affinities of substituted amines and acetamides **1**–**10** obtained by application of the ROMP2(fc)/6-311+G(d,p)//B3LYP/6-31G(d) method. All terms are given in kcal·mol^{-1}. Subscript upper-case letters N and O for molecules **6**–**10** denote protonation at nitrogen and oxygen, respectively.[a]

Molecule	$(IE)_n^{Koop}$	$(IE)_1^{ad}$	IE(exp)[b]	E(ei)$_{rex}$	$(BDE)^{\cdot+}$	PA(thr)	PA(exp)[b]
NH_3 (**1**)	$(270.3)_1$	228.5	232.2 ± 0.5	41.8	120.2	205.3	204.0
NH_2–CH_3 (**2**)	$(246.3)_1$	205.7	205.2 ± 2.3	40.6	107.8	215.7	214.9
NH_2–CH_2Ph (**3**)	$(252.5)_3$	196.7	195.8 ± 1.4	55.8	104.2	221.1	218.3
NH_2–$CHPh_2$ (**4**)	$(254.1)_5$	195.3		58.8	104.3	222.6	
NH_2–CPh_3 (**5**)	$(259.8)_7$	187.6		72.2	101.1	227.1	
$MeCONH_2$ ($\mathbf{6_N}$)	$(261.0)_1$	225.6	223.5 ± 1.6	35.4	105.0	193.0	
$MeCONH_2$ ($\mathbf{6_O}$)	$(267.9)_2$			42.3	117.8	205.8	206.4
$MeCONHCH_3$ ($\mathbf{7_N}$)	$(245.5)_1$	220.6	223.7 ± 1.2	24.9	106.6	199.6	
$MeCONHCH_3$ ($\mathbf{7_O}$)	$(264.6)_2$			44.0	117.6	210.6	212.4
$MeCONHCH_2Ph$ ($\mathbf{8_N}$)	$(249.3)_3$	205.2		43.9	97.6	206.0	
$MeCONHCH_2Ph$ ($\mathbf{8_O}$)	$(267.7)_4$			62.5	104.4	212.8	
$MeCONHCHPh_2$ ($\mathbf{9_N}$)	$(252.2)_5$	202.4		49.8	97.7	208.9	
$MeCONHCHPh_2$ ($\mathbf{9_O}$)	$(268.5)_6$			66.1	105.6	216.8	
$MeCONHCPh_3$ ($\mathbf{10_N}$)	$(253.9)_7$	184.9		69.0	81.8	210.5	
$MeCONHCPh_3$ ($\mathbf{10_O}$)	$(268.0)_8$			83.1	92.4	221.1	

[a] The numerical subscripts indicate the molecular orbital which represents the lone pair(s) of the basic atom to be protonated and from which the electron is removed in the first step of our triadic analysis in such a way that subscript 1 denotes HOMO orbital, subscript 2 stands for HOMO–1, and so on. [b] Experimental data are taken from ref.[12].

MP2(fc)/6-311+G(d,p)//B3LYP/6-31G(d) proton affinity values – the *PA*s(thr) in Table 1 – are in reasonably good agreement with experimental results where these are available,[12] as a rule being slightly higher than the measured values for nitrogen protonation and somewhat lower for protonation at oxygen. It is fair to conclude, however, that the theoretical results are reliable, being particularly useful in consideration of the trends within families of closely related compounds, so the calculated *PA*s represent a useful supplement to the experimentally measured values. The same holds for the predicted first adiabatic ionisation energies $(IE)_1^{ad}$, which lends credence to the method applied. Consequently, the computed $(IE)_1^{ad}$ values can safely substitute for missing experimental data.

Amines

Scrutiny of the results in Table 1 shows that *PA* values increase along the series **1**–**5**. In order to understand this trend, it is useful to employ the triadic formula expressed as Equation (6), which gives the difference in the *PA* values of a compound **m** relative to a standard compound denoted by **st**.

$$PA(\mathbf{m})_\alpha - PA(\mathbf{st})_\alpha = [-\Delta(IE^{Koop})_\alpha; \Delta E(ei)_\alpha; \Delta(BDE)_\alpha^{\cdot+}] \quad (6)$$

In Equation (6), contributions from the electron affinity of the proton following ionisation of the base cancels out. Further, the symbol α indicates the site of protonation, assumed here to be the same in the molecule studied and in the reference compound, and Δ stands for the difference between the compounds **m** and **st** for each of the three terms defined previously. The square brackets indicate summation of the three terms within them. It is useful to point out that there is a minus sign in front of the Koopmans' ionisation energy term because this component reflects the price to be paid for the ionisation of the molecule to be protonated. In other words, a higher $(IE)_n^{Koop}$ value results in a lower proton affinity and reduced basicity.

Let us consider the variation in *PA*s in the series **1**–**5**. It is worth reiterating that we use proton affinities (an enthalpy term) as a measure of basicity instead of gas-phase basicity itself (a free energy term) because in our analysis the contribution from entropy would cancel out in Equation (6) for compounds studied in this work. The effect of the methyl substitution in NH_3 is given by Equation (7).

$$PA[\mathbf{2(N)}] - PA[\mathbf{1(N)}] = [24.0; -1.2; -12.4] = 10.4 \text{ kcal·mol}^{-1} \quad (7)$$

We see that the basicity of methylamine is increased by 10.4 kcal·mol^{-1} and the main reason is the increased $-(IE)_n^{Koop}$ term, which is a consequence of the bond electron pair/lone electron pair repulsion. In other words, the nitrogen lone pair in methylamine is placed in the HOMO orbital (Figure 2), which lies higher in energy (i.e., it is destabilised) than the matching orbital in ammonia (Table 1). The $(IE)_n^{Koop}$ term of **2** is therefore lower, implying a less costly extraction of an electron in our triadic picture. Were only the $(IE)_n^{Koop}$ term involved, however, methylamine would be predicted to be a stronger base than ammonia by 24.0 kcal·mol^{-1}, but this positive contribution is reduced somewhat by a slightly unfavourable contribution from the relaxation energy (–1.2 kcal·mol^{-1}) and a considerably smaller bond dissociation energy (–12.4 kcal·mol^{-1}) so that the *overall* difference in basicity between molecules **1** and **2** is just 10.4 kcal·mol^{-1}.

In order to explain the increase in basicity upon phenyl substitution at the carbon of methylamine (i.e., between **2** on the one hand and molecules **3**, **4**, and **5** on the other), we evaluate the differences in *PA*s between each of **3**, **4** and **5** and the parent CH_3NH_2 (**2**) in turn through Equations (8), (9) and (10).

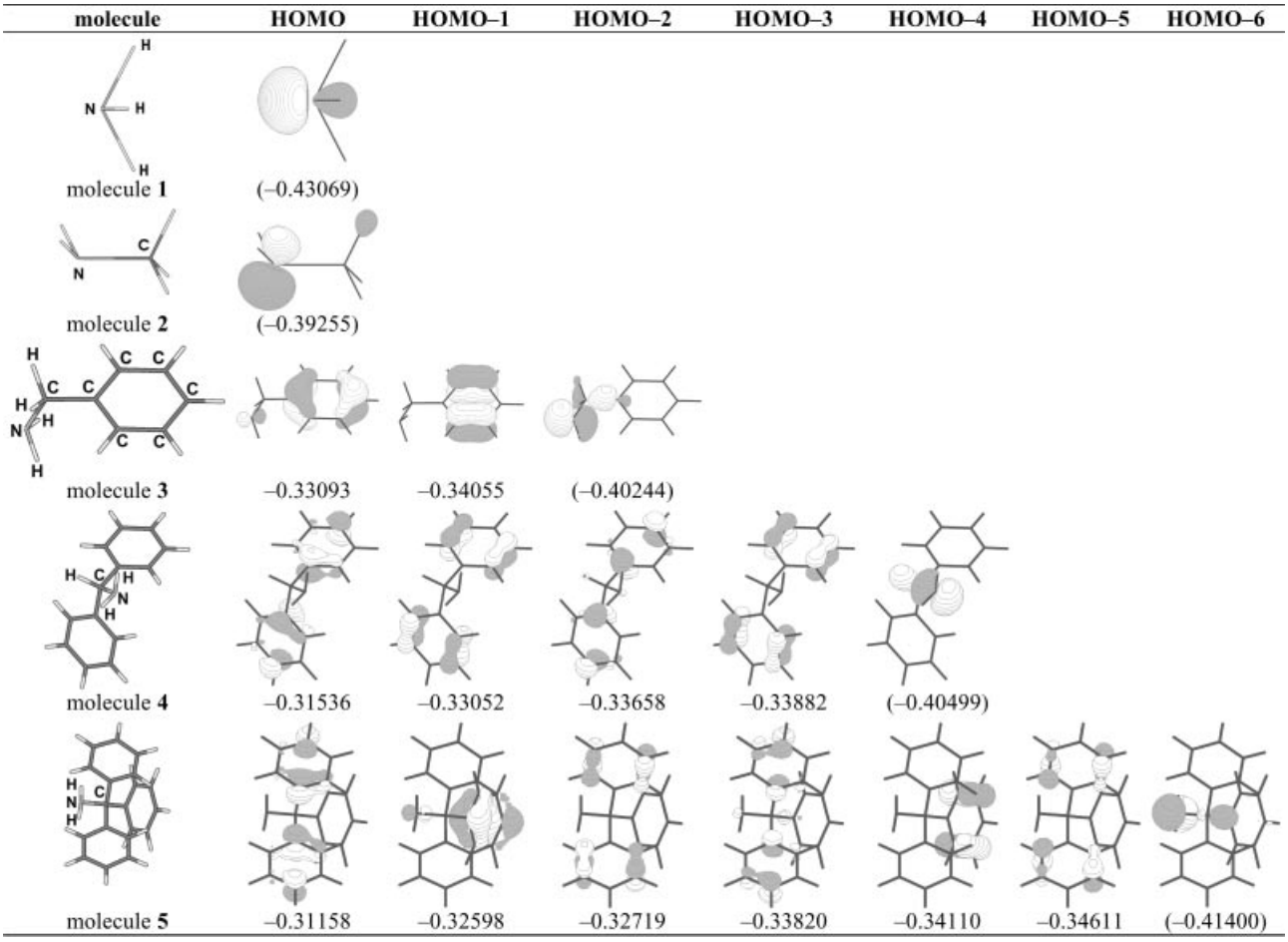

Figure 2. Schematic representation of the relevant molecular orbitals of molecules **1**–**5** together with their orbital energies (a.u.) obtained by the HF/6-311+G(d,p)//B3LYP/6-31G(d) theoretical model. The orbital energies of MOs participating in protonation the most are given in parentheses.

$$PA[\mathbf{3(N)}] - PA[\mathbf{2(N)}] = [-6.2; 15.2; -3.6] = 5.4\ \text{kcal·mol}^{-1} \quad (8)$$

$$PA[\mathbf{4(N)}] - PA[\mathbf{2(N)}] = [-7.8; 18.2; -3.5] = 6.9\ \text{kcal·mol}^{-1} \quad (9)$$

$$PA[\mathbf{5(N)}] - PA[\mathbf{2(N)}] = [-13.5; 31.6; -6.7] = 11.4\ \text{kcal·mol}^{-1} \quad (10)$$

Inspection of the highest MOs of **3** reveals that the nitrogen lone pair AO (we use AO for simplicity, although hybrid atomic orbital HAO would be more general) participates in HOMO and HOMO–2. Although the first ionisation energy corresponds to electron loss from HOMO, it appears that the lone pair AO has a very low coefficient and that the electron density on nitrogen is consequently little affected by this molecular orbital, which in turn predominantly resides on the phenyl ring. In contrast, the lone pair AO contributes strongly to the composition of the HOMO–2 molecular orbital, which will play a major role in the protonation process, so we shall consider ionisation from HOMO–2 in determining Koopmans' ionisation energy. Analogously, we select HOMO–4 and HOMO–6 (Figure 2) as dominant in the proton attachment in systems **4** and **5**. Since all of them lie rather deep, the Koopmans' ionisation term decreases the basicity, as is evident from Equations (8)–(10). It turns out, however, that this effect is overcompensated by the overwhelming influence of the relaxation energy, which increases upon phenyl substitution(s), reaching an increment of 31.6 kcal·mol^{-1} in **5**. The bond dissociation term $(BDE)^{\cdot+}$ decreases moderately along the series **3**–**5**. The end result is that the proton affinity increases by 5, 7 and 11 kcal·mol^{-1} upon single, double and triple phenyl substitution of the methyl group in NH_2CH_3. It is safe to conclude that the enhancement of basicity is a consequence of the intermediate relaxation step stimulated by large phenyl group(s).

Let us focus next on *para*-methoxy substituent effects, which were studied in order to shed light on the long range interactions in **5**. Proton affinities increase by 2.1, 4.3 and 6.5 kcal·mol^{-1}, relative to **5**, in 4-methoxy, 4,4′-dimethoxy and 4,4′,4′′-trimethoxytritylamine (Table 2), which is significant considering that there is a C(sp^3) relay between the nitrogen and the substituent(s) in the trityl group. It is interesting that their ratios are approximately 1:2:3. Comparing proton affinities of the three methoxy-substituted derivatives with that of the parent molecule **5** and writing them in the triadic form leads to Equations (11), (12) and (13).

Table 2. Triadic analysis of proton affinities of some additional compounds obtained by application of the ROMP2(fc)/6-311+G(d,p)//B3LYP/6-31G(d) method. All terms are given in kcal·mol^{-1}.

Molecule	$(IE)_n^{Koop}$	$(IE)_1^{ad}$	$E(ei)_{rex}$	$(BDE)^{\cdot+}$	PA(thr)	Protonated atom
4-Methoxytritylamine	$(256.9)_7$	176.2	80.7	91.8	229.2	nitrogen
4,4′-Dimethoxytritylamine	$(257.6)_7$	163.8	93.8	81.6	231.4	nitrogen
4,4′,4′′-Trimethoxytritylamine	$(255.0)_7$	162.6	92.4	82.6	233.6	nitrogen
$(Cyclohexyl)_3C–NH_2$	$(232.4)_1$	172.5	59.9	92.4	233.5	nitrogen
$NH_2–OH$	$(273.1)_1$	208.7	64.4	89.3	194.2	nitrogen
	$(273.1)_1$	208.7	64.4	63.7	168.6	oxygen

$$PA[\text{4-methoxytritylamine}] - PA[\mathbf{5}] = [2.9; 8.5; -9.3] = 2.1\ \text{kcal·mol}^{-1} \quad (11)$$

$$PA[\text{4,4′-dimethoxytritylamine}] - PA[\mathbf{5}] = [2.2; 21.6; -19.5] = 4.3\ \text{kcal·mol}^{-1} \quad (12)$$

$$PA[\text{4,4′,4′′-trimethoxytritylamine}] - PA[\mathbf{5}] = [4.8; 20.2; -18.5] = 6.5\ \text{kcal·mol}^{-1} \quad (13)$$

The first comment to make is that in all the molecules the active MO corresponding to the nitrogen lone pair is HOMO–6, just as in the parent compound **5** (Figure 3). Next, it follows that HOMO–6 orbitals are only moderately destabilised by the methoxy substituent(s). This effect is largest in mono- and trimethoxy derivatives, since in these cases the HOMO–6 orbital is composed of the nitrogen lone pair AO and a very small but significant contribution from the *p*-AO residing on the oxygen atom of the methoxy substituent (Figure 3). In the case of dimethoxytritylamine, on the other hand, this contribution is nonexistent due to symmetry. Consequently, the difference between the Koopmans' terms of 4,4′-dimethoxytritylamine and of the parent molecule **5** is smallest within this series of compounds, being only 2.2 kcal·mol^{-1}. It also follows that the relaxation effect is considerably increased relative to **5**, which overcomes a decrease in the bond dissociation energy, finally resulting in amplification of basicity.

It is of interest to replace phenyl groups with cyclohexyl rings and to consider the *PA* of $(cyclohexyl)_3C–NH_2$. Surprisingly enough, the *PA* of this compound (233.6 kcal·mol^{-1}) is higher than that of tritylamine (227.1 kcal·mol^{-1}) and equal to that of 4,4′,4′′-trimethoxytritylamine (233.5 kcal·mol^{-1}). Taking into account the differences between the terms in the triadic formula for the molecules $(cyclohexyl)_3C–NH_2$ and $TrNH_2$ (**5**), one obtains Equation (14).

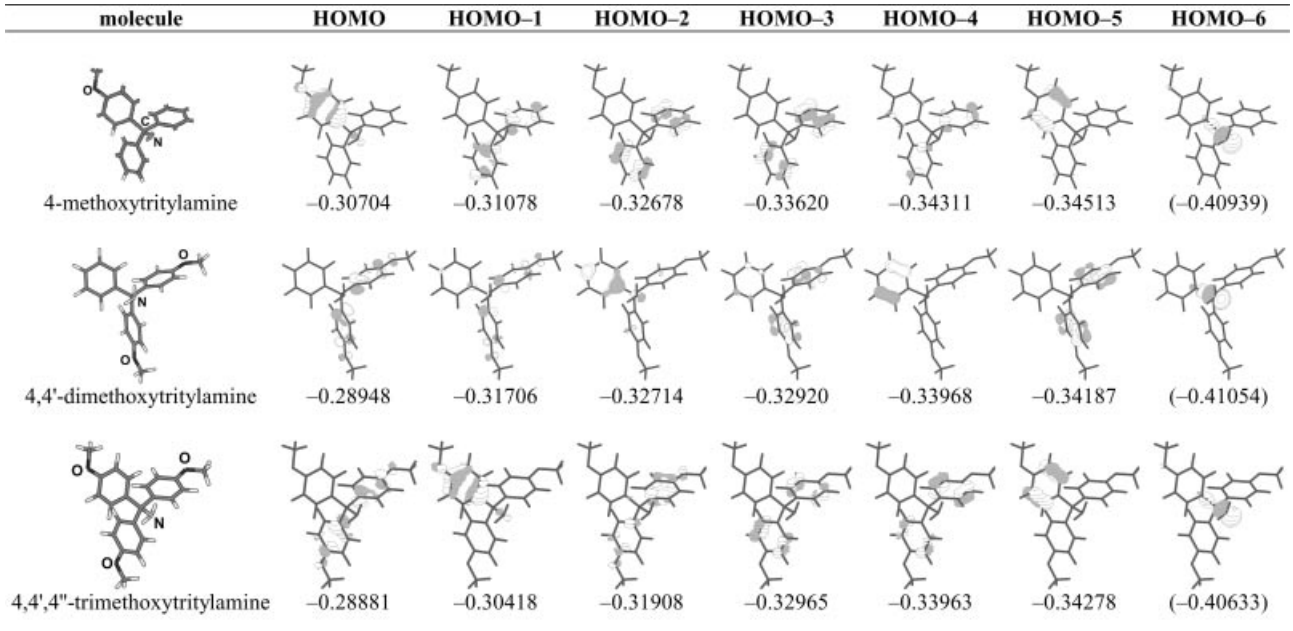

Figure 3. Schematic representation of the relevant molecular orbitals of mono-, di- and trimethoxy derivatives of tritylamine **5** together with their orbital energies (a.u.) obtained by the HF/6-311+G(d,p)//B3LYP/6-31G(d) theoretical model. The orbital energies of MOs participating in protonation the most are given in parentheses.

$$PA[(\text{cyclohexyl})_3\text{C–NH}_2] - PA[\mathbf{5(N)}] = [27.4; -12.3; -8.7] = 6.4\ \text{kcal·mol}^{-1} \quad (14)$$

It is immediately evident from the data presented in Equation (14) that it is easier to remove an electron from the nitrogen lone pair in $(\text{cyclohexyl})_3\text{C–NH}_2$ than from that in TrNH_2, by 27.4 kcal·mol^{-1}, which would indicate that the former molecule is more basic. It appears that this conjecture is correct, since the favourable contribution from the $(IE)_n^{\text{Koop}}$ term dominates over the unfavourable (decreased) relaxation (–12.3 kcal·mol^{-1}) and $(BDE)^{\cdot+}$ (–8.7 kcal·mol^{-1}) terms. It follows that the higher basicity of the amino group attached to a bulky alkyl substituent is a consequence of the initial state (i.e., the exposure of the nitrogen lone pair electron and its ease of ionisation). This is consistent with the lone pair of $(\text{cyclohexyl})_3\text{C–NH}_2$ being the high HOMO (Figure 4) whereas the lone pair of molecule **5** is accommodated in the low lying HOMO–6 (Figure 2).

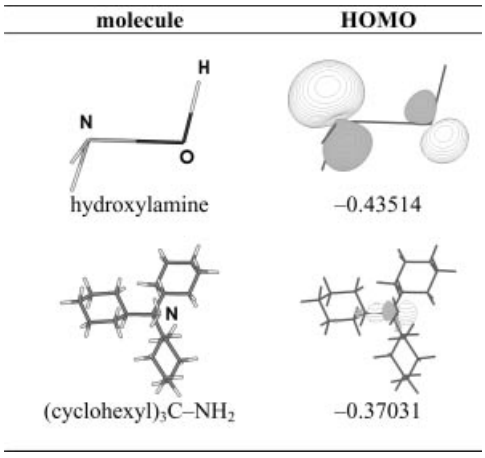

Figure 4. Schematic representation of the HOMO molecular orbital of hydroxylamine (NH_2OH) and $(\text{cyclohexyl})_3\text{C–NH}_2$ together with their orbital energies (a.u.) obtained by the HF/6-311+G(d,p)//B3LYP/6-31G(d) theoretical model.

Amides and Hydroxylamine

We now focus on the substituted acetamides and note that the *PA* of **6** is decreased relative to **1** by 12.3 kcal·mol^{-1}. Triadic analysis {$PA[\mathbf{6(N)}] - PA[\mathbf{1(N)}] = [9.3; -6.4; -15.2] = -12.3$ kcal·mol^{-1}} shows that this is a consequence of a decrease in the relaxation energy and the *BDE* term, where the latter term dominates. If we extend this approach to other corresponding pairs between amides and amines, triadic analysis offers an insight into the influence of the CH_3–C=O group on the basicity of amino nitrogen directly attached to it. For that purpose we consider the set of Equations (15), (16), (17) and (18).

$$PA[\mathbf{7(N)}] - PA[\mathbf{2(N)}] = [0.8; -15.7; -1.2] = -16.1\ \text{kcal·mol}^{-1} \quad (15)$$

$$PA[\mathbf{8(N)}] - PA[\mathbf{3(N)}] = [3.2; -11.9; -6.6] = -15.1\ \text{kcal·mol}^{-1} \quad (16)$$

$$PA[\mathbf{9(N)}] - PA[\mathbf{4(N)}] = [1.9; -9.0; -6.6] = -13.7\ \text{kcal·mol}^{-1} \quad (17)$$

$$PA[\mathbf{10(N)}] - PA[\mathbf{5(N)}] = [5.9; -3.2; -19.3] = -16.6\ \text{kcal·mol}^{-1} \quad (18)$$

It is clear from the data provided by Equations 15–18 that the overall influence of the acetyl group is unfavourable such that the resulting nitrogen basicity of molecules **6**–**10** is reduced in relation to amines **1**–**5** unsubstituted by the acetyl group. On average this effect is roughly 15 kcal·mol^{-1}. Interestingly enough, triadic analysis shows that this effect is not caused by the initial state effect. On the contrary, in all matching pairs of molecules the ionisation from nitrogen lone pair within Koopmans' approximation is easier and more beneficial in the case of acetamides. This finding provides compelling evidence that the nitrogen lone pair participates in the resonance interaction with the carbonyl group in acetamides and that it is therefore more susceptible to ionisation. It should be recalled that this interaction implies formation of the in-phase and out-of-phase combination of the C=O double bond with the lone pair AO of nitrogen. The latter describes the lone pair electron density distribution and has higher energy, but this positive contribution to the *PA* is overpowered by the contributions arising from the relaxation energy and the *BDE* term, resulting in a global decrease in basicity of acetamides.

The next question to be answered is the origin of the higher basicity of oxygen relative to nitrogen in **6**. Triadic analysis straightforwardly shows that this is due to higher bond dissociation energy of the O–H bond. The point is that the molecule "knows" only $-(IE)_1^{\text{ad}}$ and this term is the same for all (basic) atoms within the one molecule. This term is intentionally dissected into two: $-(IE)_n^{\text{Koop}}$ and $E(\text{ei})_\alpha^{(n)} = (IE)_n^{\text{Koop}} - (IE)_1^{\text{ad}}$ for interpretative purposes in the triadic analysis. One can distinguish Koopmans' ionisation energies of the N and O atoms in the acetamide series, but the relaxation energy will be changed by the same amount in the opposite direction. These two effects add up to $(IE)_1^{\text{ad}}$, which is the same for both protonation events. Therefore,

$$PA[\mathbf{m(O)}] - PA[\mathbf{m(N)}] = BDE[\mathbf{m(O)}]^{\cdot+} - BDE[\mathbf{m(N)}]^{\cdot+} \quad (19)$$

which, for ***m*** = **6**, **7**, **8**, **9** and **10**, yields 12.8, 11.0, 6.8, 7.9 and 10.6 kcal·mol^{-1}. Although Equation (19) gives the most straightforward answer, it is still helpful to consider the triadic formula in full. In the case of **6**, it appears that the HOMO–1 describing the lone pair at oxygen is lower than the HOMO by 6.9 kcal·mol^{-1}, which is in turn related to the lone pair of nitrogen. This holds as a rule in all acetamides studied (Figure 5). These differences in the $(IE)_n^{\text{Koop}}$ term are exactly recovered by a larger relaxation effect, as evidenced by the data displayed in Table 1.

In this context it is interesting to consider hydroxylamine NH_2OH, which has an N–O single bond. This system is quite different since the HOMO is delocalised and describes both lone pairs residing on N and O atoms (Figure 4). Consequently, $(IE)_1^{\text{Koop}}$ and $E(\text{ei})_{\text{rex}}$ terms are equal for protonation at both positions. The amino nitrogen, however, is substantially more basic because its *BDE* term is larger by

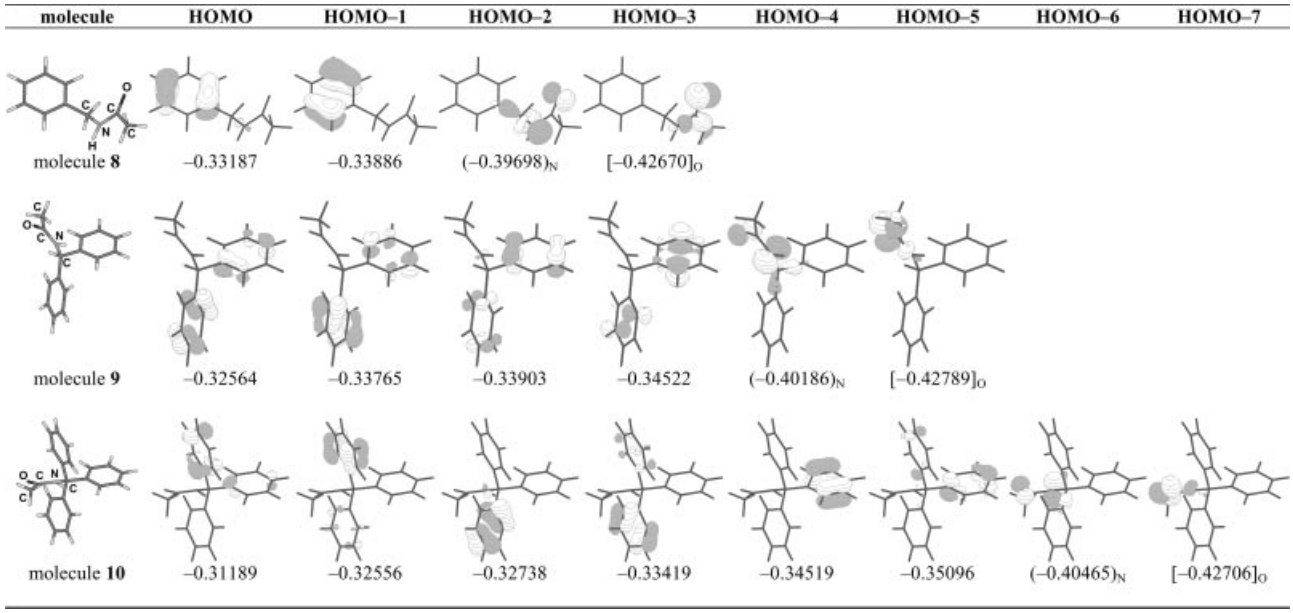

Figure 5. Schematic representation of the relevant molecular orbitals of molecules **8**–**10** together with their orbital energies (a.u.) obtained by the HF/6-311+G(d,p)//B3LYP/6-31G(d) theoretical model. The orbital energies of active lone pair MOs participating in the protonation of nitrogen (N) and oxygen (O) atoms are given in parentheses and brackets, respectively.

25.6 kcal·mol^{-1} (Table 2), in accordance with Equation (19). This large difference would imply that the resonance stabilisation in H_2N–O^+H_2 is missing, whereas no-bond double-bond resonance in H_3N^+–OH is very strong.

Let us now consider the effect of the phenyl substitution in the CH_3 group attached to nitrogen on the proton affinity of oxygen estimated relative to molecule **7**, given by the triads shown in Equations (20), (21) and (22).

$$PA[\mathbf{8(O)}] - PA[\mathbf{7(O)}] = [-3.1;\ 18.5;\ -13.2] = 2.2\ \text{kcal·mol}^{-1} \quad (20)$$

$$PA[\mathbf{9(O)}] - PA[\mathbf{7(O)}] = [-3.9;\ 22.1;\ -12.0] = 6.2\ \text{kcal·mol}^{-1} \quad (21)$$

$$PA[\mathbf{10(O)}] - PA[\mathbf{7(O)}] = [-3.4;\ 39.1;\ -25.2] = 10.5\ \text{kcal·mol}^{-1} \quad (22)$$

It appears that the increase in *PA* is a consequence of the increased relaxation energy, which dominates the negative contributions of the $(IE)^{Koop}$ and $(BDE)_O^{\cdot+}$ terms in accordance with previous results obtained for molecules **2**–**5**. The increasing $E(ei)_{rex}$ term along the series is reasonably attributable to the larger sizes of the systems, which enable better dispersion of the positive charge. The relaxation energies are comparable to those found in the series **2**–**5**, being higher by 4–7 kcal·mol^{-1}, obviously due to the additional $CH_3C{=}O$ moiety.

It was pointed out in the Introduction that the higher basicity of TrNHAc **10** in relation to MeNHAc **7** has been attributed to a lower degree of delocalisation of the lone pair in the former system due to steric hindrance. This conjecture can be substantiated by the nitrogen pyramidalisation in **10**. A degree of pyramidalisation can be estimated by Equation (23),[23]

$$DP(\%) = \left[360 - \sum_{i=1}^{3} \alpha_i\right] / 0.9 \quad (23)$$

where *DP* stands for the degree of pyramidalisation and the summation is over the bond angles α_i of the pyramidal nitrogen atom. It turns out that the nitrogen atom in MeNHAc is perfectly planar, thus enabling an optimal resonance effect between the N-lone pair and the C=O bond. On the other hand, the degree of pyramidalisation *DP*(N) in TrNHAc is 6.5% [B3LYP/6-31G(d) results], indicating that resonance is reduced. Inspection of the relevant bond lengths in Figure 6 supports this conclusion. The N–C bond in **10** is lengthened relative to that in **7** and the C=O bond is shortened. Protonation of TrNHAc at oxygen results in planarisation of the nitrogen atom, which establishes the optimal resonance effect, so a higher basicity of TrNHAc is expected theoretically and found experimentally. However, a more detailed understanding of the increased basicity of TrNHAc is provided by the more comprehensive triadic analysis as expounded above.

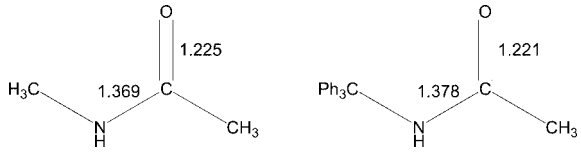

Figure 6. The relevant bond lengths (Å) for molecules MeNHAc and TrNHAc obtained at B3LYP/6-31G(d) level of theory.

In summary, we see for the amides that oxygen is more basic than nitrogen in compounds **6**–**10** due to a stronger O–H bond formed between the radical cation and the hydrogen atom, as reflected in the bond dissociation energy

term $(BDE)_O^{\cdot+}$. That **10** is considerably more basic than **6** for oxygen protonation is a consequence of the much larger relaxation effect in the former.

Summary and Concluding Remarks

The triadic formula of Equation (4) for the proton transfer reaction of Equation (2) represents the resolution of the overall reaction into three conceptually distinct processes (electron loss from the basic site to give a radical cation, transfer of the electron to a proton to give a hydrogen atom, then sigma-bond formation between the radical cation and the hydrogen atom) that may be modelled computationally even though they are not all individually susceptible to experimental scrutiny. Theoretically derived proton affinity results are in good agreement with experimentally measured values where these are available, which supports the model and allows confident prediction of results where experimental values are not available. Effects of the following substitutions upon the *PA* of the parent NH_3 molecule have been investigated: *i*) replacing a hydrogen in NH_3 by a methyl, *ii*) sequentially replacing each C–H in CH_3NH_2 by C–Ph, and *iii*) replacing each C–H in the $NHCH_3$ residue of $AcNHCH_3$ by C–Ph. Three principal causes of each change in the *PA* have been identified, and their relative contributions differ according to the nature of the structural modification. These are: *i*) destabilisation of the lone pair of the basic site, as in the change from NH_3 to CH_3NH_2 and tricyclohexylmethylamine, *ii*) relaxation effects in the radical cation after electron loss, as in the increasing *PA*s along the series CH_3NH_2, $PhCH_2NH_2$, Ph_2CHNH_2 and Ph_3CNH_2, and *iii*) changes in the bond energy term as the radical cation bonds to the hydrogen atom, as in the higher basicity of oxygen in relation to nitrogen in acetamide (**6**) and the higher basicity at N than at O in hydroxylamine. In some cases it is not possible to identify a single dominant term, implying that interplay of two or even three terms is of importance.

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