Relative Basicity of Nitrogen, Oxygen, and Sulfur Bases. The Site of Protonation in Sulfenamides and Sulfinamides Determined by ^{14}N NMR Relaxation

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Introduction

Most organic bases owe their basic properties to a nitrogen, oxygen, or sulfur atom, and the properties of ammonium, oxonium, and sulfonium ions are well known.[1] Thus (other things being equal) amines are by far the strongest, both intrinsically and because of the large stabilization of ammonium ions in water by hydrogen bonding. On the other hand, while the intrinsic stability of oxonium ions is generally lower than that of sulfur analogues, the much larger stabilization experienced by the former in water leads to strongly medium-dependent basicity differences and even to reversals in base strength. The situation is more complex when the compared basic sites are within the same molecule, especially if they are directly bonded. A typical case is offered by amides, where exclusive *O*-protonation takes place.[2]

Sulfenamides ($RSNR_2$) and sulfinamides ($RS(O)NR_2'$) (R = alkyl, aryl) may undergo protonation at any of the basic sites (N or S for the former and N, S, or O for the latter). It is generally assumed that the protonation site is the nitrogen atom in both cases;[3] however, this conclusion is admittedly based on circumstantial evidence. In fact, the reactivity of sulfenamides is dominated by the intermediacy of the *N*-protonated form,[3] which agrees with the low basicity of simple sulfides in water.[1] On the contrary, *N*-protonation of sulfinamides is at variance with the behavior of carboxylic amides and the S=O group in sulfoxides (which also protonate on oxygen).[1]

Recently, p*K*'s have been determined for a number of such derivatives; the values found (3-4) lie in the range typical of anilines and were interpreted assuming *N*-protonation.[4] In this Note we present our results, obtained by means of heteronuclear NMR relaxation measurements and theoretical calculations.

Experimental Section

Sulfenamides[5] and sulfinamides[6] were prepared by literature methods. ^{14}N NMR spectra were obtained on a Bruker AM 400 instrument (9.4 T; 28.92 MHz for ^{14}N) at 25 °C; longitudinal relaxation times (T_1) were determined with an inversion-recovery sequence including acoustic ringing suppression.[7] 1 M solutions were employed.

Results and Discussion

We have recently developed a method which enables one to determine the site of ionization of polyfunctional bases and acids.[8] This is based upon the fact that the relaxation rate of the nucleus undergoing the acid-base reaction is deeply affected by the presence or absence of a proton. For example, it is well known that the ^{14}N relaxation rate in ammonium ions is much lower than in neutral amines;[9] we have tested the applicability of this method on a number of acids and bases of widely varying structure.[8]

Because all the compounds of interest contain nitrogen, the choice of ^{14}N as the probe nucleus is the most obvious one, given its high natural abundance (99.4%); ^{17}O and ^{15}N NMR measurements are feasible only with difficulty at natural abundance, whereas the ^{33}S spectra of sulfinyl derivatives (*e.g.* sulfoxides)[9] exhibit line widths on the order of several kilohertz and hence present experimental problems.

The relaxation of ^{14}N ($I = 1$) is dominated by the quadrupolar mechanism, which depends on the coupling between the nuclear quadrupole moment and the electric field gradient (efg) at the nucleus. This mechanism leads to short relaxation times (T_1 of the order of 10^{-3} s), which are related to the line widths $W_{1/2}$ as $T_1 = 1/(\pi W_{1/2})$. As stated above, protonation of an amine-like nitrogen causes a large decrease in the relaxation rate, which is detected as an increase in T_1 or a decrease in $W_{1/2}$. It may be argued that such a criterion is not necessarily applicable to the protonation of an amide nitrogen, because of both its hybridization and the presence of an electronegative group (S, SO) directly bonded to it. In the absence of model compounds, we estimated the change in efg occurring upon protonation by means of *ab initio* theoretical calculations. Such calculations have been carried out for NH_2SH and $CH_3S(O)NH_2$ protonated at all possible sites. The results are reported in Table I as an effective nuclear quadrupolar coupling constant (NQCC), which is proportional to $W_{1/2}$ or efg. This was calculated as $(eQq_{zz}/h)^2(1 + \epsilon^2/3)$, Q being the nuclear quadrupole moment, q_{zz} the principal component of the efg tensor and ϵ its asymmetry parameter.[9] It can be easily seen that, in both cases, protonation at nitrogen causes a marked decrease in its efg, whereas protonation at other sites causes very small changes at that site. Therefore this parameter shows itself to be a sensitive and selective probe of the state of ionization, and we can safely assume that *N*-protonation will be detected as narrower ^{14}N spectral lines in this type of environment too. The efg at S in NH_2SH is affected by a factor of 2 in opposite directions by protonation at either N or S. In the case of $CH_3S(O)NH_2$, *S*-protonation causes a large decrease of the efg at S (which might be detected as a decrease in ^{33}S line widths), whereas the efg at O is

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Table I. Calculated Energies and NQCC's for NH_2SH, $CH_3S(O)NH_2$, and Their Ions

structure	E^b	ΔE^c	NQCC[a] O	NQCC[a] S	NQCC[a] N
NH_2SH	-453.989302302	-	-	25.75	0.24
$HSNH_3^+$	-454.325990788	(0.0)	-	51.23	0.00[d]
$H_2NSH_2^+$	-454.290531102	22.2	-	12.48	0.30
$CH_3S(O)NH_2$	-568.182526628	-	1.22	14.30	0.18
$CH_3S(OH)^+NH_2$	-568.538946949	(0.0)	1.64	20.15	0.21
$CH_3S(O)NH_3^+$	-568.522089329	10.6	1.15	27.18	0.00[d]
$CH_3S(H^+)(O)NH_2$	-568.475476132	39.8	1.05	1.11	0.24

[a] At HF/TZP//HF/6-31G** level, in units of 10^{14} s^{-2}. [b] Energy in au at MP2/6-31G**//HF/6-31G** level. [c] Energy (kcal/mol) relative to lowest-energy ionic structure. [d] "Zero" value implies a *ca.* 10-fold decrease in q_{zz} and a negligible intramolecular contribution to the efg; the actual line width in solution will be dominated by intermolecular effects.

scarcely affected by protonation. This renders this probe not very useful, in view of the known experimental problems related to its very low natural abundance (0.037%).[9] Energetic considerations offer useful insight: the greater intrinsic stability (by 22.2 kcal/mol) of $HSNH_3^+$ is clearly borne out, and, because this is also the most strongly solvated cation,[1] this difference will not be reversed by solvation. The results for $CH_3S(O)NH_2$ show the *O*-protonated form to be favored over the *N*-protonated one, however by a smaller amount (10.6 kcal/mol). Energies of solvation of protonated sulfinamides (the main term in the thermodynamics of gas phase to water transfer) are not available, but a rough comparison may be made taking Me_2SOH^+ and $Me_2NH_2^+$ as models. Their respective free energies of hydration are very similar (*ca.* -60 kcal mol^{-1})[1], which indicates that (within the scope of this model) the basicity order in the gas phase is probably also maintained in solution. The *S*-protonated form is much higher in energy and hence unlikely.

Because T_1 measurements are much more time-consuming than simple signal detection, it is convenient to run them only at the two extreme conditions, where ionization is either essentially zero or quantitative. To this purpose, one needs a prior, if approximate, knowledge of the p*K*. Thus we have tried to maintain consistency with the species studied in ref 4, in order to make use of those p*K* values. Distribution diagrams show that pH ≈ 0 is required to achieve >99% protonation, which was effected by HCl in MeOH (however, see below). Neutral forms were studied in MeOH. In any event, the sulfenamides containing an aliphatic nitrogen moiety (PhSNH*i*-Pr, *m*-ClC_6H_4SNH*t*-Bu, and CH_3S(*N*-piperidyl)) decomposed immediately in acid solutions, giving ^{14}N spectra consistent with the corresponding ammonium ion, even in nonhydrolytic media (CF_3SO_3H). For this reason, we used diaryl or alkyl–aryl derivatives in which the nitrogen atom is attached to a benzene ring. For such compounds, the natural term of comparison is aniline, which was also investigated as a reference compound. Chemical shifts, line widths, and relaxation times are collected in Table II.

Table II. ^{14}N Spectral Data[a]

species	neutral δ	neutral $W_{1/2}$	neutral T_1	protonated δ	protonated $W_{1/2}$	protonated T_1
$PhNH_2$[b]	-326.0	826	0.48	-332.2	215	2.60
CH_3S(*N*-piperidyl)[c]	-344.9	525	0.51	-	-	-
PhSNH*i*-Pr[c]	-339.6	967	0.20	-	-	-
m-ClC_6H_4SNH*t*-Bu[c]	-330.0	1480	0.18	-	-	-
PhSNHPh[d]	-330.8	2144	0.18	-333.3	283	1.17
$CH_3S(O)N$*i*-Pr_2[e]	-311.1	112	2.95	-307.0	106	3.56
$CH_3S(O)NHPh$[f]	-333.6	276	1.16	-329.0	370	0.77
$CH_3S(O)NHPh$[g]	-333.1	286	1.16	-335.0	408	0.74
PhS(O)NHPh[f]	-327.0	674	0.67	-326.9	509	0.51

[a] Chemical shifts in ppm from external CH_3NO_2; line widths in hertz and T_1 values in ms. [b] Neutral form generated in water–MeOH containing a small amount of NaOH; protonated form in 1 M HCl. [c] In MeOH only; decomposes in acid. [d] Neutral form in MeOH; protonated form in an HCl/MeOH mixture prepared diluting MeOH with 3 M aqueous HCl up to an apparent pH of 1. [e] Neutral form in MeOH; protonated form in concd HCl. In CF_3SO_3H, decomposition takes place, as shown by ^1H spectra; three ^{14}N signals appear, the most intense having $W_{1/2}$ = 89 Hz. [f] Neutral form in MeOH, protonated form in 1:1 MeOH/concd HCl. [g] Neutral form in 22% *t*-BuOH in water, protonated form in CF_3SO_3H; *t*-BuOH was used to compensate for the higher viscosity of CF_3SO_3H.[8]

Firstly, it can be seen that, as expected, protonation of aniline involves a marked decrease in the ^{14}N line width. The only sulfenamide which could be successfully studied is PhSNHPh, for which pK = 2.82.[4a] For this compound, the typical ^{14}N line narrowing (by a factor of 10) is observed upon protonation, which clearly indicates *N*-protonation. This result confirms earlier assumptions and is consistent with the pK value[4a] and theoretical results. For sulfinamides, if a pK of *ca.* 3–3.5 is assumed as typical,[4b] then one sees that under the conditions required for protonation no major change takes place in the ^{14}N spectrum (a small line *broadening* is observed). Recalling the theoretical results, we viewed this as strongly suggestive of protonation at oxygen. However, we note that the titration curve presented for PhS(O)NHPh in ref 4b is not complete, because the absorbance values do not reach a constant value at pH 2. This casts doubt on the reliability of the pK reported therein, which is probably *ca.* 1 unit less. In any event, recalling that carboxylic amides are more basic than ketones,[1] we may infer that sulfinamides are more basic than sulfoxides. Because the latter are completely protonated in CF_3SO_3H (*e.g.*, Me_2SO has m^* = 0.42 and pK = -1.54, and requires >87% H_2SO_4 for complete protonation)[10] we extended the measurements of sulfinamides to CF_3SO_3H to ensure complete protonation. Again, no major change took place in the ^{14}N spectra in this medium, further supporting *O*-protonation. We also note that chemical shift changes are small and similar for both series, and therefore are not diagnostic.

We conclude that sulfenamides protonate on the nitrogen atom and sulfinamides on the oxygen atom.

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