JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2000; **13:** 574–578

Review Commentary

Acyl group vs nitrogen protonation of carboxylic and non-carboxylic amides in the gas phase and water

Alessandro Bagno*

Centro CNR Meccanismi Reazioni Organiche, Dipartimento di Chimica Organica, Università di Padova, via Marzolo 1, 35131 Padua, Italy

Received 13 December 1999; revised 27 March 2000; accepted 31 March 2000

ABSTRACT: The site of protonation of carboxylic and non-carboxylic amides (whether the amido nitrogen or an atom in the acyl group, generally oxygen) was investigated through quantum chemical calculations and heteronuclear NMR measurements. The relative energies of the various ions deriving from protonation at each site were calculated both in the gas phase and in water, and NMR properties of the involved heteronuclei (nuclear shielding and electric field gradient) were also calculated 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 the reliable prediction of spectral parameters and ultimately of the protonation site. In general, amides are protonated at the acyl group, with the exception of (a) when the parent acid is strong (for which the preference is not marked), (b) the protonation site of sulfinamides may easily shift from N to O as a result of slight structural changes and (c) sulfenamides behave as substituted amines and are nitrogen bases. Copyright © 2000 John Wiley & Sons, Ltd.

KEYWORDS: amides; basicity; protonation site; *ab initio* calculations; NMR spectroscopy

INTRODUCTION

Owing to their structure, all amides may in principle undergo protonation at the nitrogen or at the acyl group[1,2] [e.g. RC(O)— for carboxylic acids, RSO_2— for sulfonic acids, —NO_2 for nitric acid). For example, for carboxamides this implies the alternative formation of R—C(O)—NHR_2^+ or R—C(OH)—NR_2^+.[1–3] However, except for this classical problem, the protonation site of amides other than carboxylic has been scarcely investigated.[1]

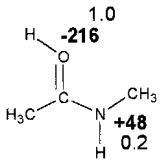
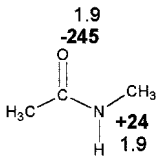
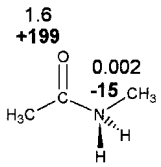
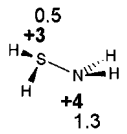
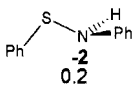
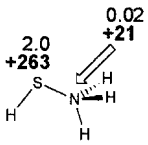
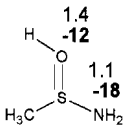
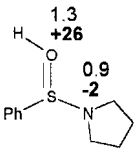
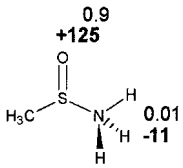
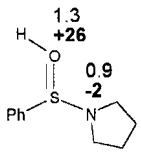
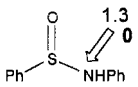
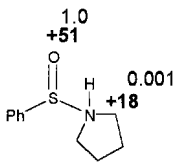
We showed previously[4–7] that a powerful means to solve this problem is the analysis of the changes in the NMR longitudinal relaxation times (T_1) of all nuclei which can act as ionization sites, coupled with suitable quantum chemical calculations.[4–9] In this paper we review the scope of this approach, including the calculation of nuclear shieldings, and also the relative stabilities, of all ionic species than can conceivably be formed from protonation at each basic site. Structures, energies and electric field gradients (efg) were calculated at the MP2/6–31++G(d,p)//HF/6–31++G(d,p) and MP2/6–311++G(d,p)//HF/6–311++G(d,p) levels.[4–9] Nuclear shielding calculations were carried out with the GIAO-HF method.[10,11] Moreover, since solvent effects will affect the relative stability of ions, energies in water were calculated with the HF-IPCM continuum solvent method.[12] Subsequently we shall compare the relative energies of the possible ionic species in the gas phase (ΔE^g, determined from MP2 calculations) and in water (ΔE^{aq}, calculated through a combination of MP2 and IPCM energies by means of a Born–Haber cycle).[4]

The comparison of calculated and experimental NMR properties is presented as follows. The relaxation time of quadrupolar nuclei such as ^{14}N and ^{17}O is proportional to the effective nuclear quadrupolar coupling constant $\chi_{eff} = \chi^2(1+ \eta^2/3)$, where χ and η depend on the efg at the nucleus in question, so that $1/T_1 \propto \chi_{eff}$.[4] We then compare the calculated values of $\chi_{eff}(BH^+)/\chi_{eff}(B)$ with the experimental counterpart $T_1(B)/T_1(BH^+)$. Hence a decrease in T_1 (i.e. an increase in relaxation rate) upon protonation will result in $T_1(B)/T_1(BH^+) > 1$, and vice versa.

Calculated shieldings (σ) are reported as the change of the isotropic component of the shielding tensor from neutral to protonated from [$\Delta\delta = \sigma(B) - \sigma(BH^+)$], which is comparable to the experimentally determined $\Delta\delta = \delta(BH^+) - \delta(B)$. The theoretical level adopted was previously shown to be successful in modeling the chemical shifts of neutral amines, amides[4] and sulfur compounds.[13]

**Correspondence to:* A. Bagno, Centro CNR Meccanismi Reazioni Organiche, Dipartimento di Chimica Organica, Università di Padova, via Marzolo 1, 35131 Padua, Italy.
E-mail: alex@chor.unipd.it

Table 1. Theoretical and experimental data for the protonation of amides at the acyl group or nitrogen

Species[a]	ΔE^{g} (kcal mol^{-1})	ΔE^{aq} (kcal mol^{-1})	Exptl[b]
Carboxylic amides			
	0.0	0.0	
	+14.5	+7.2	
Sulfenamides			
	0.0	0.0	
	−22.3	−27.4	
S-Alkyl sulfinamides			
	0.0	0.0	
	+9.6	−3.4	
S-Aryl sulfinamides			
	0.0	0.0	
	+0.7	−7.2	

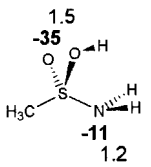
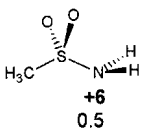
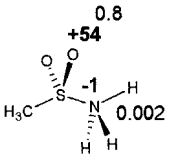
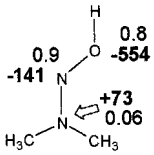
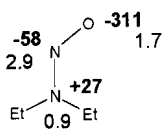
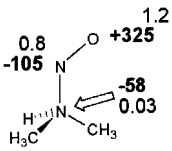
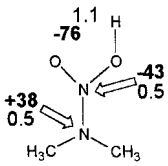
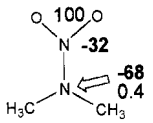
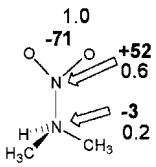
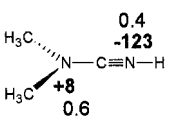
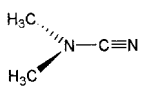
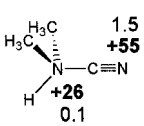
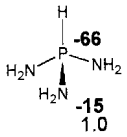
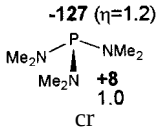
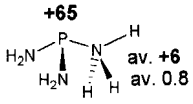
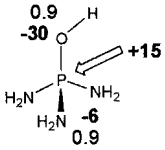
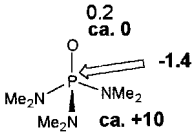
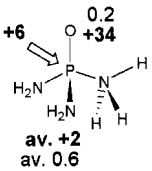
Species[a]	ΔE^{g} (kcal mol^{-1})	ΔE^{aq} (kcal mol^{-1})	Exptl[b]
Sulfonamides			
	0.0	0.0	
	−2.8	−12.4	
Nitrosamides			
	0.0	0.0	
	+10.3	+9.7	
Nitramides			
	0.0	0.0	
	+2.6	−1.9	
Cyanamides			
	0.0	0.0	
	+22.4 (NH_2); −11.7 (NMe_2)	−1.9 (NH_2); −26.5 (NMe_2)	

Table 1. Continued

Species[a]	ΔE^{g} (kcal mol^{-1})	ΔE^{aq} (kcal mol^{-1})	Exptl[b]
Phosphorous acid triamides			
	0.0	0.0	 cr
	+3.7	+3.7	
Phosphoric acid triamides			
	0.0	0.0	
	+11.0 (NH_2); +3.7 (NMe_2)	−4.4 (NH_2); +0.2 (NMe_2)	

[a] Numbers in normal and bold type refer to electric field gradient [$\chi_{eff}(BH^+)/\chi_{eff}(B)$] and nuclear shielding [$\sigma(B) - \sigma(BH^+)$] changes, respectively (see text).
[b] Numbers in normal and bold type refer to $1/T_1$ [$T_1(B)/T_1(BH^+)$] and chemical shift [$\delta(BH^+) - \delta(B)$] changes, respectively (see text). The protonation site, as determined by the method presented herein, is highlighted in bold.

RESULTS AND DISCUSSION

Using the IPCM method to model the basicity of amines

The anomalous basicity ordering of alkylamines in water ($Me_2NH > MeNH_2 > Me_3N > NH_3$) with respect to the gas phase ($Me_3N > Me_2NH > MeNH_2 > NH_3$) is due to the competition between inductive effects and solvation.[14] In order to test whether the IPCM method yields a correct aqueous basicity ordering, we compared relative energies, calculated with the above methods in the gas phase and in water, with experimental $\Delta G_{(g)}$ and $\Delta G_{(aq)}$ values.

MP2 calculations yield the typical gas-phase ordering (py $>$ $PhNH_2$ $>$ Me_3N $>$ Me_2NH $>$ $MeNH_2$ $>$ NH_3) whereas the IPCM method yields the basicity order py $<$ $PhNH_2$ $<$ NH_3 $<$ Me_3N $<$ Me_2NH $<$ $MeNH_2$ in water. Hence this approach correctly models the major features of amine basicity: (a) the large gas-phase basicity of aniline and pyridine is lower than that of alkylamines (albeit reversed in order); and (b) Me_3N is correctly predicted to be the weakest among methylamines. However, since $MeNH_2$ is incorrectly predicted to be stronger than Me_2NH, it seems that the IPCM method overestimates the stabilizing effect of hydrogen bonding (as confirmed by the stronger basicity of $PhNH_2$ than pyridine). Hence comparisons between bases with very different degrees of alkylation must be made with caution (see below).

Changes in NMR properties are also reliably modeled. The protonation shift at nitrogen[15] 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 the sign of $\Delta\delta$[15] is correctly modeled. The effect of protonation on the efg and associated T_1 is very large, as protonation or alkylation at nitrogen is known to cause a large decrease in efg.[5,6,9,15,16] The calculated χ_{eff}s decrease by 4–7 orders of magnitude, whereas the corresponding T_1 values decrease by only 10–100-fold. In any event, nitrogen protonation is clearly revealed by the large and predictable change in efg or T_1.

Amides

We present below the results obtained for several types of amide bases, obtained by the approach outlined above, i.e (a) comparison of gas-phase and aqueous energies and (b) comparison of calculated and experimental changes in NMR properties, for the tautomeric ions deriving from protonation at the alternative protonation site in the amide (nitrogen or acyl group). The results are presented in Table 1, where numbers in normal and bold type refer to changes in χ_{eff} (or $1/T_1$) and nuclear shielding (or chemical shift), respectively.

Carboxylic amides and thioamides[4,5,8,9]

According to calculations, *O*-protonation is always favored over *N*-protonation. The oxygen is strongly shielded by *O*-protonation, whereas *N*-protonation causes a similar but opposite shift in the ^{17}O spectrum. Hence ^{17}O chemical shifts should be a sensitive probe of the site of protonation. Shielding changes at nitrogen are smaller, but *N*-protonation causes a large efg decrease at nitrogen. The experimentally measured chemical shift changes, and also the failure to observe any decrease in ^{14}N relaxation rate, agree only with the calculated data for *O*-protonation, as expected. A similar picture holds for thioamides (*S*-protonation).

Sulfenamides[4,6,8,9]

N-Protonation is always favored, especially in water, in

agreement with the weak hydration of sulfonium ions. Protonation at either site causes a moderate deshielding of nitrogen, whereas the sulfur is deshielded only upon *N*-protonation (however, such ^{33}S signals are undetectable[13]). Nitrogen shifts are not a suitable probe of the protonation site, but *N*-protonation is clearly borne out by the increase in ^{14}N T_1.

Sulfinamides[4,6,8,9]

S-Protonation is unfavorable energetically[8] and will not be considered. The behavior of *S*-alkyl and *S*-aryl sulfinamides is different. Thus, although for both types *O*-protonation should be favored, this preference is overturned in water, in favor of *N*-protonation (for $MeSONH_2$ this may be related to the overestimation of the stability of $MeSONH_3^+$, as seen before).

Nitrogen shielding is not diagnostic. A large deshielding of ^{17}O is predicted if protonation takes place at nitrogen, a smaller change being predicted for *O*-protonation. The efg at N undergoes the typical large decrease upon *N*-protonation, but remains almost constant otherwise. Experimental ^{14}N results (constant T_1) are consistent with *O*-protonation. Hence, although 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, in all cases studied experimentally the data are consistent with *O*-protonation.

Methanesulfonamide[4,8,9]

$MeSO_2NH_2$ is predicted to be a nitrogen base under all conditions. Experimentally, the ^{14}N signal is slightly deshielded upon protonation, and its relaxation rate is halved; this decrease indicates that $MeSO_2NH_3^+$ is formed, although the increase is much smaller than expected. Thus, *N*-protonation is borne out but the data may indicate *O*-protonation to some extent.

N,N-Dimethylnitrosamide[4,8,9]

The most basic site of Me_2NNO is predicted to be the oxygen atom in both gas and water phases. Theory also predicts large shielding changes upon protonation, especially at O, while efg and related T_1 changes are not helpful. Experimentally (for Et_2NNO), the ^{17}O and ^{14}N (NEt_2) chemical shift changes match the predicted values for Me_2NNOH^+, strongly suggesting *O*-protonation.

N,N-Dimethylnitramide[4,8,9]

The basic sites of Me_2NNO_2 are very similar in strength, and NMR parameters for the two ions are only slightly different. Furthermore, experiments were complicated by the fast decomposition in triflic acid, which prevented us from obtaining a T_1 for the NO_2 signal; ^{17}O measurements were not attempted. The incomplete data available seem consistent with protonation occurring at both sites to a comparable extent, although we cannot rule out interference from decomposition products.

Cyanamides[4,8,9]

NH_2CN and Me_2NCN behave differently, since NH_2CNH^+ and Me_2NHCN^+, respectively, are favored in the gas phase. However, while IPCM calculations equalize the basicity of the two sites in NH_2CN, Me_2NHCN^+ remains the most stable ion also in water. The NMR spectral changes are similar for both species. However, we could not obtain satisfactory ^{14}N spectra in acids, owing to fast decomposition even at low temperature, and our best calculated estimate for Me_2NCN is protonation at the amino group.

Phosphorous acid triamides[4,8,9]

The stability of the *N*- and *P*-protonated forms is similar, but *P*-protonation is always preferred. The only significant chemical shift is at P, which is shifted in opposite directions by the two processes. Although *N*-protonation leads to the usual large efg decrease at the quaternized nitrogen, after averaging with the other two only a small decrease results; however, no χ_{eff} change at nitrogen is expected upon *P*-protonation. Experimentally, the ^{14}N T_1 remains constant and the ^{31}P signal is shielded, as expected for *P*-protonation. This is also confirmed by the T_1 decrease and the multiplicity of the ^{31}P signal (doublet).

Phosphoric acid triamides[4,8,9]

A major experimental complication is due to their possible diprotonation.[17] These are oxygen bases in the gas phase, but for $PO(NMe_2)_3$ the preference is only slight. In water, for $PO(NH_2)_3$ the preference is unaffected, whereas for $PO(NMe_2)_3$ the two ions have almost the same energy. This again points out the strong solvation of the primary amino groups. Calculated changes in NMR properties for N are not significant, and for P they change in the same way upon mono- or diprotonation. ^{17}O shieldings change to a relatively small extent. The efgs are also little affected, except at O, which is expected to decrease only by *N*-protonation. The parameters for the diprotonated ion are also not very different. NMR measurements were carried out for $PO(NMe_2)_3$ (also ^{17}O-enriched), and are complicated

by hydrolysis and partial diprotonation.[17] The small ^{17}O shift seems to indicate an average of both protonated forms, whereas trends in ^{31}P and ^{14}N shifts are inconclusive. The efg change at ^{14}N disagrees with theoretical predictions, and is probably due to an incomplete compensation of viscosity. On the other hand, the ^{17}O T_1 is consistent with *O*-protonation. In summary, trends in ^{17}O T_1s indicate *O*-protonation, but the chemical shift change is also compatible with partial *N*-protonation.

CONCLUSION

Calculations in water (with the IPCM method) alter, and often reverse, the stability order of structurally related ions in the gas phase, and such calculations are mandatory if a reliable estimate of the protonation site is sought. Calculated shielding and efg changes are often large, but not readily predictable or amenable to generalization, even for closely related species, hence the need to collect data for species as similar as possible to those studied experimentally. ^{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 acyl group, 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 result of slight structural changes; and (c) sulfenamides are nitrogen bases.

REFERENCES

1. Stewart R. *The Proton: Applications to Organic Chemistry*. Academic Press: New York, 1985.
2. Bagno A, Scorrano G, More O'Ferrall RA. *Rev. Chem. Intermed.* 1987; **7**: 313.
3. Perrin CL. *J. Am. Chem. Soc*. 1986; **108**: 6807, and references cited therein.
4. Bagno A, Bujnicki B, Bertrand S, Comuzzi C, Dorigo F, Janvier P, Scorrano G. *Chem. Eur. J*. 1999; **5**: 523, and references cited therein.
5. Bagno A, Comuzzi C, Scorrano G. *J. Chem. Soc., Perkin Trans. 2* 1993; 283.
6. Bagno A, Eustace SJ, Johansson L, Scorrano G. *J. Org. Chem.* 1994; **59**: 232.
7. Bagno A, Comuzzi C, Scorrano G. *J. Am. Chem. Soc*. 1994; **116**: 916.
8. Bagno A, Scorrano G. *J. Phys. Chem.* 1996; **100**: 1536.
9. Bagno A, Scorrano G. *J. Phys. Chem.* 1996; **100**: 1545.
10. Wolinski K, Hinton JF, Pulay P. *J. Am. Chem. Soc.* 1990; **112**: 8251.
11. Frisch MJ, Trucks GW, Schlegel HB, Gill PMW, Johnson BG, Robb MA, Cheeseman JR, Keith T, Petersson GA, Montgomery JA, Raghavachari K, Al-Laham MA, Zakrzewski VG, Ortiz JV, Foresman JB, Cioslowski J, Stefanov BB, Nanayakkara A, Challacombe M, Peng CY, Ayala PY, Chen W, Wong MW, Andres JL, Replogle ES, Gomperts R, Martin RL, Fox DJ, Binkley JS, Defrees DJ, Baker J, Stewart JP, Head-Gordon M, Gonzalez C, Pople JA. Gaussian 94, Revision C.2. Gaussian: Pittsburgh, PA, 1995.
12. Foresman JB, Keith TA, Wiberg KB, Snoonian J, Frisch MJ. *J. Phys. Chem.* 1996; **100**: 16098.
13. Bagno A. *J. Mol. Struct. (THEOCHEM)* 1997; **418**: 243.
14. Taft RW. *Prog. Phys. Org. Chem.* 1983; **14**: 247.
15. Levy GC, Lichter RL. *Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy*. Wiley-Interscience: New York, 1979.
16. Mason J (ed). *Multinuclear NMR*. Plenum Press: London, 1987.
17. Bagno A, Scorrano G. *J. Am. Chem. Soc.* 1988; **110**: 4577.