Site of Protonation of Carboxylic and Non-Carboxylic Amides in the Gas Phase and in Water

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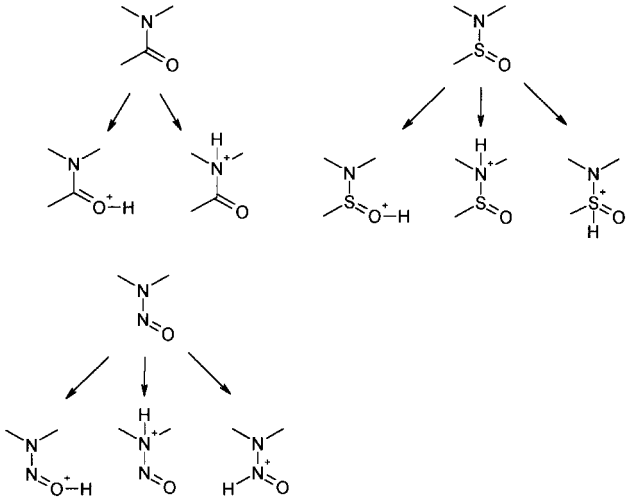
Abstract: The site of protonation of several types of amide bases (carboxylic amides and thioamides, sulfenamides, sulfinamides, sulfonamides, nitrosamides, nitramides, cyanamides, and phosphorous and phosphoric acid triamides) has been investigated through a combination of quantum chemical calculations and heteronuclear NMR measurements. Relative energies of tautomeric ions deriving from protonation at the various sites were determined both in the gas phase (by MP2 calculations) and in water (by the IPCM continuum solvation method). Relevant NMR properties of the involved heteronuclei (nuclear shielding and electric field gradient) were calculated at the GIAO-HF level, and compared with chemical shifts and relaxation rates experimentally measured in ^{14}N, ^{17}O, and ^{31}P spectra. It is shown that such a combination of theoretical and experimental tools allows a dependable prediction of spectral parameters and ultimately of the protonation site of amides. The reliability of common assumptions, like the comparison of spectral parameters of polyfunctional bases and monofunctional models, is also scrutinized and tested.

Keywords: ab initio calculations · amides · basicity · NMR spectroscopy · protonation site

Introduction

Amides are made of an acid residue and an amino group; the acid residue (e.g. RCO for carboxylic acids, RSO_2 for sulfonic acids, NO_2 for nitric acid, etc.) most often contains an oxygen atom. All amides are (generally weak) bases,[1, 2] and may undergo protonation at nitrogen or the acid residue (Scheme 1).

A classic problem is the site of protonation of carboxylic amides, which have been conclusively shown to be oxygen, rather than nitrogen, bases.[1–3] Problems of this kind are quite common (e.g., little is known concerning the protonation site of many non-carboxylic amides[1]) and have been attacked by both theoretical and experimental methods. In principle, the site of protonation can be calculated, because quantum chemical methods can provide the relative energies and proton affinities of neutral species associated with protonation at all sites. This approach, however, does not normally include solvent effects, which will affect the relative stability of ions with different solvation characteristics, and in turn may have an impact on the comparison with experimental data in solution.



Scheme 1. Possible protonation sites for some amide bases.

Several experimental approaches have been adopted to infer the structure of the protonated form of polyfunctional bases and acids. Protonation sites have been inferred from

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trends in substituent effects for compounds under study and known monofunctional bases.[1] Another frequently used approach is to study the pattern of change of the chemical shift of various nuclei in the molecule upon going from neutral to ionizing conditions. Thus, for example, it is commonly thought that the ionization site is the one for which the largest chemical shift change is observed, or for which the changes most closely match those of a compound whose ionization site is unambiguous because one of the sites has been made unavailable to ionization (e.g. by alkylation).[4, 5] The pattern of change of NMR coupling constants has also been advocated in this respect.[5, 6] However, the interpretation of such results is hampered by their empirical nature. In fact, protonation or deprotonation at any site will cause chemical shift and coupling constant changes of variable extent at all nuclei reasonably close to the ionization site (this is used to advantage in quantitative studies, where one monitors the chemical shift of protons belonging to the hydrocarbon backbone, although they are not ionization sites themselves). Since the shielding of each nucleus has a different sensitivity to the electronic changes brought about by the ionization process, the magnitude of the observed variation is not informative if the possible sites are different types of atoms, or the same type of atom in different functional groups. There is also no guarantee that the spectroscopic behavior of alkylated models is exactly the same as that of the compound under study, especially when we are dealing with small changes.[7]

We have recently shown that a powerful means to solve this problem is the analysis of the changes in the NMR relaxation time (T_1) of all the nuclei which may be ionization sites.[8–10] This is because the NMR relaxation rate of quadrupolar nuclei (e.g. ^{14}N, ^{17}O) in the extreme narrowing limit depends on the electric field gradient (efg) existing at the nucleus according to Equation (1), where $\chi = eQq_{zz}/h$ is the nuclear

$$\frac{1}{T_1} = \frac{3\pi^2}{10}\frac{2I+3}{I^2(2I-1)}\chi\left(1+\frac{\varepsilon^2}{3}\right)\tau_c \qquad (1)$$

Abstract in Italian: *Il sito di protonazione di diversi tipi di basi ammidiche (ammidi e tioammidi carbossiliche, solfenammidi, solfinammidi, solfonammidi, nitrosammidi, nitrammidi, cianammidi, triammidi degli acidi fosforoso e fosforico) è stato studiato attraverso una combinazione di calcoli di chimica quantistica e misure di NMR eteronucleare. Le energie relative degli ioni tautomerici derivanti dalla protonazione ai vari siti sono state determinate sia in fase gas (da calcoli MP2) sia in acqua (con il metodo continuo di solvatazione IPCM). Le proprietà NMR rilevanti degli eteronuclei coinvolti (schermatura nucleare e gradiente di campo elettrico) sono state calcolate al livello GIAO-HF, e paragonate con i chemical shift e le velocità di rilassamento misurate sperimentalmente negli spettri ^{14}N, ^{17}O e ^{31}P. Si mostra che tale combinazione di metodi teorici e sperimentali permette di prevedere i parametri spettrali, ed in ultima analisi il sito di protonazione delle ammidi, in maniera affidabile. Viene inoltre discussa e controllata l'affidabilità di assunzioni comuni, come il paragone dei parametri spettrali di basi polifunzionali e modelli monofunzionali.*

quadrupolar coupling constant, q_{zz} is the largest principal component of the efg tensor $\boldsymbol{q}$, $\varepsilon = |q_{xx} - q_{yy}|/q_{zz}$ is its asymmetry parameter, and τ_c is the rotational correlation time. If protonation causes an efg change (i.e., of q_{zz} and ε), this may be detected as a change in T_1 or linewidth; however, the direction of change (if any) is not easy to predict. We previously calculated the efg by ab initio quantum chemical methods for a series of mono- and polyfunctional bases and acids.[11, 12] An important point is that $\boldsymbol{q}$ depends only on the ground-state wave function, and its calculation is fast (although not necessarily accurate).[12] Therefore, this is an independent means to estimate the changes occurring upon ionization at any site. However, in order to translate the efg into relaxation times the correlation time must either be unaffected or change in a known way. Moreover, the efg at some nuclei (notably oxygen) is not overly sensitive to ionization,[12] and ^{17}O T_1's are difficult to determine at natural abundance (0.037%).

On the other hand, the experimental determination of chemical shifts is much simpler and faster than the determination of T_1's. The difficulties in the accurate calculation of the nuclear shielding tensor $\boldsymbol{\sigma}$ have now been largely overcome (although this type of calculation is still much more expensive than that of the efg), and routines which accomplish this task (by means of the IGLO[13] and GIAO[14] methods) have been incorporated into commercial quantum chemical packages.[15] Its accuracy in comparison with experimental values has been benchmarked.[16] Thus, nuclear shielding calculations complement efg calculations.

We also note that the above calculated quantities pertain to isolated molecules. The adequacy of such energies and spectroscopic properties in modeling processes taking place in solution, where differential solvation of the various ionic species comes into play, can rightly be questioned. Although one could run the calculations on a cluster formed by the solute and a small number of solvent molecules, this approach is made difficult by the fact that a meaningful solvation shell must comprise a substantial number of solvent molecules. The calculation thus becomes quite time-consuming, because of the large number of atoms and the floppiness of these systems, which generally have a large number of accessible conformations with similar energy. A much faster alternative for modeling solvent effects is provided by continuum methods. These treat the solvent as a continuous medium with a given dielectric permittivity ε, and containing a variously shaped cavity in which the solute is placed.[17] Major advances have been recently made in this field, and these computationally inexpensive methods have proved effective in several cases.[17] Such calculations have been carried out to predict the solvent effect on proton transfer equilibria of ammonium ions,[18, 19] alcohols,[20, 21] and tautomeric ions from the ionization of polyfunctional bases[22] and acids.[23] Lately, the isodensity polarizable continuum method (IPCM), which employs a solute-shaped (rather than spherical) cavity, has been proposed as a general-purpose way of calculating the solvent effect on chemical equilibria and reactions.[15, 24] Kawata et al. successfully applied the RISM-SCF method (a combination of ab initio and statistical mechanics) to the basicity order of methylamines in water.[25] However, no large-scale database is

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yet available to assess the performance of these methods, especially with regard to the modeling of proton transfers in water (which involve strong local interactions like hydrogen bonding).

Finally, we remind the reader that we assume protonation to yield a single static protonated species, whereas in solution both tautomeric ions may coexist in variable amounts and may also undergo proton exchange on the NMR time scale. Therefore, caution must be exercised when comparing experimental and calculated results, particularly when the ions have a similar stability.

To summarize, we have undertaken an experimental and computational study intended to: a) assess the performance of the IPCM method in determining proton-transfer energetics in water; b) assess whether calculated shielding changes match chemical shift changes upon protonation in solution; c) compare the performance of the two methods (changes in efg and T_1 vs. nuclear shielding and chemical shift); d) finally, investigate the site of protonation (acid residue or nitrogen) in non-carboxylic amides.

Results

Theoretical methods and calculations: Structures and energies of the various ionic species (calculated at the MP2/6-31 + + G(d,p)//HF/6-31 + + G(d,p) or MP2/6-311 + + G(d,p)//HF/6-311 + + G(d,p) levels), as well as the efg's (calculated at the HF/TZP level), for many species were available from a previous study.[11, 12] For some amide types (carboxamides and sulfinamides) we extended the scope of the above work to include the species actually investigated experimentally. Furthermore, for all the neutral and ionized species, chemical shielding calculations were carried out with the GIAO-HF method, and energies in water were calculated with the HF-IPCM method ($\varepsilon = 78.5$), with the 6-311 + + G(2d,2p) or 6-31G(d,p) basis sets (Gaussian 94 implementation).[15]

The species dealt with theoretically are representatives of carboxylic amides, thioamides, sulfenamides, sulfinamides, sulfonamides, nitrosamides, nitramides (often called nitrosamines and nitramines), cyanamides, and phosphorous and phosphoric acid triamides. They were chosen to be as similar as possible to the species that can be studied experimentally, while keeping computational demands reasonable. Some simple amines were also considered as models.

Although the efficiency of quadrupolar relaxation is generally expressed by the value of χ, the T_1 in solution is effectively determined by $\chi_{\text{eff}} = \chi^2(1 + \varepsilon^2/3)$ (sometimes called quadrupolar splitting constant), whose dimensions are s^{-2} (or MHz^2). In fact, χ_{eff} is directly linked to T_1 or the linewidth $W_{1/2}$ because $W_{1/2} \propto 1/T_1 \propto \chi^2(1 + \varepsilon^2/3)$ [Eq. (1)]. Hence, if the correlation time is kept constant in the solutions used for measurements on the neutral (B) and protonated (BH^+) base, the equalities $\chi_{\text{eff}}(BH^+)/\chi_{\text{eff}}(B) = W_{1/2}(BH^+)/W_{1/2}(B) = T_1(B)/T_1(BH^+)$ hold. For this reason, throughout this paper we will report calculated efg's as effective nuclear quadrupolar coupling constant (χ_{eff}) and its change $\chi^{\text{R}}_{\text{eff}} = \chi_{\text{eff}}(BH^+)/\chi_{\text{eff}}(B)$. The following values of Q (in fm^2) were used in the calculation of χ_{eff}: ^{14}N, 2.02; ^{17}O, -2.558; ^{33}S, -6.78.[26, 27]

Calculated shieldings (σ) are reported as the isotropic component of the shielding tensor, and its change from neutral to protonated form $\Delta\delta = \sigma(B) - \sigma(BH^+)$, which is comparable to the experimental $\Delta\delta$ value.

Calculation of solvent effects: In the IPCM method, the cavity shape is iteratively computed from the solute electron density.[15, 24] The difference between the energy obtained for the isolated species and for the same species in the continuum medium gives an estimate of its solvation energy. If we consider a base B capable of forming two conjugate acids (A_1 and A_2) by protonation at different sites, our goal is to estimate the energy involved in the proton transfer equilibrium between the two tautomeric ions A_1 and A_2, both in the gas phase and in water. If we denote the latter quantities with $\Delta E_{(g)}$ and $\Delta E_{(aq)}$, respectively, a Born–Haber cycle shows that the latter can be expressed as in Equation (2), where E^s_i is the

$$\Delta E_{(aq)} = \Delta E_{(g)} + (E^s_2 - E^s_1) \quad (2)$$

solvation energy of species i. Indeed, by comparing solvation energies for the two ions one could obtain their energy difference in water, a quantity which should model the expected stability difference in that solvent. But, of course, electron correlation must be taken into account for a meaningful estimation of relative energies, even of the isolated species. To this effect, although one could run an MP2-IPCM calculation, previous experience with Onsager's SCRF method showed that the two effects (electron correlation and solvent effect) are roughly additive.[28] Hence, we calculated the gas-phase energy by MP2 calculations, as seen before, and solvation energies at the Hartree–Fock level. Thus, if we consider $\Delta E_{(aq)}$ an unknown, $\Delta E_{(g)} = E^{\text{MP2}}_2 - E^{\text{MP2}}_1$ is the relative energy in the gas phase, and $E^s_i = E^{\text{IPCM}}_i - E^{\text{HF}}_i$ is the solvation energy of species i, in turn given by the difference in energy in solution (from an IPCM calculation) and in the gas phase (from a Hartree–Fock calculation with the same basis set). Hence Equation (3) holds, and $\Delta E_{(aq)}$ can be determined from a combination of MP2 and HF-IPCM data, the latter being obtained in the same calculation.

$$\Delta E_{(aq)} = (E_2 - E_1)^{\text{MP2}} + (E_2 - E_1)^{\text{IPCM}} - (E_2 - E_1)^{\text{HF}} \quad (3)$$

General considerations on NMR measurements: The nuclei experimentally studied by NMR are ^{14}N ($I = 1$), ^{17}O ($I = 5/2$), and ^{31}P ($I = 1/2$); spectral assignment was made by comparison with reference data.[29] Although ^{33}S ($I = 3/2$) NMR data would be valuable, signals of thiocarbonyl compounds have not yet been detected satisfactorily, and those of thiol-type sulfur are so broad that they have only been obtained in few cases and under unsuitable conditions (e.g., neat liquids).[30] In the course of this work, we detected only the ^{33}S signal of $MeSO_2NH_2$ in aqueous medium (see below).

Although the linewidth is visually appealing, the T_1 is more accurate (if more time-consuming), and is independent of distortions from Lorentzian lineshape due to spurious factors, like the rolling baselines which are often obtained for quadrupolar nuclei.[29] For this reason, whenever possible we

Table 1. Calculated and experimental basicity of amines in the gas phase and in water.[a]

Species	ΔE (HF)[b]	ΔE (IPCM)[c]	ΔE (MP2)[b]	$\Delta E_{(aq)}$[d]	$\Delta\Delta E_{(aq)}$[e]	$\Delta\Delta G_{(g)}$[f]	$\Delta\Delta G_{(aq)}$[f]
NH_3	216.0	297.1	211.5	292.6	0.0	0.0	0.0
$MeNH_2$	228.0	298.8	227.3	298.1	−5.6	−9.8	−1.9
Me_2NH	236.0	298.9	234.0	297.0	−4.4	−17.1	−2.1
Me_3N	241.2	298.5	238.1	295.4	−2.8	−22.0	−0.8
py	235.1	288.5	230.9	284.3	8.2	−17.7	5.5
$PhNH_2$	222.9	284.4	223.7	285.2	7.3	−6.9	6.3

[a] In kcal mol^{-1}; $\Delta E = -[E(\text{ammonium ion}) - E(\text{amine})]$. [b] Data from ref. [11], except $MeNH_2$ and Me_3N (HF or MP2/6-311++G(2d,2p)//6-311G(d,p)). [c] HF-IPCM/6-311++G(2d,2p)//HF/6-311++G(d,p). [d] Calculated basicity in water [see Eq. (3)]. [e] Values of $\Delta E_{(aq)}$ relative to NH_4^+. [f] Experimental gas-phase and aqueous basicities relative to NH_3.[32]

have determined T_1 in addition to $W_{1/2}$. For ^{17}O at natural abundance (0.037%) this is usually infeasible, and consequently only linewidths were measured except where ^{17}O-enriched materials could be used.

Amines as models of *N*-protonated amides: Amines have been considered as model bases for testing the IPCM method and the changes in the efg and shielding at nitrogen. It is well known that the anomalous ordering of the basicity of alkylamines in water ($Me_2NH > MeNH_2 > Me_3N > NH_3$) stems from a competition between the inductive effect of the methyl groups and the solvation of the ammonium ion.[31, 32] Quantum chemical calculations on the isolated species yield a basicity order increasing with alkyl substitution, like in the gas phase; therefore it is of interest to ascertain whether a relatively simple solvation model like IPCM can reproduce the observed basicity ordering.

Protonation or alkylation at nitrogen (whether in an aliphatic or aromatic amine, or pyridine) is known to cause a large decrease of efg, which is reflected in small ^{14}N linewidths for ammonium salts.[29] This is in fact the best known example of the effect of protonation on the efg. Ammonia, the methylamines, pyridine and aniline were chosen as models; for reasons which will be discussed later, pyrrolidine was also included.

Absolute and relative energies, calculated with the above methods in the gas phase and in water, are reported in Table 1 and compared with experimental $\Delta G_{(g)}$ and $\Delta G_{(aq)}$ values. Relevant quantities are compared in Figure 1. In Table 2, the NMR parameters of the ^{14}N nucleus are collected (shielding, efg, and their experimental counterparts δ and T_1) together with their changes between neutral and protonated form ($\Delta\delta = \delta(BH^+) - \delta(B)$ and ($T_1^R = T_1(B)/T_1(BH^+)$). The latter is proportional to the change in χ_{eff} (χ_{eff}^R) if the correlation time is

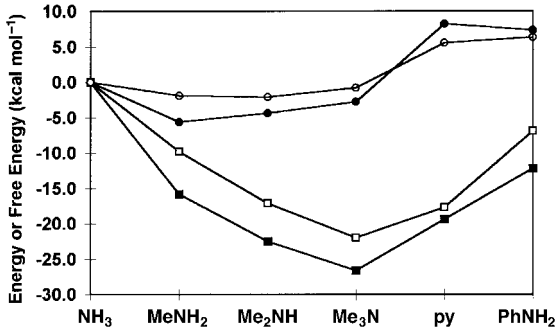

Figure 1. Calculated and experimental basicity of amines (relative to NH_3). Calculated $\Delta E_{(g)}$ (■); calculated $\Delta E_{(aq)}$ (●); experimental $\Delta G_{(g)}$ (□); experimental $\Delta G_{(aq)}$ (○).

constant [see Eq. (1)], but also depends on the solution viscosity,[29] which remains essentially constant in the dilute aqueous acid media required to protonate these strong bases. Hence no special correction is necessary (however, see below).

Table 2. Calculated and experimental NMR properties of ^{14}N in neutral (water) and protonated (aq. HCl) amines.

Species	Calculated				Experimental			
	σ[a]	$\Delta\delta$[b]	χ_{eff}[c]	χ_{eff}^R[d]	δ[e]	$\Delta\delta$[f]	T_1[g]	T_1^R[h]
NH_3	266.1	–	21.9	–	–	–	–	–
NH_4^+	243.6	+22.5	0	–	–	–	–	–
$MeNH_2$	254.3	–	29.0	–	−373	–	0.75	–
$MeNH_3^+$	238.2	+16.1	2×10^{-5}	7×10^{-7}	−360	+13	21.7	0.03
Me_2NH	247.8	–	34.5	–	–	–	–	–
$Me_2NH_2^+$	231.3	+16.5	5.0×10^{-3}	1×10^{-4}	–	–	–	–
Me_3N	249.8	–	–	–	–	–	–	–
Me_3NH^+	225.3	+24.5	–	–	–	–	–	–
pyrNH[i]	234.8[j]	–	27.0	–	−340	–	–	–
$pyrNH_2^+$	237.3[j]	−2.5	0.022	8×10^{-4}	−335	+4	–	–
$PhNH_2$	209.4	–	35.1	–	−326	–	0.48	–
$PhNH_3^+$	216.6	−7.2	1.6×10^{-2}	5×10^{-4}	−332	−6	2.60	0.18
py[k]	−87.0	–	35.5	–	−87	–	0.29	–
pyH^+	69.9	−156.9	1.2	0.03	−180	−93	28.0	0.01

[a] Isotropic component of the chemical shielding tensor [$\sigma = (\sigma_{11} + \sigma_{22} + \sigma_{33})/3$, ppm], calculated at the GIAO-HF/6-311++G(2d,2p)//HF/6-311G(d,p) level, except where noted. [b] $\Delta\delta = \sigma(B) - \sigma(BH^+)$. [c] Effective nuclear quadrupolar coupling constant (MHz^2); data from ref. [12], except for pyrrolidine (this work). [d] $\chi_{eff}^R = \chi_{eff}(BH^+)/\chi_{eff}(B)$. [e] ^{14}N chemical shifts. [f] $\Delta\delta = \delta(BH^+) - \delta(B)$. [g] Longitudinal relaxation time in ms. [h] $T_1^R = T_1(B)/T_1(BH^+)$. [i] Pyrrolidine. [j] GIAO-HF/6-31+G(d,p)//6-31+G(d,p). [k] Pyridine.

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Amides (all types): All amides investigated herein are weak bases, that is, require strong acid media to be converted to the protonated form.[1, 2] Common acid systems, like H_2SO_4 or CF_3SO_3H (trifluoromethanesulfonic acid; hereafter triflic acid), have moderate or large viscosities both as neat liquids ($\eta = 24.2$ and 3.3 mPa s, respectively) and when mixed with water.[26, 33] Hence, in order to compare relaxation data among different media, the viscosity should be known or kept constant. It was previously found that use of aqueous solutions of *t*BuOH makes it possible to vary the viscosity in a suitable range while keeping the environment largely aqueous.[8–10] Thus, for example, the viscosity of triflic acid is compensated for by running the measurements on the neutral species in a 22% w/w aqueous solution of *t*BuOH (see Table 5). This approach was used throughout this work, except for carboxylic amides. In this case the spectra of the neutrals were obtained in water, and dipolar relaxation times of ^{13}C determined, to better assess the effect of the solvent change on the correlation time.

Tables 3 and 4 list the energies calculated in the gas phase or water and NMR properties (shieldings, electric field gradients, and their changes as seen for amines), respectively. Table 5 reports experimental NMR results (chemical shifts, T_1 or $T_2^* = 1/\pi W_{1/2}$, and their changes).

Carboxylic amides and thioamides: MeCONHMe, MeCONMe$_2$, HCSNH$_2$, and MeCSNMe$_2$: These bases are protonated at the acyl group (O or S),[1–3, 34, 35] so they were investigated to provide a bona fide case of amides which are *not N*-protonated. Owing to their importance, two typical carboxamides (MeCONHMe and $MeCONMe_2$) have been investigated in more detail. Although the efg at N and O has already been calculated for $HCONH_2$ and its ionized forms,[12] we repeated this calculation for MeCONHMe, which was studied experimentally. $MeCONMe_2$ and $MeCSNMe_2$ were previously studied by ^{14}N NMR.[8] In this work, the protonated form was obtained in triflic acid to ensure quantitative protonation, and we also chose to employ water as the solvent for obtaining the spectra of the neutral amide, keeping in mind the viscosity ratio between triflic acid and water (3:1). Thus we determined the ^{13}C T_1 and NOE values of the carbonyl carbon of MeCONHMe and $MeCONMe_2$ in water and triflic acid (Table 6), to check whether protonation entails changes in the molecular dynamics that are not accounted for from viscosities.

The values of $T_1^{DD} = T_1(NOE_{max}/NOE)$ decrease by a factor of 3 upon protonation, which is just the ratio of the viscosities of the two solvents. Therefore, triflic acid has no effect on the correlation time other than that due to the larger friction in the liquid, and it is legitimate simply to compensate for its viscosity with appropriate water/*t*BuOH mixtures.

Sulfenamides: NH$_2$SH and PhSNHPh:[36] Calculated energies[11] and efg's,[12] and ^{14}N experimental data,[9] were available.

Sulfinamides: MeSONH$_2$, MeSONHPh, and *N*-pyrrolidinylbenzenesulfinamide: Calculated energies[11] and efg's[12] for $MeSONH_2$, and ^{14}N experimental data for MeSONHPh and PhSONHPh[9] were available. From such results *O*-protonation was indicated as favored, but this conclusion was later challenged by Mikolajczyk et al.[37] on the basis of IR, ^{15}N, and ^{13}C NMR measurements on some aryl ($ArSONR_2$) and *O*-methylated [$ArS(OMe)NR_2^+$] sulfinamides in nonaqueous solvents (e.g. HCl/CH_2Cl_2). As the discrepancy might actually arise from differences in base structure and solvent,[37] in order to provide a consistent basis for comparing the two sets of results, we calculated the same parameters for pyrrolidine,

Table 3. Basicity of amides in the gas phase and in water (HF-IPCM and MP2 calculations).[a]

Species	ΔE (HF)	ΔE (IPCM)	ΔE (MP2)	ΔE (aq)[b]	Protonation site in gas phase/water
MeCONHMe					O
$MeCONH_2Me^+$	18.7	11.3	14.5	7.2	
$MeC(OH)NHMe^+$	0.0	0.0	0.0	0.0	
$HCSNH_2$					S
$HCSNH_3^+$	22.7	15.8	14.4	7.4	
$HC(SH)NH_2^+$	0.0	0.0	0.0	0.0	
NH_2SH					N
NH_3SH^+	−18.4	−23.5	−22.3	−27.4	
$NH_2SH_2^+$	0.0	0.0	0.0	0.0	
$MeSONH_2$					O/N
$MeSONH_3^+$	18.6	5.6	9.6	−3.4	
$MeS(OH)NH_2^+$	0.0	0.0	0.0	0.0	
MeSONHPh					O
$MeSONH_2Ph^+$	17.5	15.2	8.7	6.5	
$MeS(OH)NHPh^+$	0.0	0.0	0.0	0.0	
PhSONpyr					O/N
$PhSONHpyr^+$	7.0	0.7	0.7	−7.2	
$PhS(OH)Npyr^+$	0.0	0.0	0.0	0.0	
$MeSO_2NH_2$					N
$MeSO_2NH_3^+$	5.2	−4.5	−2.8	−12.4	
$MeSO_2(H)NH_2^+$	0.0	0.0	0.0	0.0	
Me_2NNO					O
Me_2NHNO^+	17.9	17.3	10.3	9.7	
Me_2NNOH^+	0.0	0.0	0.0	0.0	
Me_2NNO_2					O/N
$Me_2NHNO_2^+$	6.4	1.9	2.6	−1.9	
$Me_2NNO_2H^+$	0.0	0.0	0.0	0.0	
NH_2CN					CN/NH_2
NH_3CN^+	26.9	2.6	22.4	−1.9	
NH_2CNH^+	0.0	0.0	0.0	0.0	
Me_2NCN[c]					
Me_2NHCN^+	15.1	0.3	−11.7	−26.5	NMe_2
Me_2NCNH^+	0.0	0.0	0.0	0.0	
$P(NH_2)_3$					P
$P(NH_2)_2NH_3^+$	12.2	12.2	3.7	3.7	
$HP(NH_2)_3^+$	0.0	0.0	0.0	0.0	
$PO(NH_2)_3$					O/N
$PO(NH_2)_2NH_3^+$	17.4	2.0	11.0	−4.4	
$P(OH)(NH_2)_3^+$	0.0	0.0	0.0	0.0	
$PO(NMe_2)_3$[d]					O
$PO(NMe_2)_2NHMe_2^+$	10.7	7.2	3.7	0.2	
$P(OH)(NMe_2)_3^+$	0.0	0.0	0.0	0.0	

[a] Data for each entry is reported as 1) neutral; 2) form protonated at the amino nitrogen; 3) form protonated at the acid residue. MP2 energies for $HCSNH_2$, NH_2CN, Me_2NNO, Me_2NNO_2, NH_2SH, $MeSO_2NH_2$, $P(NH_2)_3$, $PO(NH_2)_3$, and related ions from ref. [11]; MeCONHMe, MeSONHPh, PhSONpyr, and Me_2NCN from this work (same level, except where noted). ΔE's are relative to the form protonated at the acid residue. [b] See Equations (2) and 3. [c] MP2 and IPCM/6-311++G(d,p)//HF/6-311++G(d,p). [d] MP2 and IPCM/6-31G(d,p)//6-31G(d,p).

Table 4. Calculated NMR properties of neutral and protonated amides.[a]

Species		σ	$\Delta\delta$	χ_{eff}	χ^R_{eff}	Species		σ	$\Delta\delta$	χ_{eff}	χ^R_{eff}
MeCONHMe	N	171.1	–	24.4	–	Me_2NNO	*N*O	−429.3	–	70.5	–
	O	−49.6	–	105.8	–		NMe_2	42.7	–	26.0	–
$MeCONH_2Me^+$	N	186.3	−15.1	0.04	2×10^{-3}		O	−524.8	–	246	–
	O	−248.3	+198.7	164.1	1.6	Me_2NHNO^+	*N*O	−324.0	−105.3	54.9	0.8
$MeC(OH)NHMe^+$	N	123.0	+48.1	6.0	0.2		NMe_2	100.9	−58.2	0.85	0.03
	O	166.0	−215.7	102.9	1.0		O	−850.2	+325.4	303.5	1.2
$HCSNH_2$	N	136.8	–	14.7	–	Me_2NNOH^+	*N*O	−288.3	−141.0	66.7	0.9
	S	256.5	–	1340	–		NMe_2	−30.3	+73.0	1.69	0.06
$HCSNH_3^+$	N	182.8	−46.0	0.17	0.01		O	29.2	−554.0	185.2	0.8
	S	−642.5	+899.0	2920	2.2	Me_2NNO_2	*N*O_2	−155.4	–	8.9	–
$HC(SH)NH_2^+$	N	107.2	+29.6	4.5	0.3		NMe_2	110.0	–	50.2	–
	S	433.8	−177.3	1470	1.1		O	−148.7	–	240	–
NH_2SH	N	275.3	–	34.7	–	$Me_2NHNO_2^+$	*N*O_2	−103.2	+52.2	5.7	0.6
	S	464.1	–	2890	–		NMe_2	106.6	−3.4	10.0	0.2
$HSNH_3^+$	N	254.2	+21.1	0.65	0.02		O	−219.4	−70.7	225	1.0
	S	201.0	+263.1	5750	2.0	$Me_2NNO_2H^+$	*N*O_2	−112.0	−43.4	4.8	0.5
$NH_2SH_2^+$	N	271.0	+4.3	44.0	1.3		NMe_2	72.4	+37.6	24.0	0.5
	S	461.3	+2.8	1400	0.5		O	−72.3	−76.4	260	1.1
$MeSONH_2$[b]	N	175.8	–	27.0	–	NH_2CN	NH_2	255.8	–	31.6	–
	O	221.1	–	112.1	–		CN	33.4	–	21.1	–
$MeSONH_3^+$	N	186.9	−11.1	0.21	0.01	NH_3CN^+	NH_2	237.4	+18.4	2.7	0.1
	O	95.7	+125.3	101.6	0.9		CN	−34.6	+68.0	32.8	1.6
$MeS(OH)NH_2^+$	N	193.8	−18.0	30.3	1.1	NH_2CNH^+	NH_2	246.6	+9.2	27.5	0.9
	O	232.8	−11.7	154.6	1.4		CN	147.4	−114.0	6.3	0.3
$MeS(OMe)NH_2^+$	N	201.0	−25.2	30.5	1.1	Me_2NCN[d]	NMe_2	251.4	–	41.2	–
	O	250.4	+29.3	176.0	1.6		CN	34.8	–	21.2	–
MeSONHPh[c]	N	163.3	–	28.5	–	Me_2NHCN^+	NMe_2	224.9	+26.5	3.4	0.1
	O	248.4	–	106.3	–		CN	−20.3	+55.1	32.0	1.5
$MeSONH_2Ph^+$	N	172.7	−9.3	0.14	0.005	Me_2NCNH^+	NMe_2	243.1	+8.3	25.0	0.6
	O	163.1	+85.3	104.9	1.0		CN	157.6	−122.8	7.9	0.4
$MeS(OH)NHPh^+$	N	187.0	−23.6	30.9	1.1	$P(NH_2)_3$	N	213.6	–	20.6	–
	O	253.5	−5.1	136.2	1.3		P	280.5	–	–	–
PhSONpyr[c]	N	193.4	–	34.0	–	$P(NH_2)_2NH_3^+$	N	207.3	+6.3	16.0	0.8
	O	300.8	–	107.5	–		P	215.4	+65.1	–	–
$PhSONHpyr^+$	N	175.6	+17.8	0.036	0.001	$HP(NH_2)_3^+$	N	228.3	−14.7	21.1	1.0
	O	249.8	+50.9	103.4	1.0		P	346.1	−65.6	–	–
$PhS(OH)Npyr^+$	N	195.8	−2.4	30.8	0.9	$PO(NH_2)_3$	N	217.7	–	24.3	–
	O	274.3	+26.5	135.3	1.3		P	348.4	–	–	–
$PhS(OMe)Npyr^+$	N	199.7	−6.2	31.8	0.9		O	231.5	–	107.5	–
	O	292.5	+8.3	153.1	1.4	$PO(NH_2)_2NH_3^+$	N	215.3	+2.4	14.9	0.6
$MeSO_2NH_2$	N	173.8	–	29.3	–		P	342.6	+5.8	–	–
	O	146.3	–	76.4	–		O	197.2	+34.2	19.4	0.2
	S	210.7	–	161	–	$P(OH)(NH_2)_3^+$	N	223.9	−6.2	21.7	0.9
$MeSO_2NH_3^+$	N	174.4	−0.6	0.055	0.002		P	333.1	+15.3	–	–
	O	92.5	+53.8	65.2	0.8		O	261.2	−29.7	100.8	0.9
	S	166.4	+44.3	1040	6.5	$P(OH)(NH_2)_2(NH_3)^{2+}$[e]	N	218.7	−1.0	14.3	0.6
$MeSO_2(H)NH_2^+$	N	184.5	−10.7	35.0	1.2		P	331.6	+16.8	–	–
	O	181.7	−35.4	115	1.5		O	256.3	−24.8	121.8	1.1
	S	189.1	+21.6	376	2.3						

[a] See footnotes to Table 2. Values of χ_{eff} recalculated from ref. [12], except MeSONHPh, PhSONpyr, Me_2NCN (including ions), and $P(OH)(NH_2)_2(NH_3)^{2+}$ (this work). [b] HF/6-311++G(2d,2p)//HF/6-31+G(d,p). [c] HF/6-31+G(d,p)//6-31+G(d,p). [d] efg for neutral and ions also calculated at the HF/6-311++G(2d,2p) level. [e] Relative values with respect to neutral form.

N-pyrrolidinylbenzenesulfinamide (PhSONpyr), and its protonated and *O*-methylated forms, as well as IPCM energies and chemical shieldings also for the other sulfinamides. Calculated ^{13}C shieldings for pyrrolidine, PhSONpyr, and their protonated forms are given in Table 7.

In order to cross-check ^{14}N results, we also recorded ^{17}O spectra of $MeSONH_2$ and MeSONHPh. The latter is stable in CH_2Cl_2 saturated with HCl gas (0.3–0.4 M) and in concd. aq. HCl. However, water solubility is too low for ^{17}O NMR, and the spectrum of the neutral was obtained in H_2O/MeCN. $MeSONH_2$ is also stable in HCl/CH_2Cl_2, where the ^1H methyl signal is deshielded by 0.04 ppm. The ^1H spectrum in concd. aq. HCl shows an intense NH_4^+ peak clearly indicating hydrolysis. The ^{17}O spectrum shows a signal ($\delta = 133$) whose assignment is uncertain, as the probable products also fall in a similar region (e.g. MeSOOMe, $\delta = 142$).[38]

Sulfonamides: $MeSO_2NH_2$: Calculated energies and efg's were available.[11, 12] $MeSO_2NH_2$ was reported to be protonated only in superacids;[39] accordingly, we obtained the protonated form in triflic acid. Although ^{14}N, ^{17}O, and ^{33}S spectra might be obtained, we could only detect the ^{33}S signal

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Table 5. Experimental NMR properties of neutral and protonated amides.[a]

Base/Solvent	atom	δ[b]	$\Delta\delta$[c]	T_1[d]	T_1^R[e]
MeCONHMe					
H_2O	N	−269	–	1.44	–
	O	260	–	2.21	–
CF_3SO_3H	N	−245	+24	0.76	1.9[f]
	O	15	−245	1.18	1.9[f]
$MeCONMe_2$					
H_2O	N	−270	–	0.92	–
	O	260	–	2.11	–
CF_3SO_3H	N	−242	+28	0.66	1.4[f]
	O	15	−245	1.13	1.9[f]
$MeCSNMe_2$[g]					
31% *t*BuOH	N	−226	–	0.88	–
54% H_2SO_4	N	−167	+59	1.13	0.8
PhSNHPh[h]					
MeOH	N	−331	–	0.18	–
MeOH/HCl	N	−333	−2	1.17	0.2
$MeSONH_2$					
CH_2Cl_2	O	114	–	–	–
HCl/CH_2Cl_2	O	114	0	–	–
$MeSONiPr_2$[h]					
MeOH	N	−311	–	2.95	–
concd. HCl	N	−307	+4	3.56	0.8
MeSONHPh[h]					
1) MeOH	N	−334	–	1.16	–
2) 1:1 concd. HCl/MeOH	N	−329	−5	0.77	1.5
1) 2:1 $H_2{}^{16}O/CH_3CN$	O	150	–	–	–
2) concd. aq. HCl	O	134	−16	–	–
1) 22% *t*BuOH	N	−333	–	1.16	–
2) CF_3SO_3H	N	−335	−2	0.74	1.6
1) CH_2Cl_2	O	102	–	–	–
2) HCl/CH_2Cl_2	O	101	−1	–	–
PhSONHPh					
MeOH	N	−327	–	0.67	–
1:1 concd. HCl/MeOH	N	−327	0	0.51	1.3
$MeSO_2NH_2$					
22% *t*BuOH	N	−290		0.55	–
CF_3SO_3H	N	−284	+6	1.07	0.5
Et_2NNO					
22% *t*BuOH	*N*O	152	–	0.29	–
	NEt_2	−118	–	0.99	–
	N*O*	618	–	0.5*	–
CF_3SO_3H	*N*O	94	−58	0.1*	2.9
	NEt_2	−91	+27	1.08	0.9
	N*O*	307	−311	0.3*	1.7
Me_2NNO_2					
22% *t*BuOH	*N*O_2	−27	–	170	–
	NMe_2	−214	–	0.34	–
CF_3SO_3H	*N*O_2	−59	−32	1.7*	100
	NMe_2	−282	−68	0.82	0.4
Me_2NCN					
1) 22% *t*BuOH	CN	−196	–	0.99	–
	NMe_2	−372	–	0.54	–
2) CF_3SO_3H[i]	CN	−72	+123		
1) H_2O	CN	−199	–		
	NMe_2	−369	–	0.8*	–
2) 23% H_2SO_4[f, j]	CN	−199	0	1.6*	1.4
	NMe_2	−369	0	0.7*	1.1
$P(NMe_2)_3$					
MeOH	N	−370	–	0.57	–
	P	142.1	–	6.0, $\eta = 0.0$	–
MeOH/HCl	N	−362	+7.7	0.55	1.0
	P	15.0[k]	−127.1	4.7, $\eta = 1.2$	–
$PO(NMe_2)_3$					
1) 49% *t*BuOH	N	−357	–	0.32	–
	O	79	–	0.58	–
	P	28.9	–	–	–
2) 72% H_2SO_4[l]	O	82	+3	0.32	1.8
	P	27.5	−1.4	–	–
1) 22% *t*BuOH	N	−361	–	0.22	–
2) CF_3SO_3H	N	−357	+4	0.14*	1.6
1) 24% *t*BuOH	N	−361	–	0.29	–
2) 64% $HClO_4$	N	−344	+17	0.15	1.9
1) H_2O	O	87	–	1.31	–
2) 70% $HClO_4$	O	82	−5	1.75	0.7[f]

[a] Data from this work, except where noted. When more than one neutral/acid system was studied, relative values are reported with respect to entry 1. [b] Chemical shifts δ relative to the appropriate reference (see Experimental Section). [c] $\Delta\delta = \delta(BH^+) - \delta(B)$. [d] T_1's in ms, except for ^{31}P (in s). Entries marked with an asterisk report $T_2^* = 1/\pi W_{1/2}$ rather than T_1. [e] $T_1^R = T_1(B)/T_1(BH^+)$. [f] Does not include correction for higher viscosity (see text). [g] ^{14}N data from ref. [8]. [h] ^{14}N data from ref. [9]. [i] Vigorous reaction; spectrum not reproducible and assignment uncertain. [j] An additional unassigned peak at $\delta = -305$, growing with time. [k] Doublet, $J_{PH} = 600$ Hz. [l] ^{14}N signal is not detectable.

Table 6. ^{13}C chemical shifts, T_1's, and NOE's of the carbonyl carbon in neutral and protonated MeCONHMe and $MeCONMe_2$.[a]

Base/Solvent	δ	T_1	NOE	T_1^{DD}
MeCONHMe				
water	177.6	38.0	1.15	66.7
CF_3SO_3H	177.2	13.0	1.17	22.2
$MeCONMe_2$				
water	174.3	53.4	1.09	98.0
CF_3SO_3H	174.3	16.7	1.08	30.9

[a] Chemical shifts δ with respect to TMS; T_1's and T_1^{DD}'s in s.

Table 7. Calculated ^{13}C shieldings.[a]

Species	σ (C-α)	$\Delta\delta$ (C-α)	σ (C-β)	$\Delta\delta$ (C-β)
pyrNH	159.0	–	179.0	–
$pyrNH_2^+$	155.9	+3.1	179.5	−0.5
PhSONpyr	162.8	–	178.6	–
$PhSONHpyr^+$	157.3	+5.5	179.6	−1.0
$PhS(OH)Npyr^+$	157.5	+5.3	179.2	−0.7
$PhS(OMe)Npyr^+$	157.3	+5.5	179.1	−0.6

[a] HF/6-31 + G(d,p)//6-31 + G(d,p). Each entry is the average of values for nonequivalent carbons.

of the neutral ($\delta = -13$; cf. −9 for $MeSO_2NMe_2$[40]), but ^{33}S and ^{17}O spectra cannot be obtained in triflic acid, owing to strong interference from the solvent.

Nitrosamides: Me_2NNO and Et_2NNO: The parent compound NH_2NO has been much studied theoretically, and it is now well known that the amino-protonated form (NH_3NO^+) is essentially dissociated into $H_3N\cdots NO^+$ (see[11] and references therein). This behavior led us to the conclusion that this is too simple a model to allow for a meaningful comparison with stable, *N*-alkyl nitrosamides, and we took Me_2NNO as our model.[11, 12] Previous calculations[11] were in favor of *O*-protonation, and showed that *N*O-protonation is very unfavorable and need not be further considered. ^{14}N and ^{17}O NMR

experiments were run on the less volatile Et_2NNO. In both neutral and acidic medium the ethyl groups are not equivalent, which was suggested as evidence for *O*-protonation,[41] but kinetic data have been interpreted as indicative of significant *N*-protonation.[41, 42] The *N*O signal in triflic acid could only be detected with a 600 MHz instrument, owing to its huge width ($W_{1/2} = 2.4$ kHz).

Nitramides: Me_2NNO_2:[11, 43, 44] ^{14}N Experiments were complicated by the fast decomposition in triflic acid, which prevented us from obtaining a T_1 for the slowly relaxing (sharp) NO_2 signal; we did not attempt any ^{17}O measurement.

Cyanamides: NH_2CN and Me_2NCN:[11, 45–48] Early ^{14}N measurements on NH_2CN were interpreted as C*N*-protonation;[47] the opposite conclusion (amino *N*-protonation) was reached from potentiometric measurements, which also afforded a pK value of ca. 1.[48] Very recently Kallies and Mitzner[19] challenged this value, and suggested C*N*-protonation both in gas phase and in water. Accordingly, we ran ^{14}N measurements both in triflic acid and in 23 % H_2SO_4 (sufficient for protonating a base with p$K = 1$). We could not obtain satisfactory ^{14}N spectra of either cyanamide in triflic acid, since its addition (even at low temperature) caused a vigorous reaction, particularly with NH_2CN. The ^{1}H spectrum showed the formation of NH_4^+ or $Me_2NH_2^+$, and the ^{14}N spectrum was not reproducible and its assignment uncertain. Me_2NCN dissolved in 23 % H_2SO_4 with no apparent reaction, but the ^{14}N spectrum showed both signals at the same frequency as in water, and a new peak ($\delta = -305$) increasing over 10–20 minutes, and eventually becoming the only remaining signal.

Phosphorous acid triamides: $P(NH_2)_3$ and $P(NMe_2)_3$:[49, 50] Comparing experimental and theoretical results is somewhat complicated by the nitrogen atoms, which lie in different environments in the rigid calculated structure but become equivalent if free rotation is allowed. *N*-Protonation leads (as usual) to a large efg decrease at the quaternized nitrogen; when this is averaged with the others (unaffected), a χ_{eff}^R of 0.8 results. If the values are averaged there is no χ_{eff} change at nitrogen upon *P*-protonation. The experimental study was carried out on $P(NMe_2)_3$ in MeOH and at pH 1 (apparent value in water/MeOH). In the acid solution the ^{31}P signal appears as a doublet, $J = 600$ Hz (a typical value for $^1J_{PH}$).[51]

Phosphoric acid triamides: $PO(NH_2)_3$ and $PO(NMe_2)_3$: This computational study too is complicated by the presence of three equivalent nitrogens. NMR measurements were carried out for $PO(NMe_2)_3$ (HMPA). A major experimental complication results from the possibility of having substantial amounts of diprotonated form in strongly acidic media.[52] In fact, the protonation parameters of the first equilibrium ($m^* = 0.46$, p$K = -0.97$) are such that the first protonation is complete in 72 % H_2SO_4 ($\eta = 12$ mPa s). The second equilibrium ($m^* = 0.5$, p$K = -5.5$)[52] is essentially complete in 100 % H_2SO_4. However, in 72 % H_2SO_4 hydrolysis of HMPA takes place, and the sharp ^{14}N signal of $Me_2NH_2^+$ thus formed renders the much broader one of HMPA undetectable because of their close chemical shifts. Moreover, we could not obtain a satisfactory ^{17}O spectrum at natural abundance, because in 49 % *t*BuOH the HMPA signal ($\delta \approx 80$)[53] is partly superimposed on that of *t*BuOH, whereas the viscosity of 72 % H_2SO_4 is too high, and only the broad sulfonyl signal could be detected. Alternatively, we used 65 % or 70 % $HClO_4$ ($H_0 = -6.39$ and -7.75[54], $\eta = 3.3$ and 4.4 mPa s, respectively[55]) and CF_3SO_3H ($H_0 = -14.1$[56]). Diprotonation should take place in the latter, but only to a small extent in $HClO_4$. In 65 % $HClO_4$, the ^{14}N signal is again superimposed to the sharp $Me_2NH_2^+$ signal, and the spectrum was processed by a Gaussian deconvolution. Given these complications, we synthesized (by oxidation of HMPT with ^{17}O-enriched H_2O_2) and made ^{17}O measurements on ^{17}O-enriched HMPA. The spectrum in 49 % *t*BuOH showed peaks at $\delta = 79$, 119 and 417; these were assigned to HMPA, residual H_2O_2, and (tentatively) an unidentified amine *N*-oxide, respectively. The latter two peaks in fact disappear in the acid solution.

Discussion

General considerations: A first evaluation of the general reliability of calculated shieldings is provided by their comparison with experimental δ values. Figure 2 reports

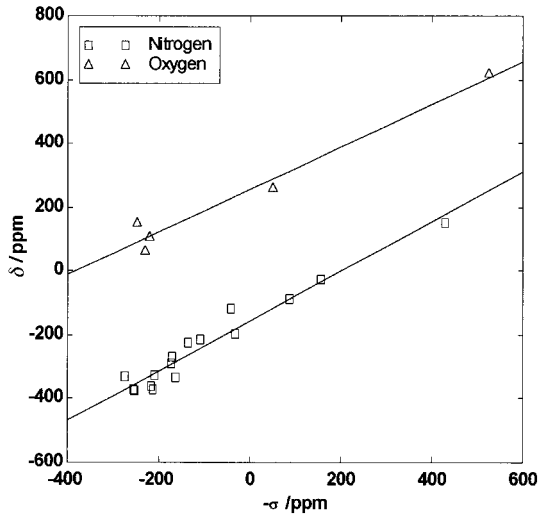

Figure 2. Comparison of experimental (δ) and calculated chemical shifts ($-\sigma$) for nitrogen and oxygen. Line fitting to the data yields slope = 0.80, intercept = −156.4 (N); slope = 0.67, intercept = 256.3 (O).

experimental δ values vs. $-\sigma$ for N and O in neutral species (see also ref. [30]). A well-defined linear relationship is found, although nitrogen shifts are crowded in the amine–amide region ($\delta \approx -300$) and some scatter is evident. However, considering the substantial solvent difference, and the large solvent dependence of such shifts, the accuracy of calculated protonation shifts is probably enough. The comparison of proton affinities has been presented elsewhere.[11]

Even a quick perusal of Tables 2, 4 and 5 shows immediately that large shielding and efg changes often take place at all heteronuclei upon protonation. Interpretation of such changes at a molecular level (MO energies, symmetry, charge

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density),[29, 57] is outside the scope of this work, which is rather aimed at establishing the accuracy of calculated properties, and especially their changes upon protonation, in predicting the site of protonation of amide bases. Therefore we will just accept the values as guidelines for this purpose. We also remark that some nuclear sites become nonequivalent upon protonation (e.g. nitro oxygens in $Me_2NN(O)(OH)^+$), and have different NMR parameters. We present these data as averages for consistency with data in solution, where fast proton exchange occurs.

We should firstly address the issue whether changes in chemical shift provide a reliable guideline for predicting protonation sites. We will only discuss N and O data, as those for S and P are too limited; patterns of efg's have been presented elsewhere.[12] Protonation at the amide nitrogen may shield or deshield N itself. The change is < 50 ppm and generally ca. 10 ppm; the change is smallest for $MeSO_2NH_2$. Hence, although the expected changes are well outside experimental error, they fall in a range where solvent effects may substantially alter the picture. There is no relationship between the type of *N*-substitution (alkyl or aryl) and the sign of $\Delta\delta$ as compared to amines. The $\Delta\delta$ for protonation at the acid residue may have the same or the opposite sign.

$\Delta\delta$ values for oxygen often exceed 100 ppm; for nitrosamides the change is much larger (300–500 ppm). *O*-Protonation shields the oxygen itself (except in the case of PhSONpyr), but most variations are expected for *N*-protonation; these changes often (but not always) have an opposite sign.

These remarks should suffice to point out that no general pattern can be drawn from the behavior of N and O chemical shifts, and that parallelism between amides and amines is not well defined. Hence, although shielding changes are generally large and informative (as will be detailed below), they do not by themselves answer the question sought, as theoretical data for species belonging to the same functional group are necessary.

Amines: The comparison of experimental and calculated gas-phase basicities Table 1, Figure 1) qualitatively reproduces structural effects on the basicity of amines of different types. Considering that no attempt at reaching thermochemical accuracy[58] was made (i.e., no vibrational and thermal contributions were calculated, so that we are in fact comparing calculated ΔE's with experimental ΔG's), this result highlights the good predictive power of such calculations, although (not surprisingly) the two data sets yield different numerical values. Similar considerations apply to solution basicities, as detailed below.

With regard to the basicity order in water, an important point is related to the performance of IPCM calculations. Silla et al.[18] successfully reproduced the irregular basicity order of methylamines in water by means of a polarizable continuum method, and so did Kawata et al.[25] with a RISM-SCF method. The importance of electron correlation in estimating the inductive effect exerted by methyl groups was emphasized.[18]

The IPCM method affords the following basicity order in water: pyridine $< PhNH_2 < NH_3 < Me_3N < Me_2NH < MeNH_2$. The general features of amine basicity are reproduced: thus, the large gas-phase basicity of aniline and pyridine, which is due mainly to the polarizability of the hydrocarbon backbone,[31] is correctly brought down to size (albeit reversed in order). Likewise, Me_3N is correctly predicted to be the weakest among methylamines, together with ammonia. However, $MeNH_2$ is incorrectly predicted to be stronger than Me_2NH, whereas experimental values are opposite and differ very little. It seems therefore that the IPCM method as applied herein overestimates the stabilizing effect of hydrogen bonding, presumably through the solvent polarization exerted by the positively charged N^+-H hydrogens (see also the larger basicity of $PhNH_2$ than pyridine). Hence, although the approach is only partly successful, it correctly predicts the major features of the effect of solvation on nitrogen bases. However, caution is called for when comparing bases with very different degrees of alkylation but similar base strength.

Calculated and experimental NMR properties generally agree well. The magnitude of the protonation shift at nitrogen[59] is reproduced by the GIAO-HF method to within 1–3 ppm for $MeNH_2$ and $PhNH_2$, and not very well for pyridine (a difference of 64 ppm), but the characteristic inversion in sign[59] (deshielding for aliphatic amines and shielding for anilines and pyridine) is clearly borne out. Pyrrolidine too has a negative calculated $\Delta\delta$ (-2.5 ppm), which compares favorably with the experimental value of $+4$, much smaller than for acyclic amines.[59]

The electric field gradient at nitrogen is not much affected by alkylation, but there is a definite trend towards its increase with substitution,[12] matching experimental ^{14}N T_1's (although the longer correlation time undoubtedly plays a role). The effect of protonation on the efg and associated T_1 is very large.[8, 9, 12, 29] Calculated χ_{eff}'s decrease by 4–7 orders of magnitude; the corresponding T_1^R values decrease only by factor of 10–100, which is due to the intervention of other effects (notably intermolecular efg's) in causing quadrupolar relaxation.

In any event, nitrogen protonation is clearly revealed by the large and predictable change of efg or T_1, whereas the change in chemical shift (except for pyridine) is rather small, and lies in a range where spurious factors (like solvent effects) may contribute to the observed quantity. Shielding calculations including solvent effect have appeared (see e.g. ref. [60]), but the scope and accuracy of such calculations for our purpose is presently unknown.

Carboxylic amides and thioamides: *O*-Protonation is favored over *N*-protonation both in the gas phase (by ca. 10 kcal mol^{-1}) and in water. Our IPCM calculation reduces the preference to 7 kcal mol^{-1}. Nitrogen is slightly shielded ($\Delta\delta = -15$) by *N*-protonation, whereas *O*-protonation causes a larger and opposite shift ($\Delta\delta = +50$). Shielding changes at oxygen are very large and opposite. Thus, *N*-protonation causes a 200-ppm *deshielding*, whereas O-protonation entails a 200-ppm *shielding*. Hence, ^{17}O chemical shifts should be a sensitive probe of the site of protonation. Protonation at either site causes only small efg changes at ^{17}O; however, the largest change (χ_{eff} increasing by 50 %) is actually found for *N*-

rather than *O*-protonation. *N*-Protonation causes, as usual, a large ^{14}N efg decrease; however, it also decreases, albeit by a much smaller amount, upon protonation at oxygen.

Experimentally, MeCONHMe and $MeCONMe_2$ show the same behavior. The variations in the chemical shift are very similar, that is, $\Delta\delta = 24-28$ ppm (^{14}N), and $\Delta\delta = -245$ ppm (^{17}O). These values fully agree with the above calculations and clearly indicate *O*-protonation. Experimental T_1^R values of Table 5 must be divided by 3 to account for the higher viscosity of triflic acid, which yields $T_1^R = 0.5-0.6$ for both N and O. Hence, failure to observe any large ^{14}N T_1 increase is also clearly indicative of *O*-protonation.

The energetics of protonation of $HCSNH_2$ favor *S*- over *N*-protonation by 14 kcal mol^{-1}. Again, IPCM data reduce this figure by a half, which is probably due to an overemphasis of the solvation of $HCSNH_3^+$ as seen before. Trends in chemical shielding are similar to those found for amides: thus, the nitrogen nucleus is shielded (-46 ppm) in $HCSNH_3^+$ and deshielded ($+30$ ppm) in $HC(SH)NH_2^+$. The sulfur nucleus is deshielded by no less than 900 ppm if *N*-protonation takes place, whereas a 177-ppm shielding is expected for *S*-protonation. Hence, the protonation site could be very easily decided upon if ^{33}S chemical shifts were available. Again, the efg at N decreases very much upon *N*-protonation. The efg at S is affected by *N*- rather than *S*-protonation.

Experimentally, the ^{14}N signal is deshielded by 59 ppm and, again, there is no substantial change of T_1; both observations confirm *S*-protonation.

Sulfenamides: Although sulfenamides ($RSNR_2$) are formally the amides of sulfenic acids, they may also be viewed as thio-substituted amines. In a previous study,[9] we indicated *N*-protonation of PhSNHPh from the energetics and the large increase in the ^{14}N T_1, which is reproduced theoretically (*S*-protonation would induce an increase in χ_{eff} at N). In other words, the efg at the nitrogen of NH_2SH behaves like that of a typical amine. IPCM data correctly highlight the weak hydration of sulfonium ions,[2, 31, 32, 34, 35] and indicate an even larger preference (27 vs. 22 kcal mol^{-1}) for *N*-protonation in water. Trends in nuclear shielding are peculiar, in that protonation at either site causes a moderate ($\Delta\delta = 4-20$ ppm) deshielding of nitrogen, whereas the sulfur is deshielded by 260 ppm only if *N*-protonation takes place. This would be a very useful complement to efg changes, but ^{33}S signals for sulfenamides are likely to be excessively broad even for the neutral species, and much more so for $HSNH_3^+$. Nitrogen shifts are not a suitable probe of the protonation site (experimental ^{14}N chemical shifts remain constant).

Sulfinamides: Although they possess three protonation sites (O, S, N), previous calculations[9, 11] showed that *S*-protonation is quite unfavorable energetically, and will not be further considered. Contrasting results were reported concerning their site of protonation. ^{14}N Spectra of $MeSONiPr_2$, MeSONHPh, and PhSONHPh showed no change in T_1 upon going from neutral to protonated form, with $\Delta\delta = 2-3$.[9] Calculations indicated $MeS(OH)NH_2^+$ to be more stable than $MeSONH_3^+$ by 11 kcal mol^{-1}.[9, 11] On the other hand, Mikolajczyk et al.[37] obtained ^{15}N and ^{13}C spectra of aryl sulfinamides ($ArSONR_2$) in nonpolar solvents (CH_2Cl_2, $MeNO_2$), and compared such protonation shifts with those of parent amines and of *O*-methylated derivatives [methoxyaminosulfonium salts, $ArS(OMe)NR_2^+$] assumed to model $ArSONHR_2^+$ and $ArS(OH)NR_2^+$. However, the assumption that the difference in chemical shift between amine and ammonium ion, or sulfinamide and methoxyaminosulfonium ion, exactly model the sought quantities must be tested. The theoretical estimation of the energetics of proton transfer in water, and of the shielding changes for all species, offers an independent source of information.

The preferred protonation site in the gas phase is oxygen for $MeSONH_2$ and MeSONHPh, with ΔE (MP2) $= 9-10$ kcal mol^{-1}, but for PhSONpyr the energy gap is very small (0.7 kcal mol^{-1}). Solvent water shifts the protonation site to nitrogen for $MeSONH_2$ and PhSONpyr, but not for MeSONHPh; in any event ΔE remains rather small, at $3-7$ kcal mol^{-1}. Thus, the base strengths of N and O in sulfinamides are rather similar and solvent-sensitive. A first generalization that can be drawn from these limited data is that *S*-aryl and *S*-alkyl sulfinamides are nitrogen and oxygen bases, respectively (albeit with a blurred preference). The apparent exception of $MeSONH_2$ can be again traced to the overemphasis of the IPCM method in modeling the hydration of non-alkylated ammonium ions.

Nitrogen shielding is not diagnostic, because a change with the same sign and similar magnitude ($\Delta\delta = -10$ to -24) is predicted to take place upon protonation at either site (for $MeSONH_2$ and MeSONHPh); the sign of $\Delta\delta$ is also opposite to that of simple amines. For PhSONpyr, $\Delta\delta$ for *N*- and *O*-protonation or methylation have opposite signs, and that predicted for *N*-protonation is deshielding ($\Delta\delta = 18$). Hence, there is no general trend whereby experimental nitrogen shifts can be used to infer the protonation site, which calls for great caution when assuming similarity of behavior with amines.

On the contrary, ^{17}O chemical shifts are quite sensitive to protonation, albeit in a peculiar way. A substantial deshielding ($\Delta\delta = 50-120$) is predicted if protonation takes place at nitrogen, whereas a smaller and erratic change ($\Delta\delta = -12$ to $+26$) is predicted for *O*-protonation. The chemical shift change induced by *O*-methylation is similar to that induced by protonation in the case of PhSONpyr, but opposite for $MeSONH_2$, which suggests that methoxysulfonium salts are poor models of *O*-protonated species, at least with regard to ^{17}O chemical shifts.

The picture provided by χ_{eff}'s is quite simple. The efg at O is not much affected by protonation, with χ_{eff}^R between 0.9 and 1.6 (it is difficult to relate such small changes to experimental data). Conversely, χ_{eff} at N undergoes the typical large decrease (100-fold) upon *N*-protonation, but remains almost constant otherwise. Hence, ^{14}N T_1's should be a powerful tool for this problem.

Another tool employed[37] was the analysis of ^{13}C shifts. It was found that, upon protonation, the chemical shift of the pyrrolidine C-α in PhSONpyr follows the same trend as pyrrolidine, and opposite to that of $PhS(OMe)Npyr^+$. However, the magnitude of such shifts is small ($\Delta\delta < 4.5$ ppm). Table 7 shows that *N*- or *O*-protonation or *O*-methylation of PhSONpyr causes a 5-ppm deshielding of C-α, and a 1-ppm

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shielding of C-β. Protonation of pyrrolidine (obviously at nitrogen) also results in changes similar in sign and magnitude (+3 ppm at C-α and −0.5 ppm at C-β). Hence, no confidence can be given to this test because the expected shifts are small, and spurious effects (like different solvents and counterions[37]) may take over.

Available ^{14}N results[9] for MeSON*i*Pr$_2$, MeSONHPh, and PhSONHPh in aqueous medium agree with *O*-protonation; the constancy of T_1 values is especially indicative. In CH_2Cl_2, ^{17}O chemical shifts remain constant. This could imply that protonation is either not occurring, or is occurring at oxygen. However, the ^{1}H protonation shift of $MeSONH_2$ in CH_2Cl_2/HCl is only 0.04 ppm (typical values are 0.5–1 ppm).[52, 61] Although the absolute figure is not diagnostic in itself, it indicates that the extent of protonation in CH_2Cl_2/HCl is probably low. However, the observed shift of the S=O band to higher wave numbers in the IR spectra of *N*,*N*-diethyl *p*-toluenesulfinamide in CH_2Cl_2/HCl[37] is indeed consistent with a shortening of the S–O bond, and hence with *N*-protonation.

Hence, calculations show that sulfinamides have a small preference for either site of protonation, which may switch from O to N in response to slight structural or solvent changes. Although a comparison of experimental and calculated chemical shifts shows that NMR evidence assumed to indicate *N*-protonation is circumstantial, the different conclusions can be ascribed to the very similar basicity of both sites, as discussed above.

Sulfonamides: These bases may undergo *O*- or *N*-protonation; the latter process was found to be slightly more favored (by 2.8 kcal mol^{-1}). IPCM results enhance this difference to 12.4 kcal mol^{-1}. Hence, $MeSO_2NH_2$ should be a nitrogen base also in water, but the extent of preference might be overestimated, as seen before.

N-Protonation leaves nitrogen shielding essentially constant, while O is deshielded by $\delta\Delta = 50$ ppm; *O*-protonation shields both N and O, while S is shielded in both cases. efg calculations indicate a substantial increase of χ_{eff}(S) in both protonated forms, which would severely hinder the detection of the ^{33}S signal even without practical difficulties. *N*-Protonation entails the usual large decrease ($\chi^R_{eff} = 0.002$); *O*-protonation would cause a much smaller and opposite effect.

Experimentally, the ^{14}N signal is deshielded by 6 ppm upon protonation, and its T_1 is doubled. The small $\Delta\delta$ is probably the result of a solvent effect; the T_1 increase indicates that $MeSO_2NH_3^+$ is formed, although the increase is much smaller than expected. Thus, *N*-protonation is borne out[39] but the data may be compatible with some intervention of *O*-protonation. Kricheldorf[62] interpreted $\Delta\delta(^{15}N) = -4.6$ as *N*-protonation, but the acid used (CF_3COOH, $H_0 = -2.7$[63]) is far too weak to protonate $MeSO_2NH_2$ ($H_0 < -9$ is required).[39]

Nitrosamides: The most basic site of Me_2NNO is predicted to be the oxygen atom in both gas and aqueous phases, by ca. 10 kcal mol^{-1}. Theory also predicts large shielding changes upon protonation, especially at O. The efg at *N*Me$_2$ decreases to a similar extent in both protonated forms, and remains essentially constant for the nitroso N and O. Hence, T_1 arguments are not helpful.

Experimentally, the ^{17}O N*O* signal is shielded ($\Delta\delta = -311$ ppm), and the ^{14}N NEt_2 signal is deshielded ($\Delta\delta = +27$ ppm) upon protonation. The sign of these changes reasonably matches the predicted ones for Me_2NNOH^+ ($\Delta\delta = -554$ and +73 ppm, respectively), and is opposite to the corresponding ones for Me_2NHNO^+ ($\Delta\delta = +325$ and −58 ppm). The change at *N*O is not informative. In summary, *O*-protonation is strongly suggested.

Nitramides: The basic sites of this amide type (oxygen and amino nitrogen) are very similar in strength in gas phase and water. The only potentially useful shielding change is that of *N*O$_2$, as opposite shifts are expected for *N*- and *O*-protonation (the others change little or in the same way). *N*-Protonation entails a relatively small χ_{eff} decrease (only a factor of 5), not distant from the change caused by *O*-protonation; other efg's change even less, so in this case spectroscopic parameters do not distinguish the two forms well. The situation is complicated by the instability of Me_2NNO_2 in triflic acid; thus, no ^{17}O data, nor a ^{14}N T_1 for the *N*O$_2$ signal, could be obtained. The observed $\Delta\delta$ for *N*O$_2$ (−32 ppm) agrees best with *O*-protonation, but in that case one would expect $\Delta\delta > 0$ for *N*Me$_2$, whereas $\Delta\delta = -68$ ppm. Although we cannot rule out the possibility that decomposition products are interfering, the data seem consistent with protonation occurring at both sites to a comparable extent. A more detailed analysis is prevented by experimental problems.

Cyanamides: Two such bases (NH_2CN and Me_2NCN) have been investigated (Table 3), and present substantial differences. While NH_2CN is protonated at C*N* in the gas phase (ΔE(MP2) = 22.4 kcal mol^{-1}),[19] the energy balance for Me_2NCN is overturned, and Me_2NHCN^+ is favored by 11.7 kcal mol^{-1}. This behavior is unique among the bases studied herein. IPCM calculations equalize the relative basicity of the two sites in NH_2CN, C*N*-protonation being now favored by just 1.9 kcal mol^{-1}. Conversely, Me_2NHCN^+ is also the more stable ion in water (by 26.5 kcal mol^{-1}). NMR spectral changes are rather similar for both species; amino-protonation causes a deshielding of both nitrogens and the typical efg decrease at the amino N, while it increases at C*N*. C*N*-protonation entails a small shielding at NR_2 and a large deshielding at C*N* ($\Delta\delta$ = ca. −120 ppm); efg changes are less marked. Kallies and Mitzner[19] ran accurate MP2 and SCI-PCM calculations on NH_2CN, and reached the conclusion that C*N*-protonation is favored also in water, with a larger energy difference than ours. It is presently unclear whether this difference stems from the different theoretical model. These authors also suggested that the quoted p*K* value for cyanamide (1.2) is grossly incorrect. Although the base strength of the two amides may differ, in 23 % H_2SO_4 the ^{14}N spectral data of Me_2NCN are the same as in water, which indicates a very small protonation extent. Hence we confirm that the quoted p*K* is probably incorrect. Given the different calculated protonation sites of NH_2CN and Me_2NCN, it would be very interesting to have an experimental verification. The protonation site proposed by Peips et al. and Beck et al.,[48]

that is, the amino nitrogen, is consistent with the reported pK value of 1.2 (the range of an amine substituted with an electron-withdrawing group), but, as seen above, this value is probably wrong. On the other hand, Witanowski et al. obtained the ^{14}N spectrum of NH_2CN and Me_2NCN in a pioneering study.[47] The chemical shifts of the neutrals ($\delta = -184$ (CN) and -386 (NMe_2)) agree with our own, if allowance is made for the different solvents. The spectrum of NH_2CN in 2 M aq. HCl was found to consist of a single peak at $\delta = -270$, which was attributed to an exchange-averaged peak due to both the cyano and amino signals, arising from a series of protonation–tautomerization equilibria via the cyano-protonated form. However, the observed chemical shift agrees well with the one ($\delta = -305$) we observed *in addition* to the true Me_2NCN peaks (which disappeared in a few minutes). In other words, the observed spectrum was simply that of decomposition products. Hence, any experimental conclusion (including a pK determination) is hampered by the reactivity of both cyanamides in acids, and our best estimate for Me_2NCN (from theoretical results) is protonation at the amino group.

Phosphorous acid triamides: The energy difference between the *N*- and *P*-protonated forms is small (3.7 kcal mol^{-1}), $HP(NH_2)_3^+$ always being more stable. The only significant chemical shift is at phosphorus, which is shifted in opposite ways by the two processes. The efg at N decreases only a little upon *N*-protonation, because three signals (two of which are unaffected) are averaged. Experimentally, the ^{14}N T_1 remains constant and the ^{31}P signal is shielded by 127 ppm, as predicted for *P*-protonation (but $\Delta\delta$ is much larger). For this strong base[49, 50] slow proton exchange conditions are attained, and the ^{31}P signal appears as a doublet, which unambiguously indicates *P*-protonation. As a further proof, we note that its T_1 decreases and the NOE increases from 0.0 to its maximum value of 1.2, as expected. *P*-Protonation of $P(NEt_2)_3$ and related compounds has in fact been demonstrated.[49, 50] No evidence for *N*-protonation is found, which somewhat contrasts with the small $\Delta E_{(aq)}$ of 3.7 kcal mol^{-1}; again, this is probably due to an overestimation of the solvation of the non-alkylated model.

Phosphoric acid triamides: $PO(NH_2)_3$ is an oxygen base in the gas phase,[11] but for $PO(NMe_2)_3$ the preference is much less marked (ΔE(MP2) = 11.0 and 3.7 kcal mol^{-1}, respectively). IPCM results for $PO(NH_2)_3$ still indicate oxygen as the preferred basic site, but for $PO(NH_2)_3$ the two sites are almost leveled. Once again, this points out the large stabilization enjoyed by the primary amino groups, which is not present in $PO(NMe_2)_3$. The combination of data yielding $\Delta E_{(aq)}$ points to a shift of the basic site to nitrogen for $PO(NH_2)_3$, whereas no difference is found for $PO(NMe_2)_3$, with a $\Delta E_{(aq)}$ of only 0.2 kcal mol^{-1}. Calculated changes in NMR properties are small; for N they are not significant, and for P they change in the same way upon mono- or diprotonation. ^{17}O shielding offers a better prospect ($\Delta\delta = -30$ or $+34$ ppm). efg's are also little affected, except at O, which is expected to decrease only by *N*-protonation. The parameters for the diprotonated ion are not very different too.

Activity coefficient behavior in aqueous H_2SO_4 (as expressed by the solvation parameter $m^* = 0.46$) suggests *O*-protonation by comparison with other bona fide oxygen bases like ketones, sulfoxides, and carboxamides.[2, 35, 52] On the other hand, on the basis of pK values from kinetic data, and substituent effects, Haake[64] proposed predominant *N*-protonation for phosphonamides of the type $PhP(O)(NMe_2)O^-NMe_4^+$, whose structures are, however, dissimilar from triamides. An experimental verification is hindered by the relatively small spectral changes expected and by the restrictions in the acid that can be used, since triflic acid is strong enough to diprotonate $PO(NMe_2)_3$, and the viscosity of H_2SO_4 with the required concentration is too high; concd. aq. $HClO_4$ was found to be the best choice. The small ^{17}O shift ($\Delta\delta$ between $+3$ and -5) seems to indicate an average of both protonated forms (which should cause almost equal and opposite changes), whereas trends in ^{31}P and ^{14}N shifts are inconclusive. The value of ^{14}N T_1^R (1.8, determined between 49% *t*BuOH and 72% H_2SO_4) disagrees with all theoretical predictions, and is probably due to an incomplete compensation of viscosity. On the other hand, the ^{17}O T_1 in 70% $HClO_4$ (1.7 ms) is longer than in water (1.3 ms); if one allows for the larger viscosity of the acid (4.4 vs. 1 mPa s) the change is even larger ($T_1^R = 0.2$), and definitely points to a decrease of efg in the protonated form, which is consistent with *O*-protonation. In summary, theoretical results point out that the basicity of O and N in this molecule is quite similar. Trends in ^{17}O T_1's indicate *O*-protonation, but the chemical shift change is also compatible with partial *N*-protonation.

Summary and Conclusion

Quantum chemical calculations are a powerful tool for predicting energies and patterns of NMR properties of the parent bases and ions that can be formed from protonation of amines and a variety of amides. It has been shown that IPCM calculations in water alter, and often reverse, the stability order of structurally related ions in the gas phase, and hence provide a necessary complement to calculations for isolated species whenever a comparison with solution data is required. Shielding calculations predict both the absolute chemical shift range and, especially, the change to be expected for the formation of a given species. Even though the discrepancy with experimental data may amount to tens of ppm, trends thus established are often sufficient for the purpose. As such, they can be used as a structural tool, but the patterns of change are complicated and do not lend themselves to easy generalizations. In particular, we have shown that assumptions regarding similarity of spectroscopic behavior between amides and monofunctional models must be carefully scrutinized and tested. For problems of this type, it seems that ^{17}O chemical shifts and ^{14}N relaxation times (or linewidths) are the most useful data, being sensitive to protonation in a selective and predictable way.

In general, amides are protonated at the acid residue, but with several exceptions: a) when the parent acid is strong (sulfonic, nitric) the preference is not marked; b) the protonation site of sulfinamides may easily shift from N to O as a

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result of slight structural changes; c) sulfenamides behave as substituted amines and are nitrogen bases.

Experimental Section

Materials: Except where stated, all compounds studied are commercial or their preparation was previously reported. For some ^{17}O experiments ^{17}O-depleted water ($H_2{}^{16}O$) was used as solvent (CIL, 99.99 % ^{16}O).

^{17}O-enriched $PO(NMe_2)_3$ was synthesized by oxidation of $P(NMe_2)_3$ with 28 % *w/w* $H_2{}^{17}O_2$ in acetonitrile and a catalytic amount of $HClO_4$. $H_2{}^{17}O_2$ was prepared from $H_2{}^{17}O$ vapor (11.16 % ^{17}O, CIL) in an electric discharge.[65] The mass and ^1H NMR spectra were the same as those of an authentic sample.

MeCONHMe and $MeCONMe_2$ were enriched in ^{17}O by exchange with $H_2{}^{17}O$. The amide (1 mL, ca. 16 mmol) was mixed with enriched water (250 μL, 4.5 mmol) and concd. HCl (300 μL, 6 mmol); the solution was heated for 4.5 h at 80 °C and neutralized with 10 M NaOH. The amide was extracted with $CHCl_3$ (3 × 20 mL); after evaporating the solvent, 96–98 % of the amide was recovered. The intensity of the $M+1$ peak in the mass spectra was not higher than was expected due to ^{13}C; therefore the enrichment is < 3 %, that is, ca. 100 times the natural abundance (0.037 %), and permits overnight T_1 measurements.

N,N-dimethylnitramide was prepared by nitrolysis of DMF with 99 % HNO_3 in Ac_2O.[66]

NMR measurements: ^{14}N, ^{17}O, ^{13}C, and ^{31}P NMR measurements were run unlocked at 25 °C on a Bruker AM 400 instrument at 28.92 MHz (^{14}N), 54.24 MHz (^{17}O), 100.57 MHz (^{13}C), 161.98 MHz (^{31}P). Some measurements were carried out on a Bruker DMX 600 instrument (43.38 MHz for ^{14}N, 81.37 MHz for ^{17}O). Generally, 0.5 M solutions were employed in 5- or 10-mm tubes. Samples for ^{13}C and ^{31}P spectra were degassed by freeze–pump–thaw cycles. ^{14}N, ^{17}O, ^{13}C, and ^{31}P chemical shifts (δ) are externally referenced to $MeNO_2$, H_2O, Me_4Si, and 85 % H_3PO_4, respectively; they are believed to be accurate to within ± 0.1 ppm for ^{13}C and ^{31}P, and ± 2 ppm for ^{14}N and ^{17}O. T_1 values were obtained by inversion–recovery with acoustic ringing suppression[67] (^{14}N, ^{17}O-enriched) or by saturation–recovery (^{13}C, ^{31}P). T_1 and T_1^{DD} values are given in s for ^{13}C and ^{31}P, in ms for ^{14}N and ^{17}O. Linewidths were obtained from Lorentzian fitting of the peaks. ^{13}C and ^{31}P NOE's were determined by nonselective proton irradiation over 2–4 times the previously obtained T_1.

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