Selectivity in Proton Transfer, Hydrogen Bonding, and Solvation

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Received December 2, 1999

ABSTRACT

The site of protonation (or deprotonation) of polyfunctional bases and acids can be determined through the comparison of experimental NMR properties (chemical shift and relaxation rates) with the corresponding data calculated by quantum chemical methods. The results can be interpreted in terms of the competition between intrinsic base strengths and solvation. Qualitatively similar criteria are found to hold for hydrogen bonding. The selective enrichment in a cosolvent in the solvation shell of a solute dissolved in a solvent mixture (preferential solvation) can be determined through the analysis of intermolecular cross-peak intensities in NOESY spectra.

Introduction

Proton transfer is perhaps the most fundamental elementary chemical event, and leads to a large increase in the reactivity of neutral organic molecules when they are converted to their charged, conjugate acid or base form. Hence, the long-standing general interest in methods capable of probing the extent of the proton-transfer process.[1]

While in the gas phase the proton donor itself is generally unsolvated, proton transfers in condensed phases involve solvated protons, generally the conjugate acid of the solvent. Thus, in water the familiar expression $B + H^+ \rightleftharpoons BH^+$ is nothing but shorthand for eq 1, where $H^+_{(aq)}$ represents a hydrated hydronium ion, e.g. $H_3O(H_2O)_n^+$.

$$BH^+_{(aq)} \rightleftharpoons B_{(aq)} + H^+_{(aq)}; \qquad K = \frac{a_B a_{H^+}}{a_{BH^+}} \qquad (1)$$

Base (or acid) strengths in solution are determined by the interplay of structural and solvation effects on all species involved (mostly on the charged species). It is now well-known that gas-phase and solution basicities often follow a different pattern; indeed, the understanding of the underlying factors has been a major breakthrough of physical organic chemistry.[2] Since most concepts are common to both protonation and deprotonation equilibria of neutral molecules, hereafter we will refer to such processes as "ionization" (in a proton-transfer sense). In solution, most organic molecules are very weak bases or acids and ionize only in concentrated nonideal solutions, which has hampered the determination and interpretation of the parameters related to proton transfer. Moreover, many such species are also "polyfunctional", i.e., exhibit at least two conceivable protonation or deprotonation sites, and the nature of the ionized species is of interest in itself.[1]

Solvent effects stem from weaker interactions than proton transfer, ranging from hydrogen bonding to dipole−dipole and dispersion interactions. All of these involve the approach of two molecules, often in a preferred orientation characterized by the relative positions of atoms belonging to each interacting molecule. Hydrogen bonding is qualitatively similar to proton transfer, although no charges are separated, the energies involved are much lower, and the equilibrium distance r_{HB} in A−H···B is longer. The latter two interactions may take place in a variety of orientations; for organic molecules, these can be characterized by the relative position of hydrogen atoms, which are generally the most exposed to intermolecular interactions. Consistently with the ideas seen for proton transfer, emphasis has been given to probing the selective formation of hydrogen bonds in polyfunctional acceptors, and the selective enrichment in a cosolvent in the solvation shell of a solute dissolved in a solvent mixture (preferential solvation).

In this Account we present recent contributions related to answering the following questions: (a) What is the base/acid strength of a given molecule? (b) What is the base/acid strength of a given medium? (c) Given several alternatives, where does the proton go, or come from, in proton transfer and hydrogen bonding? (d) Is it possible to probe and understand the microscopic structure of the solvation shell?

Ionization Equilibria in the Gas Phase and Solution

In the gas phase, base or acid strengths are expressed as GB or PA values,[3] and in solution as the equilibrium constant (pK) for eq 1, while the ΔH is obtained through its temperature dependence.

An acidity scale for the gas phase is given by the bracketing sequence of bases,[3] whereas the acidity scale in solution is the familiar pH scale, *if applicable*. Questions a and b are then answered, since for any base $\log([BH^+]/[B]) = -pH + pK$. Therefore, if pH and p$K$ are known, the

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10.1021/ar990149j CCC: $19.00
Published on Web 06/01/2000

ionization ratio $I = [BH^+]/[B]$ is also known, and one can determine the conversion of B to BH^+ at any pH. More importantly, the common slope of −1 for all bases implies that for any pair of bases the equality $\log I_1 - \log I_2 = pK_1 - pK_2$ holds through the whole pH scale, and the pK is all one needs to characterize the base strength (since NH_3 has pK = 9.24, it is a weaker base than Me_2NH with pK = 10.78, without further discussion).

These ideas are so firmly rooted that such remarks may seem trivial enough. However, since most organic molecules are weak bases or acids, they ionize in media enormously far from the standard state, and to which the pH scale does not apply at all. Indeed, 98% sulfuric acid is ca. 18 M, and its "pH" would be just −1.2, whereas its protonating power is known to be around 10^8 times as much.[4] The reason for this departure from ideality is that such a large increase in acid concentration entails a dramatic decrease in the water concentration and activity, and hence in the ability of the solution to solvate the ions formed (especially H_3O^+). In other words, the necessary acidity change is intermingled with a solvent effect on the acid−base equilibrium, which is reflected in large activity-coefficient terms (γ_i), so that eq 2 must be used.[4]

$$\log I = \log [H^+] + \log \frac{\gamma_B \gamma_{H^+}}{\gamma_{BH^+}} + pK \qquad (2)$$

The new term in eq 2 is evaluated by the empirical recognition that, given a pair of bases, such terms are linear in one another throughout the acid concentration range. It is then convenient to define a reference base B*, and make use of the fact that $\log(\gamma_B\gamma_{H^+}/\gamma_{BH^+}) = m^* \log(\gamma_{B^*}\gamma_{H^+}/\gamma_{B^*H^+}) = m^*X$, B* being defined in such a way that X can be independently determined. The X (excess acidity) function then acquires the status of a generally applicable function of acidity, which serves the purpose of evaluating base strengths also in nonideal media, from $\log I - \log [H^+] = m^*X + pK$.[4,5] Each base can (and does) have a different m^* value; there is no reason it should not, since m^* contains the acidity dependence of its own activity coefficients. The important implication is that now, in general, $\log I_1 - \log I_2 \neq pK_1 - pK_2$; i.e., knowing the p$K$ is not sufficient to determine the relative extent of protonation at a given acid strength, because each base responds differently (through its own activity coefficients) to the acid. Thus, although the pK of Me_2S (−6.95) is much lower than that of Me_2O (−2.48), Me_2S is quantitatively protonated in 98% sulfuric acid while Me_2O is not, simply because its higher m^* (1.3 vs 0.2) implies that its $\log I$ increases much more steeply with acidity. With these ideas in mind, it becomes obvious that there is no way to unambiguously define the relative basicity of two molecules without explicit reference to the actual acid concentration, because the magnitude, and even the sign, of $\Delta \log I$ may change.

The m^* parameter also has a chemical significance, since it semiquantitatively probes the solvation of BH^+. Thus, high m^* implies low solvation, so that, e.g., Me_2SH^+ is less hydrated than Me_2OH^+,[6] as illustrated by the relationship between m^* and free energies of hydration of BH^+ in Figure 1. Chemically meaningful trends hold for the effect of different basic atoms, charge delocalization,[6−10] and even steric effects.[11] The m^* and pK range spanned by typical organic functional groups is depicted in Figure 2. A corresponding treatment has been developed also for some strongly basic media.[12]

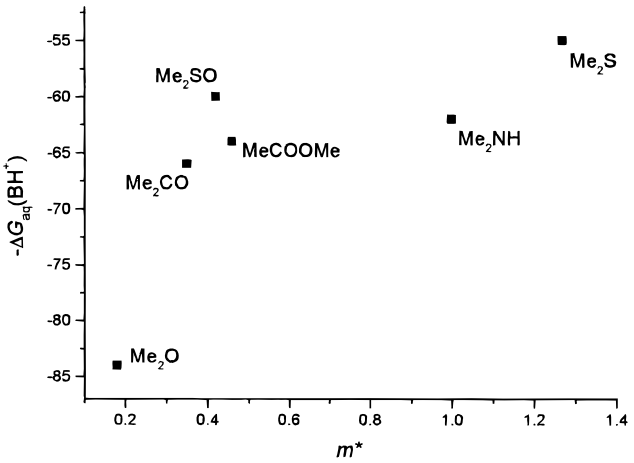


FIGURE 1. Correlation between m^* and $\Delta G_{aq}(BH^+)$ (kcal/mol) for bases sharing the same hydrocarbon backbone.

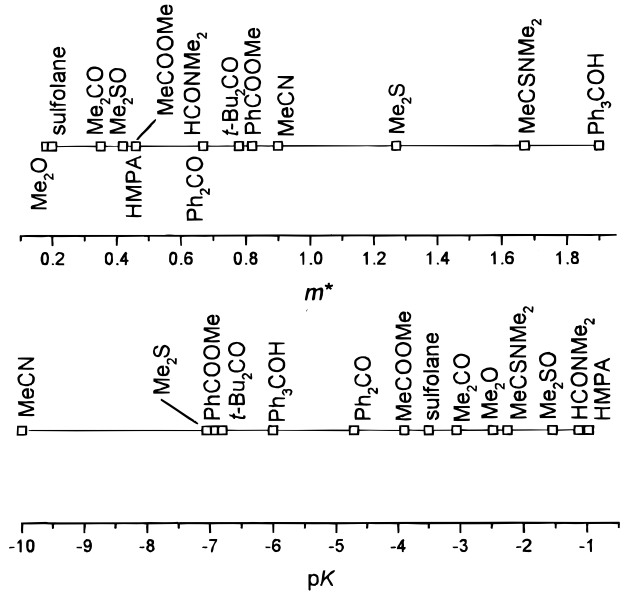


FIGURE 2. m^* and pK range of common organic molecules.

Polyfunctional Bases and Acids

Extensive compilations of the base and acid strengths of neutral organic species are available for the gas phase,[3] water,[1] and DMSO.[13] These data mostly refer to monofunctional bases (or acids), i.e., species for which only one atom or group (site) can be reasonably conceived of as the site of ionization, at least under conditions compatible with a given solvent system.

In the case of polyfunctional bases and acids, sometimes there is hardly any doubt of the ionization site. Thus, under monoprotonation conditions one expects morpho-

line to be a nitrogen rather than an oxygen base, on account of the very different base strengths of secondary aliphatic amines and ethers. However, when the comparison is made between two similar functional groups, such as the ring and side-chain nitrogens in histamine or pyrimidines,[14] it is not obvious which one is the more basic. Likewise, even the simplest carboxylic amide features two basic sites (O and N) whose strength cannot be predicted by simple arguments, since resonance in the amide group will render the involved atoms quite different from those in their respective parent functional groups (amine or ketone). The long quest for a solution to this problem[15] testifies to the difficulties that are encountered.

Experimental and Theoretical Methods. Several spectroscopic techniques have been employed for elucidating the structure of such tautomeric ions, most often NMR. Virtually all of them involve the comparison of the change in some property due to the acid−base process. What to make of such changes is, unfortunately, often an open question. A widely used approach amounts to making one of the sites unavailable to ionization, generally by alkylation; the ions thereby obtained should hopefully model those deriving from the polyfunctional species. Many concerns apply to this approach, however, and there is no guarantee that the changes in spectroscopic properties of such species reflect the ones sought in a dependable way.[16,17]

Likewise, ^{1}H NMR chemical shifts at different acid concentrations can be used to build titration curves for quantitative studies.[6,7,9,11] The problem is that such changes occur for all protons and heteronuclei "reasonably close" to the ionization site. It has often been assumed that the chemical shift of the actual protonation site changes to a larger extent than those of other sites. However, there is no guarantee that an observed change in chemical shift can be per se ascribed to the formation of a specific ionic species. For instance, since the nitrogen in aliphatic amines is deshielded by 10−20 ppm upon protonation, one would erroneously conclude that *N*-methylacetamide and *N*,*N*-dimethylacetamide are nitrogen bases too, because their nitrogen is also deshielded by ca. 25 ppm upon protonation. The situation becomes even more puzzling if one considers ^{17}O chemical shifts too, since these undergo a 200 ppm shielding which cannot be compared to a reliable model.[17,18]

In a similar fashion, the ^{14}N NMR signals of ammonium salts are much sharper than those of neutral amines.[19] This is due to the higher local symmetry at a tetrahedral (rather than pyramidal) center, which causes the electric field gradient (efg) at the ^{14}N nucleus to be very low and eventually translates into relatively slow relaxation rates or narrow signals. This criterion can be used to establish the state of ionization of a nitrogen center. A typical result is depicted in Figure 3, which reports the ^{14}N spectra of neutral and protonated 4-aminopyridine. The signal of the amino nitrogen is not much affected by protonation (26 ppm deshielding). By far, the most prominent change is observed for the ring nitrogen, which becomes shielded by ca. 100 ppm and much narrower (longer T_1). This

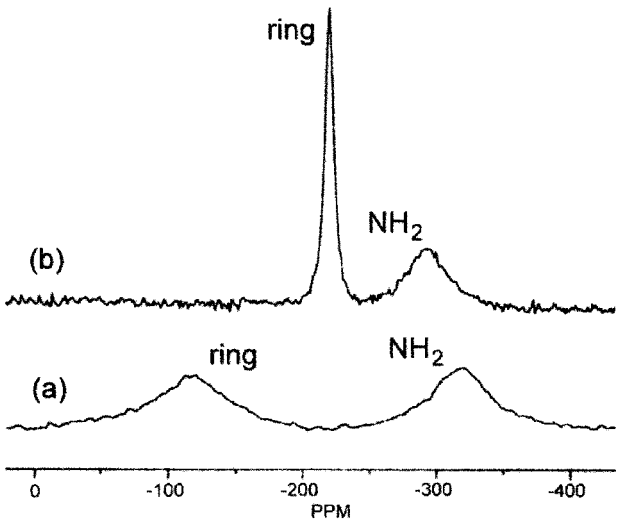


FIGURE 3. ^{14}N NMR spectrum of 4-aminopyridine in aqueous (a) and acidic (b) solution.

comparison allows one to conclude that 4-aminopyridine is predominantly protonated at the ring nitrogen.[1,18]

However, extending these concepts is not straightforward. One can legitimately wonder whether the nitrogen environment in an *N*-protonated amide is more or less symmetric than in the neutral or *O*-protonated amide; moreover, for processes such as $R_2C{=}O \rightarrow R_2C{=}OH^+$, $R_2NH \rightarrow R_2N^-$, etc., the direction of the efg change at the involved heteronucleus is difficult to predict by simple arguments. Therefore, although NMR data contain the desired information, this is encoded in a way that requires some a priori knowledge of the change to be expected.

Finally, experimental gas-phase basicity measurements have also been used to probe the energetics of proton transfer for polyfunctional bases and acids.[14,20,21] Such data are directly linked to calculated energies and structures, as follows.

By means of quantum chemical calculations one can estimate the relative stability of the ions deriving from ionization at each site, no matter how improbable their occurrence in solution may be, and the changes in spectroscopic properties occurring upon ionization. Even though it is possible to compute proton affinities to chemical accuracy, this is not strictly necessary for studies in solution, since the solvation of ionic species differing only in the protonation site may affect their stability to a larger degree.[22,23] This recognition, of course, opens the question of how to model such solvation energies. Recent work has demonstrated that continuum solvent models (where the solvent is represented by a continuous medium of given dielectric permittivity in which the solute is placed) are a convenient method to deal with such effects.[24] We have employed such methods in several instances, after verifying that they successfully coped with the primal benchmark (the basicity order of alkylamines in the gas and water phases).[17] However, the continuum-solvent approach is not appropriate if one is interested in hydrogen bonding in inert solvents, where the specific donor−acceptor interaction must be investigated.

The relevant NMR properties to calculate are the nuclear shielding, which is related to the chemical shift, and the electric field gradient (efg) at the nucleus, which is connected to the line width and T_1 of the signals of quadrupolar ($I > 1/2$) nuclei.[25]

The chemical shift δ is related to the nuclear shielding σ through a reference compound as $\delta = \sigma_{ref} - \sigma$. The shielding tensor σ contains a diamagnetic (σ_d) and a paramagnetic (σ_p) component, the latter being overwhelming for practically all nuclei beyond the proton. By its very nature, the structural dependence of σ_p (unlike that of σ_d) is so capricious that trends in chemical shifts of heteronuclei often defy chemical intuition. However, there are now efficient and reliable techniques for such calculations by ab initio or DFT methods.[25]

The largest principal component of the efg tensor (q_{zz}) is related to the nuclear quadrupolar coupling constant $\chi = e^2Qq_{zz}/h$ (Q is the nuclear quadrupole moment), but the longitudinal relaxation rate in solution is actually determined also by the asymmetry parameter $\eta = |q_{xx} - q_{yy}|/q_{zz}$, so that $1/T_1 = K\chi^2(1 + \eta^2/3)$; hereafter, we will denote $\chi^2(1 + \eta^2/3)$ as χ_{eff}.[17,19,26]

The relaxation of spin 1/2 nuclei is also quite useful. For such nuclei (notably ^{1}H and ^{15}N), changes in the dipolar relaxation rate are readily translated into the desired information, since $1/T_1^{DD} \propto 1/r_{XH}^6$, where, typically, r_{XH} is the distance between the X nucleus and a nearby hydrogen.[26] Since the addition or removal of a proton may drastically alter this value, deprotonation can, for instance, be highlighted by an increase in T_1.[16]

The experimental/computational protocol can be summarized as follows: (a) The chemical shift and relaxation time T_1 of the NMR signal of each conceivable ionization site are determined under neutral and ionizing conditions, thus obtaining the respective changes $\Delta\delta = \delta(BH^+) - \delta(B)$ and $T_1(B)/T_1(BH^+)$. (b) $\Delta\delta$ is then compared with the shielding difference $\sigma(B) - \sigma(BH^+)$ calculated for the neutral and all ionized forms. (c) If the involved nucleus is quadrupolar, the T_1 change is compared with the calculated efg change $\chi_{eff}(BH^+)/\chi_{eff}(B)$. Otherwise, the dipolar contribution to T_1 is extracted with an NOE measurement.

Finally, by the comparison of calculated and experimental spectral changes one can infer the probable structure of the ion. In this way we circumvent the difficulties inherent in the accurate calculation of absolute values of σ and χ,[25] but it should be kept in mind that the above comparisons are expected to hold within the scope of the respective theoretical methods (for instance, solvent effects are not included).

Sites of Protonation of Polyfunctional Bases: Unsymmetrical Hydrazines. It is assumed[1] (from indirect evidence) that alkyl hydrazines are protonated at the most substituted nitrogen (N-1; $R-NH_2^+-NH_2$), and aryl hydrazines at the least substituted one (N-2; $Ar-NH-NH_3^+$). However, gas-phase calculated basicities are quite similar, which indicates that the preference is largely dictated by solvation, as confirmed by continuum solvent calculations. Although the above picture is found to hold in general, we were able to show that Me_2NNH_2 and 4-methoxyphenylhydrazine are significantly protonated at both N-1 and N-2.[27]

Amides. Carboxylic amides are known to be oxygen bases, but much less is known about other amide types, e.g., sulfinamides, nitrosamines, etc.[17−19,23,28] All such bases bear at least two protonation sites, i.e., the nitrogen and the acid residue (often an oxygen),[29] as in Chart 1. The questions then are as follows: (a) Are amides nitrogen or oxygen bases? (b) Is this an intrinsic molecular property or is it again dictated by solvation?

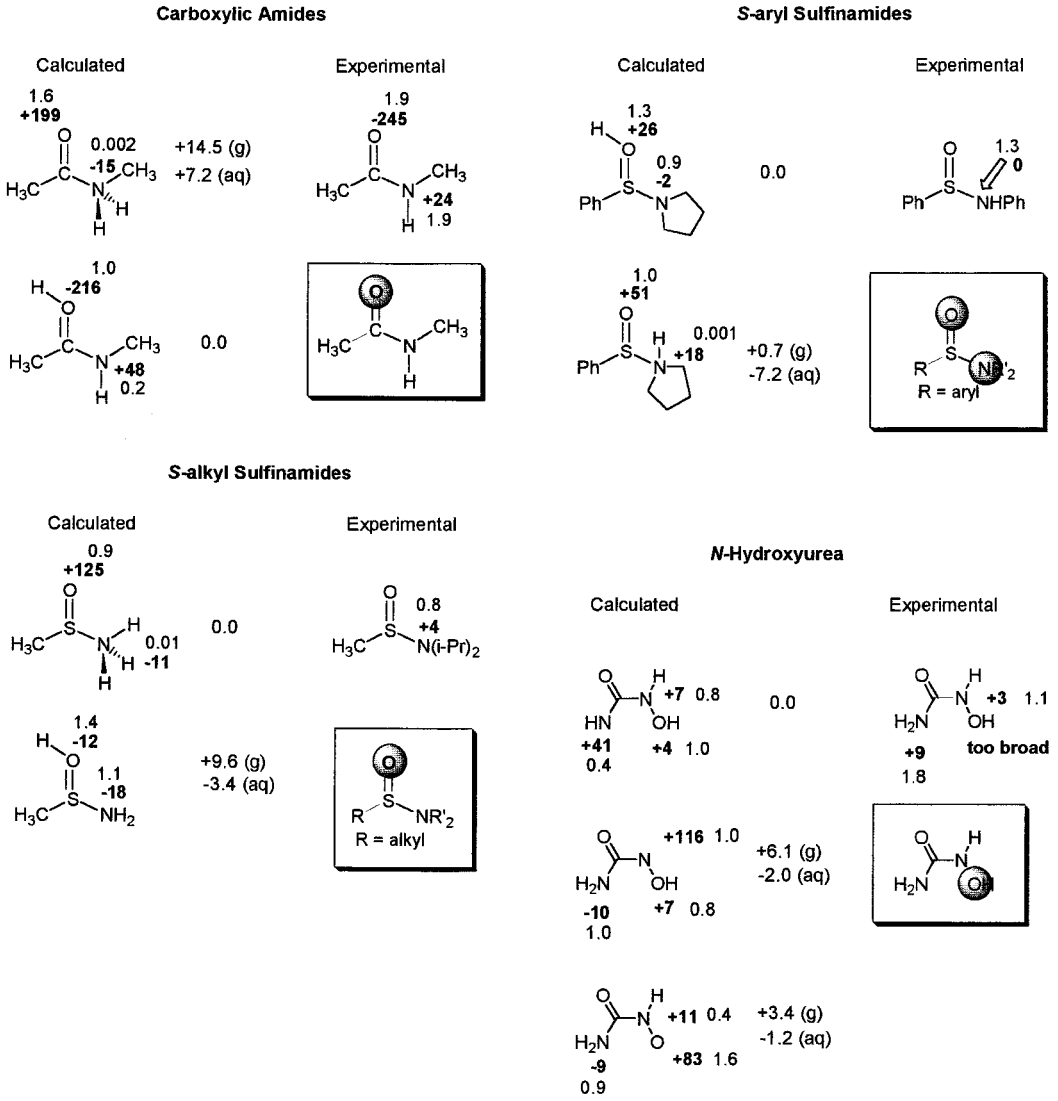
Chart 1 also shows the calculated energetics of protonation and the NMR changes predicted theoretically for carboxylic amides.[17] The intrinsically stronger *O*-basicity is borne out, as well as a substantial stabilization in water of the *N*-protonated form, since the energy gap is reduced, albeit not overturned. Interestingly, in small-ring lactams the calculated energy gap is much smaller than in acyclic amides,[20] but so far no experimental evidence has been obtained in support of *N*-protonation.

NMR properties offer conclusive evidence. Both the ^{14}N and, especially, ^{17}O chemical shifts are affected in opposite directions by *N*- or *O*-protonation. *N*-Protonation causes a marked decrease in the efg at nitrogen (as typical for amines); however, the change for *O*-protonation is only slightly smaller. More disquietingly, efg changes at *oxygen* are larger when the *nitrogen* is protonated. Experimental results fully agree with these predictions, since the $\Delta\delta(^{17}O)$ for protonation is −245 ppm, and only slight changes in the T_1 of ^{14}N are found, confirming *O*-protonation.

Hence, the combination of calculated energies and NMR properties, when compared with the corresponding experimental data, provides the correct information even when chemical intuition would hardly assist in the interpretation of NMR data.

This analysis has been extended to the very heterogeneous family of non-carboxylic amides. We present sulfinamides as a case history. The results obtained in our first study[28] (no change of ^{14}N chemical shift and T_1, and computed energetics) indicated *O*-protonation (Chart 1). Later, Mikołajczyk and co-workers[30] challenged these results from IR and ^{15}N evidence, which prompted us to investigate ^{17}O spectra.[17] Surprisingly, the $\Delta\delta(^{17}O)$ was also close to zero; this circumstance would lend much support to *N*-protonation, except that the calculated shieldings for the *O*-protonated species predict the same. (Ironically, had we run ^{17}O NMR in the first place, the data would have been incomprehensible without the help of shielding calculations, having $\Delta\delta \approx 0$ for both sites!). The study was then extended to some *S*-aryl sulfinamides studied by Mikołajczyk, whereby it turned out that the two data sets simply cannot be compared. The basicity of N and O in sulfinamides depends so strongly on the substitution at sulfur and the solvent that for *N*-pyrrolidinylbenzenesulfinamide the two ions differ by just 0.7 kcal/mol in the gas phase. Hence, this is a case for solvation exerting a strong effect on the energetics, since such a close energy gap may be easily overturned in solution (or even by different solvents). Therefore, the possibility for protona-

Chart 1. Calculated Relative Energies and Changes in NMR Parameters Occurring upon Ionization of Selected Polyfunctional Bases and Acids[a]



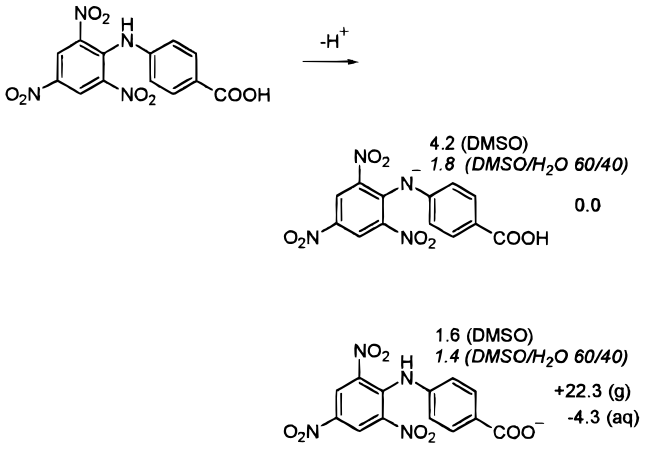
[a] Numbers in boldface are the nuclear shielding ($\sigma(B) - \sigma(BH^+)$) or the chemical shift ($\delta(BH^+) - \delta(B)$) change; numbers in normal typeface are the effective nuclear quadrupolar coupling constant ($\chi_{eff}(BH^+)/\chi_{eff}(B)$) or the T_1 ($T_1(B)/T_1(BH^+)$) change for the nucleus indicated. Calculated energies (kcal/mol) are referenced to one of the ionic species. The ionization site is circled.

tion at either site should be decided on a case-by-case basis.

Sites of Deprotonation of Polyfunctional Acids. There has been considerable debate as to whether hydroxamic acids (R−CO−NHOH) are nitrogen or oxygen acids;[16] *N*-hydroxyurea (H_2N−CONHOH) even has three deprotonation sites (Chart 1). The deprotonation site of aceto- and benzohydroxamic acids was determined by recourse to ^{17}O and ^{15}N NMR. Thus, the ^{15}N signal in MeCONHOH failed to show any T_1 increase (which would have indicated removal of its attached hydrogen), and showed an enormous increase in the ^{17}O line width of the hydroxyl-amino oxygen. The results for PhCONHOH were just the opposite. Hence, these acids have different deprotonation sites (O and N, respectively) even though in the gas phase *N*-deprotonation is favored in both cases. With the help of shielding calculations we could probe the more complicated case of *N*-hydroxyurea, whose ionized forms (Chart 1) differ very little in energy.[31] By comparing experimental and calculated ^{17}O and ^{14}N chemical shifts and, especially, line widths, we could highlight its predominant *O*-deprotonation. Once again, the final result cannot be generalized in terms of a prescribed behavior for a given functional group.

The last case history[32] concerns a seemingly unlikely proposition: i.e., is an amine a stronger or weaker *acid* than a carboxylic acid? The answer is, again, "it depends". The amino group in 2,4,6-trinitrodiphenylamine-4′-carboxylic acid (**1**) (Scheme 1) is a relatively strong acid; its nitrogen anion is weakly solvated owing to charge delocalization, and may compete with the −COOH group if the solvent cannot provide the stabilization needed for the more strongly solvated $-COO^-$. This differential stabilization can be provided just by a change in the ratio of the components in a water/DMSO mixture. Thus, in DMSO and the gas phase, **1** is a nitrogen acid, but an oxygen acid in 60% DMSO/water (as shown again by ^{15}N relaxation). This reversal is dictated entirely by the solvent,

Scheme 1. Deprotonation of 1[a]



[a] Calculated energies (kcal/mol) are referenced to the *N*-deprotonated species. The ^{15}N T_1 values (s) for the amino nitrogen are also given.

since gas-phase calculated acidities are reversed in order (*N*-deprotonation favored by 22 kcal/mol), and is predicted by continuum-solvent calculations (*O*-deprotonation in water or DMSO favored by 4 kcal/mol).

Similarly, a large solvent effect was demonstrated for pyrrole- and indolecarboxylic acids, which are deprotonated at −COOH in water (as one expects), but may behave as nitrogen or oxygen acids in the gas phase, the calculated gap between their intrinsic acidities being 1−3 kcal/mol.[21]

Patterns of NMR Properties and Solvation Energies. Although NMR data can be interpreted in terms of the nature of the proton-transfer process, such information does not follow general patterns, and theoretical modeling is necessary for species as close as possible to the ones that can actually be investigated.

However, whereas NMR properties are not very sensitive to substitution at the amide group,[17] the energetics are deeply affected. We have already seen the effect of replacing alkyl with aryl for hydrazines and sulfinamides. The other major effect is observed when the basicity of species differing by the degree of alkylation at nitrogen (e.g. H_2NCN vs Me_2NCN, H_2NNO vs Me_2NNO, etc.) are compared, where the least substituted ion is more stabilized in water,[17] for the same reasons which lie at the root of the larger aqueous basicity of Me_2NH over Me_3N. This increased stability may be so large that differently substituted species may have different ionization sites.

When the substitution pattern is not an issue, if the intrinsic stabilities differ by more than ca. 20 kcal/mol, no inversion in the ionization site is expected (carboxamides, sulfenamides), although solvation may reduce this gap. Conversely, when they differ by less than 2−3 kcal/mol (sulfonamides, nitramides, phosphoramides), nonexclusive formation of any ionic species is found with a large solvent influence.[17,23] On the contrary, solvent effects on anions are so large that for hydroxamic acids and **1** the deprotonation site is inverted even though stability differences are 10−20 kcal/mol.

Hydrogen Bonding and Solvation

Hydrogen Bonding. Although a variety of methods exist for probing the formation of hydrogen bonds, it is still difficult to pinpoint the donor and acceptor atoms participating in a specific one. Given the analogies with proton transfer, it is straightforward to extend the concepts seen above. However, hydrogen-bonded systems are inherently more complex, since the energetics are much smaller (multiple hydrogen bonds are in fact quite common), as are the spectral changes at the acceptor atoms (e.g., calculated efg changes are 0.5−0.9). Thus, the experimental data are more difficult to interpret, because changes in the molecular dynamics and solvent effects must be taken into account. However, when this is done, a satisfactory agreement can be reached between calculated efg and experimental T_1 changes.[33]

Preferential Solvation. The solvation shell of a solute dissolved in a solvent mixture may be (and generally is) selectively enriched in one cosolvent. When this happens, the solute is said to be preferentially solvated, and this has an obvious bearing on all its properties related to solvation, since its immediate surroundings may be substantially different from the bulk solution. We have developed and applied a method capable of identifying the preferred cosolvent, and the extent of such a preference.[34,35]

The nuclear Overhauser effect (NOE) between spatially close spins in the same molecule is an established technique for probing structure and conformation. To maximize this effect, intermolecular NOEs are suppressed, overlooked, or considered a nuisance altogether. On the contrary, since nonspecific intermolecular interactions are best probed through the nuclei that are most likely to "feel" each other (generally the protons), one can emphasize intermolecular NOEs in a standard 2D NOESY measurement, and thus extract the useful information contained therein. Whereas Wüthrich and co-workers successfully investigated the solvation of proteins,[36] we concentrated on small molecules.

The intermolecular dipolar relaxation rate is proportional to the spin concentration furnished by the solvent *N*, the mutual diffusion coefficient *D*, and the approach distance *r* as $1/T_1^{DD,inter} \propto N/Dr$, all these factors being related to solvation. As expected, a NOESY spectrum obtained using solvents with low deuterium content and an appropriate mixing time contains cross-peaks at the solute and solvent frequencies, indicating intermolecular cross-relaxation, as in Figure 4. These cross-peaks have different integrated intensities. Is it possible to relate them to the composition of the solvation shell? The answer is yes, provided that all the underlying factors are taken into account. Thus, if a_{AB} and a_{AC} are the cross-peak intensities between solute A and solvents B and C, respectively, their ratio can be calculated from the theory of intermolecular relaxation. Hence, if e.g., $(a_{AB}/a_{AC})_{exptl} > (a_{AB}/a_{AC})_{calcd}$, then the solute will be preferentially solvated by solvent B. This qualitative result can also be recast in a form leading to a

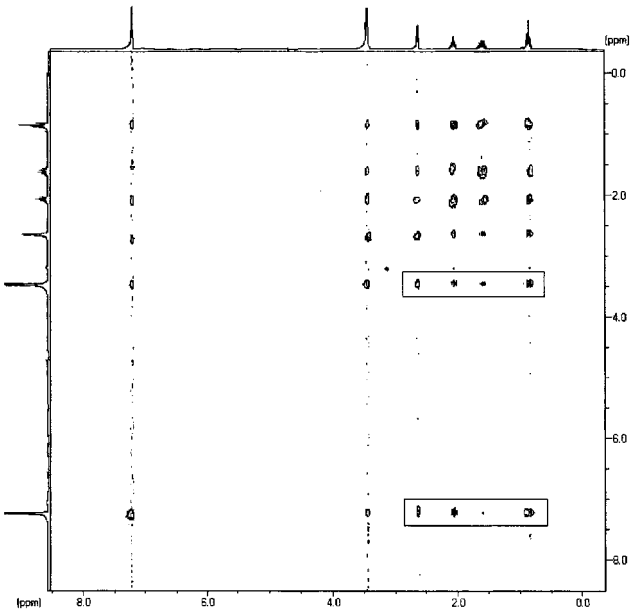


FIGURE 4. NOESY ^{1}H NMR spectrum of *N*-methylbutyramide in 1:1 dioxane/benzene (mixing time 3 s). Intermolecular cross-peaks are highlighted in boxes.

semiquantitative estimate of the enrichment in that solvent.[35]

Such data have revealed several interesting aspects. First, preferential solvation cannot always be understood in terms of a prevailing solute−solvent interaction. Taking phenol as the solute, the preference for DMSO over water is related to the stronger acceptor power of the former solvent. Conversely, its preference for acetonitrile over water is mainly due to the large degree of microheterogeneity in the water/acetonitrile mixture, i.e., fleeting acetonitrile homoaggregates which provide a favorable environment for the largely hydrophobic phenol solute. These findings are confirmed by the analysis of the dependence on the water:organic solvent ratio.

Surprisingly, *N*-methylbutyramide in water/acetonitrile and dioxane/benzene always prefers the least polar component, despite the established notion of amides being polar, hydrophilic substances. This behavior was ascribed to the additional capability of such solvents to stabilize the aliphatic chain of the solute by dispersive interactions, over a moderate capability for dipole−dipole ones. Hence, the striking conclusion that the solvation of molecules possessing both polar and apolar functionalities may be dictated by the "side chain" rather than by the "functional group".

On the theoretical side, owing to their collective nature these phenomena cannot be treated with simple models. MD simulations, however, can be employed to elucidate the microscopic structure of the solvation shell.[37]

Summary and Conclusions

We have investigated proton transfer, hydrogen bonding, and solvation, placing an emphasis on selectivity issues, i.e., the relative basicity or hydrogen-bonding acceptor power of different molecular sites, and preferential solvation in mixed media. All such phenomena involve the approach, or covalent bonding, of hydrogen atoms to some other atom in the probe molecule. Hence, our interest in analyzing the influence of nearby protons on the NMR properties of the acceptor nuclei, whether as changes in chemical shift or relaxation rate. The interplay between theoretical calculations (of energies, structures, and NMR properties) and their experimental counterparts provides a powerful tool for the investigation of such problems. Valuable insight can then be obtained into the factors that determine the preference for a specific proton-transfer process (the close balance between basicity and solvation), or for the preferential solvation of a neutral solute (the competition between hydrogen bonding and dispersive stabilization). We hope to have conveyed the idea that this combined effort provides a reliable framework for further progress in this area.

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AR990149J