Deprotonation of Amides and Polyfunctional Imides Probed by Heteronuclear NMR and Quantum Chemical Calculations

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The site of deprotonation of several types of amide acids (carboxylic amides and imides, sulfonamides, cyanamide, *N*-hydroxyurea) has been investigated by 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 and in water (by the IPCM continuum solvation method). NMR properties (nuclear shielding and electric field gradient) of the involved heteronuclei were calculated and compared with experimental ^{14}N, ^{17}O and ^{33}S chemical shifts and relaxation rates. It is shown that the combination of theoretical and experimental tools allows a reliable prediction of spectral parameters and ultimately of the deprotonation site of polyfunctional acids.

Introduction

Although nitrogen-containing organic compounds are best known for their basic properties, a number of such compounds also exhibit acidic properties.[1] The most important functionality of this kind is the amide group; thus, amides of the type R−C(O)NHR′ can undergo deprotonation to form the resonance-stabilized R−C(O)NR′$^-$ anion. Amides derived from some non-carboxylic acids (e.g. sulfonamides) are even stronger acids than carboxamides, owing to the stronger electron-withdrawing power of the sulfonyl group. The acidity of carboxylic imides is larger than that of similar amides,[1,2] which is generally attributed to the larger degree of resonance stabilization in the anion. However, if more than one amide or imide group coexist in the molecule, one may wonder which one is the preferred site for proton abstraction in a medium of given base strength.

Several approaches have been advocated to infer the structure of the protonated form of polyfunctional bases and acids, e.g. trends in substituent effects for compounds under study and known monofunctional bases, patterns of change of the chemical shift of various nuclei, especially in connection with model compounds whose ionization site is unambiguous. However, the interpretation of such results is hampered by their empirical nature, as we have recently discussed.[3]

In principle, the site of protonation can be calculated, because quantum chemical methods can provide the relative energies and proton affinities of ionic species deriving from protonation at all sites.[4,5] However, the presence of the solvent will generally affect the relative stability of ions, which will in turn affect the comparison with experimental data in solution. A convenient way of modeling solvent effects is provided by continuum methods;[6] 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. Lately, the Isodensity Polarizable Continuum Method (IPCM), which employs a solute-shaped cavity, has been proposed as a general-purpose way of calculating the solvent effect on chemical equilibria and reactions.[7]

In previous works,[3,8−12] we have shown that the general problem of identifying the ionization site in a polyfunctional molecule can be attacked by analyzing the changes in the NMR chemical shift, relaxation time (T_1) or the line width ($W_{1/2}$) of all the nuclei which may be ionization sites (generally N, O, S), because these spectral parameters depend on the nature of the ionic species formed by the proton-transfer process. However, it must be emphasized that these changes are generally quite complex, and require a theoretical modelling of such data, which can be done by ab initio quantum chemical methods. Hence, the combination of ab initio calculations (yielding the relative stability of all possible ionic species and NMR-spectroscopic properties), and the experimental determination of the above-mentioned NMR parameters, generally allows to identify the preferred ionization site without recourse to unwarranted assumptions or empirical criteria.

In fact, we have previously applied the above approach in a number of instances (e.g. the protonation of nitrogen heterocycles,[8] hydrazines,[9] various amide types,[3,8,10] or the deprotonation of hydroxamic acids[11] and [(trinitrophenyl)amino]benzoic acids[12]). In particular, we have shown that the relative solvation energy of the ions that may form (e.g. a nitrogen or an oxygen anion) may have a substantial impact on the preferred ionization site in solvents where strong ion-solvent interactions take place, like water or DMSO.[9,12]

Following our interest in this area, we present herein our results concerning the deprotonation of nitrogen acids,

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which is aimed at: (a) assessing the performance of the IPCM method in predicting relative proton-transfer energetics of anions in water; (b) assessing whether calculated NMR properties match the analogous ones for deprotonation in water, and establishing trends in NMR properties, especially of nitrogen; (c) investigating the site of deprotonation in some polyfunctional amide-type acids.

Methods

The NMR relaxation rate of quadrupolar nuclei ($I > 1/2$; e.g. ^{14}N, ^{17}O, ^{33}S) in the extreme narrowing limit depends on the electric field gradient (efg) at the nucleus according to Equation 1.

$$1/T_1 = (3\pi^2/10)[(2I + 3)/I^2(2I - 1)]\chi^2(1 + \eta^2/3)\tau_c \quad (1)$$

$\chi = eQq_{zz}/h$ is the nuclear quadrupolar coupling constant, q_{zz} is the largest principal component of the efg tensor $\boldsymbol{q}$, $\eta = |q_{xx} - q_{yy}|/q_{zz}$ is its asymmetry parameter and τ_c the rotational correlation time.[13] If deprotonation causes an efg change, this may result in a change in T_1[5,13] which is normally reflected also in a change in the line width $W_{1/2}$, since for these nuclei the quadrupolar mechanism (Equation 1) is the dominating relaxation pathway, and the relationship $1/T_1 = \pi W_{1/2}$ holds.[13] However, the line width is difficult to measure accurately, and may be prone to errors if spurious factors alter the line shape. Hence, whenever possible we have carried out the determination of T_1.

In order to translate the efg into relaxation times, the correlation time must either be unaffected or change in a known way. In the cases dealt with herein, the comparison is made between weakly acidic solutions (0.1 M HCl) and 1 M NaOH, whose viscosity ($\eta = 1.2$ mPa s)[14] is 20% larger than that of water. Hence, relaxation times in such basic media must be slightly corrected by that factor to be compared with the data in 0.1 M HCl, whose viscosity[14] is not appreciably different from that of water.

Changes in chemical shift can also be related to the structure of the ion being formed; however, we have previously found[3] that the patterns of change of chemical shifts are unpredictable, and require a previous calculation of the nuclear shielding tensor in order to interpret them in terms of chemical structure.

Theoretical Methods and Calculations

The geometry of all species was optimized at the HF/6-311++G(d,p) level. For the calculation of NMR properties and energies, the 6-311++G(2d,2p) basis set was used; nuclear shieldings were calculated with the GIAO-HF method,[15] and electric field gradients at the Hartree-Fock level. For polyfunctional acids, relative energies of anionic species in the gas phase and water were calculated with the MP2(FC) and HF-IPCM/6-311++G(2d,2p) methods,[7] respectively, assuming $\varepsilon = 78.5$ (see below).

Although the efficiency of quadrupolar relaxation is generally expressed by the value of χ, the T_1 in solution (where rotational averaging takes place) is determined by $\chi_{eff} = \chi^2(1 + \eta^2/3)$, whose dimensions are s^{-2} (or MHz^2). In fact, χ_{eff} is directly linked to T_1 or $W_{1/2}$, since $W_{1/2} \propto 1/T_1 \propto \chi^2(1 + \eta^2/3)$ (Equation 1). Hence, if the correlation time is kept constant in the solutions used for measurements on the neutral (AH) and deprotonated (A^-) acid, the equalities $\chi_{eff}(A^-)/\chi_{eff}(AH) = W_{1/2}(A^-)/W_{1/2}(AH) = T_1(AH)/T_1(A^-)$ hold. For this reason, throughout this paper we will report calculated efg′s as effective nuclear quadrupolar coupling constant (χ_{eff}) and their changes $\chi_{eff}^R = \chi_{eff}(A^-)/\chi_{eff}(AH)$ to allow for a comparison with line widths in solution. The following values of Q were used in the calculation of χ_{eff}: ^{14}N, 2.02; ^{17}O, −2.558; ^{33}S, −6.78 fm^2.[14]

Calculated shieldings (σ) are reported as the isotropic component of the shielding tensor, and its change from neutral to protonated form $\Delta\delta = \sigma(AH) - \sigma(A^-)$.

It must be recalled that calculated χ_{eff} and σ values pertain to the isolated species, whereas solution T_1′s and chemical shifts depend on the corresponding value in solution. As the efg in molecules is largely intramolecular, we expect the two values to be similar. Similar considerations should also apply to chemical shifts, although much less is known in this case.

Calculation of Solvent Effects

The IPCM method models the solute with a shape iteratively computed from the electron density.[7] Since we are only concerned with relative acidities, solvent effects have been calculated only for polyfunctional acids. Hence, if we consider an acid AH capable of forming two conjugate bases (B_1 and B_2) by deprotonation at different sites, the energy difference between each anion as an isolated species and in the chosen continuum is an estimate of its solvation energy, which allows one to obtain their energy difference in water, i.e. a quantity which should be a better model of the expected stability difference in a given solvent. In a previous paper,[3] we have shown that a good approximation to the desired quantity can be obtained as follows. If we denote gas-phase and aqueous relative energies as $\Delta E_{(g)}$ and $\Delta E_{(aq)}$, respectively, a Born−Haber cycle shows that the latter can be expressed as in Equation 2.

$$\Delta E_{(aq)} = \Delta E_{(g)} + (E_2^s - E_1^s) \quad (2)$$

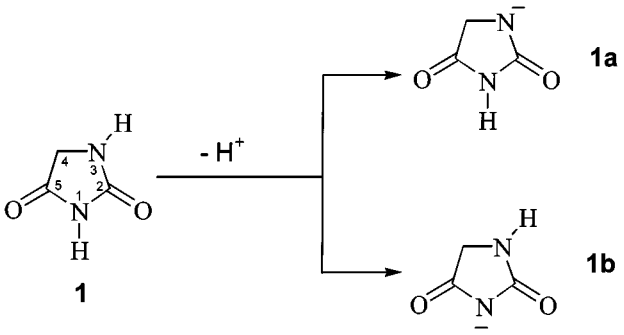
E_i^s is the solvation energy of species i (B_1 or B_2). If $\Delta E_{(g)} = E_2^{MP2} - E_1^{MP2}$ is the relative energy in the gas phase, and $E_i^s = E_i^{IPCM} - E_i^{HF}$ is the solvation energy of species i, in turn given by the difference in energy in solution (from an IPCM calculation) and in the gas phase (from a Hartree−Fock calculation with the same basis set), $\Delta E_{(aq)}$ can be determined from a combination of MP2 and HF-IPCM data, as in Equation 3.

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

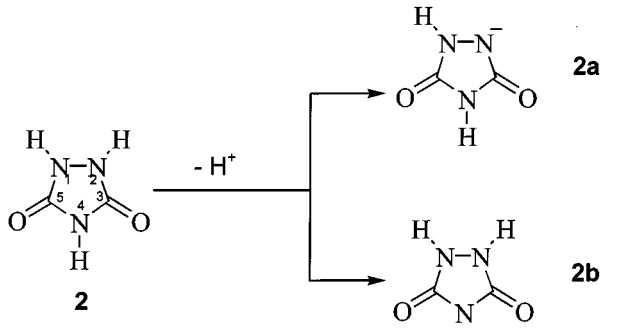
Results and Discussion

Because our goal is a comparison with experimental NMR data in solution, all species investigated were chosen to be amenable to experimental study. The study includes both simple, monofunctional nitrogen acids (HCN, NH_2CN, CF_3CONH_2, $MeSO_2NH_2$, $PhSO_2NH_2$, succinimide) and polyfunctional ones (hydantoin, urazole, *N*-hydroxyurea). For comparison, a simple nitrogen acid ($MeNH_2$) was also investigated theoretically. The values of pK_a in water for the acids investigated (HCN: 9.21;[14] NH_2CN: 16.9 in DMSO;[2,16] CF_3CONH_2: 10.36;[17] $MeSO_2NH_2$: 10.8;[18] $PhSO_2NH_2$: 10.0;[19] succinimide: 9.35;[20] hydantoin: 9.12;[21] urazole: 5.8;[22−24] *N*-hydroxyurea: 10.6[25]) are such that all are > 99% deprotonated at pH = 14 (1 M NaOH). The spectra of neutral acids were obtained in 0.1 M HCl to suppress ionization.

The last three acids [hydantoin (**1**), urazole (**2**), *N*-hydroxyurea (**3**)] possess more than one acidic site. The structures of these acids and their anions are sketched in Schemes 1−3.

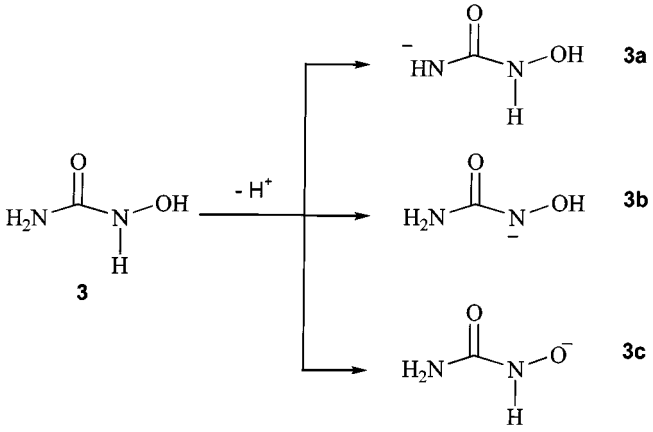


Scheme 1. Numbering and deprotonated forms of hydantoin (**1**)



Scheme 2. Numbering and deprotonated forms of urazole (**2**)

Relative energies in the gas phase and solution for all anionic species deriving from the deprotonation of polyfunctional acids (Equation 3), and calculated NMR properties for neutrals and anions, are reported in Tables 1 and 2. The calculated geometries of all species are available on the WWW under http://www.wiley-vch.de/home/eurjoc in PDF format or from the author in PDB format.



Scheme 3. Deprotonated forms of *N*-hydroxyurea (**3**)

NMR Measurements

The nuclei experimentally studied by NMR are ^{14}N (I = 1), ^{15}N (I = 1/2), ^{17}O (I = 5/2) and ^{33}S (I = 3/2). Where necessary, signal assignment was made by comparison with reference data, if available, or by comparison with calculated shieldings. Whenever possible we have determined T_1 in addition to $W_{1/2}$, because of its higher accuracy. For ^{17}O signals at natural abundance (0.037%) and the broad ^{14}N signals of $PhSO_2NH_2$ (poorly soluble in aqueous media), the S/N ratio is too low to allow T_1 measurements; hence, line widths were measured and converted to $T_1 = 1/\pi W_{1/2}$. Experimental NMR data are collected in Table 3.

Hydrogen Cyanide

HCN is, strictly speaking, a carbon acid, but is interesting owing to the large participation of nitrogen in stabilizing the negative charge. The nitrogen nucleus in CN^- is predicted to be slightly deshielded ($\Delta\delta$ = +8 ppm), and the efg is scarcely affected by deprotonation, as χ_{eff}(N) in CN^- is smaller than in HCN by only a factor of 0.8.[5]

HCN was generated by careful acidification (with concd. aq. HCl) of an aqueous solution of KCN in a screw-cap NMR tube. Because of the hazard of this manipulation, we only ensured that an acidic pH was attained, but no attempt was made to check its value. The ^{14}N signal of HCN is very sharp (as known for cyano nitrogen atoms), but for CN^- it is even sharper (χ_{eff}^R = 0.4). Deprotonation causes a 29-ppm deshielding. Hence, although experimental NMR properties are enhanced with respect to the calculated ones, they follow the same trend.

Cyanamide

Deprotonation of the neutral yielding the $^-$HNCN anion is calculated to entail a modest shielding of the amino N ($\Delta\delta$ = −17 ppm) and a large shielding of the cyano N ($\Delta\delta$ = −85 ppm). However, if fast proton exchange between the two nitrogen atoms is allowed for, their average shield-

Table 1. Acidity of polyfunctional amides and imides in the gas phase and in water (HF-IPCM and MP2 calculations)[a]

Species	ΔE (HF)	ΔE (IPCM)	ΔE (MP2)	ΔE (aq)[b]	Deprot. site in gas phase/water
Hydantoin (**1**)					imido N
1a (amino deprot.)	5.4	9.6	4.2	8.4	
1b (imino deprot.)	(0.0)	(0.0)	(0.0)	(0.0)	
Urazole (**2**)					N-1
2a (amino deprot.)	(0.0)	(0.0)	(0.0)	(0.0)	
2b (imino deprot.)	10.9	2.2	13.3	4.6	
N-Hydroxyurea (**3**)					NH_2/*N*O
3a ($^-$HN−CO−NHOH)	(0.0)	(0.0)	(0.0)	(0.0)	
3b ($H_2N-CO-NOH^-$)	6.0	−2.1	6.1	−2.0	
3c [$H_2N-CO-N(H)O^-$]	2.8	−1.8	3.4	−1.2	

[a] Relative energies in kcal/mol; see Equation 3 for definitions. − [b] See Equations 2 and 3.

ing (σ = 195.5 ppm) is such that $\Delta\delta(NH_2) = +61$ ppm and $\Delta\delta(CN) = -162$ ppm.

The second deprotonation yields the $[N=C=N]^{2-}$ dianion, in which both nitrogen atoms become equivalent; its shielding is rather close to that of NH_2 in the neutral. The formation of $^-$NHCN somewhat decreases the efg at NH_2, and largely decreases that at CN. Conversely, the efg in NCN^{2-} is much lower than for all other species (χ_{eff}^R = $2-3 \times 10^{-4}$ MHz^2), and is similar to that in ammonium ions.[5]

The ^{14}N spectrum of neutral cyanamide was obtained in water, rather than in dilute aqueous HCl, owing to its great sensitivity to hydrolysis in such media.[3] It shows signals at $\delta = -200$ (CN) and $\delta = -368$ (NH_2). In 1 M NaOH, a single ^{14}N signal appears at $\delta = -306$ [i.e. $\Delta\delta(NH_2) = +62$ ppm and $\Delta\delta(CN) = -106$ ppm], and sharper than both. This is consistent with the formation of either $[N=C=N]^{2-}$ or $[H-N=C=N]^-$ with fast proton exchange, as the predicted changes are rather similar. The expected increase in T_1 is indeed found, and its magnitude is close to the expected average change for $[H-N=C=N]^-$. In summary, deprotonation of cyanamide can be conveniently monitored by ^{14}N NMR; however, a precise distinction between mono- and di-deprotonated forms is hindered by the equivalence of both sites in both anions.

Monofunctional Amides and Imides

(a) Trifluoroacetamide

It was previously shown[4] that the deprotonation of formamide at each of its two non-equivalent NH_2 hydrogen atoms gives rise to two anions differing by 3.5 kcal/mol in energy, in favor of the isomer having the remaining hydrogen atom *cis* to the oxygen atom, whereas efg values differ very little. Deprotonation causes a decrease of χ_{eff}(N) (by a factor of 0.5) and also of χ_{eff}(O) (by a factor of 0.7).[5] However, the acidity of normal amides is too small to be conveniently measured in aqueous solution,[2] whereas CF_3CONH_2 is much stronger. Since there is no guarantee that the same spectral changes apply also in this case, we also calculated the energy and NMR properties of the neutral and deprotonated forms. Calculations for CF_3CONH_2 yielded essentially the same results previously known for $HCONH_2$: Thus, also in this case deprotonation gives preferentially the anion with the N−H *cis* to the oxygen atom, with the same stability difference (3.5 kcal/mol). Changes in efg are also very similar, the largest variation being predicted for N (a 50% decrease). Deprotonation is predicted to cause a sizable deshielding at N ($\Delta\delta$ = 63 ppm), and a large shielding at O ($\Delta\delta = -132$ ppm); changes within 5 ppm are calculated for the *trans* isomer, too. It proved impossible to provide an experimental verification, as CF_3CONH_2 undergoes rapid hydrolysis in 1 M NaOH. In fact, a ^{14}N-NMR spectrum taken immediately after dissolution showed a weak signal at $\delta = -275$ (as in 0.1 M HCl) and an intense one at $\delta = -376$, increasing with time. Although these results indicate an ongoing reaction, the constancy of the amide chemical shift also suggests that the base concentration used is too weak to deprotonate the amide to any appreciable extent. To further prove this statement, we tried to obtain a spectrum in 10 M NaOH, but only a peak at $\delta = -380$ was observed. The latter, falling in the typical amine region, is due to NH_3, as expected and confirmed by a spectrum of 30% NH_4OH ($\delta = -380$, $W_{1/2}$ = 142 Hz). Hence, CF_3CONH_2 is rapidly hydrolyzed and is not significantly deprotonated in 1 M NaOH. This finding sharply contrasts with the proposed p*K* value of 10.36,[17] and suggests that the latter should be revised.

(b) Succinimide

For this model imide acid, calculations predict a 62-ppm deshielding and a 78-ppm shielding for O and N, respectively. On the other hand, the efg change is very small for O, and none for N.

When dissolved in 1 M NaOH, succinimide readily forms a white gelatinous precipitate; the ^{14}N-NMR spectrum, even of a freshly prepared solution, shows two signals at $\delta = -140$ and -270. The succinimidate peak can be assigned from the above calculated values as the one at $\delta = -270$, which results in a $\Delta\delta$ of −65 ppm with respect to the neutral, in agreement with the calculation. T_1 values are also in agreement, as the value in NaOH (1.0 ms, or 1.2 ms corrected for viscosity) is similar to the one in HCl (1.4 ms), as predicted.

Table 2. Calculated NMR properties of O, N and S nuclei in acids and their deprotonated forms

Species	Nucleus	σ[a]	$\Delta\delta$[b]	q_{zz}[c]	η[d]	χ_{eff}[e]	χ_{eff}^{R}[f]
$MeNH_2$	N	254.7	–	1.126	0.157	28.8	–
$MeNH^-$	N	242.2	+12.5	0.939	0.011	19.9	0.7
HCN	N	−28.2	–	1.222	0	33.6	–
CN^-	N	−36.3	+8.2	1.091	0	26.8	0.8
NH_2CN	NH_2	255.8	–	1.164	0.335	31.7	–
	CN	33.0	–	0.925	0.670	22.1	–
^-HNCN	NH	272.6	−16.8	−0.780	0.647	15.6	0.5
	CN	118.0	−85.0	−0.540	0.947	8.5	0.4
NCN^{2-}[g]	N	227.6	+28.2, −194.6	0.0176	0	0.007	2.2×10^{-4}, 3.2×10^{-4}
CF_3CONH_2	N	181.1	–	−0.450	0.180	4.6	–
	O	−52.2	–	1.744	0.219	112	–
CF_3CONH^-	N	117.9	+63.2	0.575	0.999	9.9	2.1
	O	79.4	−131.6	1.428	0.549	81.0	0.7
Succinimide	O	−77.3	–	1.709	0.223	107	–
	N	95.2	–	0.720	0.093	11.7	–
Deprotonated succinimide	O	−15.0	+62.3	1.603	0.100	93.1	0.9
	N	17.5	−77.7	0.701	0.482	11.9	1.0
$MeSO_2NH_2$[h]	O	148.9	–	−1.338	0.135	65.0	–
	N	174.5	–	1.105	0.387	28.9	–
	S	215.3	–	−0.811	0.600	187	–
$MeSO_2NH^-$[i]	O	143.5, 160.0	+5.4, −11.1	−1.487	0.096	80.1	1.2
	N	169.1	+5.4	−0.886	0.606	19.8	0.7
	S	190.7	+24.6	−0.532	0.889	90.7	0.5
Hydantoin (**1**)	O-2	58.2	–	1.478	0.178	79.7	–
	O-5	−56.7	–	1.675	0.175	102	–
	N-1	122.3	–	0.839	0.041	15.9	–
	N-3	192.8	–	1.148	0.111	29.8	–
1a	O-2	129.8	−71.6	1.318	0.719	73.6	0.9
	O-5	25.8	−82.5	1.541	0.186	86.8	0.8
	N-1	133.2	−10.9	0.741	0.307	12.8	0.8
	N-3	109.7	+83.1	−0.810	0.223	15.0	0.5
1b	O-2	82.0	−23.8	1.458	0.387	80.6	1.0
	O-5	18.3	−75.0	1.534	0.221	86.4	0.8
	N-1	61.5	+60.8	0.621	0.963	11.4	0.7
	N-3	191.8	+1.0	1.184	0.072	31.6	1.1
Urazole (**2**)	O	93.4	–	1.398	0.354	73.5	–
	N-4	138.6	–	0.906	0.067	18.5	–
	N-1,N-2	165.4	–	1.453	0.524	51.9	–
2a[i]	O-3, O-5	169.6, 159.8	−76.2, −66.4	−1.246, 1.282	0.990, 0.864	74.1, 74.4	1.0
	N-4	132.1	+6.5	0.862	0.170	16.9	0.9
	N-1, N-2	136.2, 81.0	+29.2, +84.4	1.089, −1.292	0.242, 0.033	27.2, 37.6	0.6
2b	O	130.6	−37.2	1.346	0.675	75.4	1.0
	N-4	86.8	+51.8	−0.672	0.774	12.2	0.7
	N-1,N-2	166.8	−1.4	1.463	0.475	51.8	1.0
N-Hydroxyurea (**3**)	C*O*	55.2	–	1.472	0.239	79.7	–
	N*O*	268.5	–	−2.421	0.902	269	–
	NH_2	193.1	–	0.959	0.188	21.0	–
	*N*O	121.8	–	1.526	0.745	62.2	–
3a	C*O*	131.0	−75.8	1.275	0.864	73.3	0.9
	N*O*	264.7	+3.8	−2.422	0.900	269	1.0
	NH	151.6	+41.5	−0.632	0.404	9.5	0.4
	*N*O	114.8	+7.0	1.458	0.807	52.3	0.8
3b	C*O*	144.4	−89.2	1.294	0.918	77.4	1.0
	N*O*	261.0	+7.5	2.204	0.840	217	0.8
	NH_2	203.0	−9.9	0.949	0.168	20.5	1.0
	*N*O	5.7	+116.1	−1.688	0.183	64.9	1.0
3c	C*O*	151.3	−96.1	1.274	0.934	75.7	0.9
	N*O*	185.1	+83.4	3.405	0.066	419	1.6
	NH_2	201.9	−8.8	0.930	0.250	19.9	0.9
	*N*O	110.8	+11.0	1.047	0.283	25.3	0.4

[a] Isotropic component of the nuclear shielding tensor: $\sigma = (\sigma_{11} + \sigma_{22} + \sigma_{33})/3$ in ppm. – [b] $\Delta\delta = \sigma(AH) - \sigma(A^-)$ in ppm. – [c] Largest principal component of efg (Equation 1) in au (0.97174×10^{22} V/m^2). – [d] Asymmetry parameter (Equation 1). – [e] Effective nuclear quadrupolar coupling constant $\chi_{eff} = \chi^2(1 + \eta^2/3)$ in MHz^2 (10^{12} s^{-2}). – [f] $\chi_{eff}^{R} = \chi_{eff}(A^-)/\chi_{eff}(AH)$. – [g] Changes with respect to neutral. – [h] Both oxygen atoms have the same properties. – [i] Relative values are reported as averages only.

Table 3. Experimental ^{14}N-, ^{17}O- and ^{33}S-NMR properties of neutral and deprotonated acids

Acid/solvent	Atom	δ[a]	Δδ[b]	T_1[c]	T_1^{R}[d]
Hydrogen cyanide					
1 M HCl	N	−135	−	3.6	−
1 M NaOH	N	−106	+29	9.6	0.4
Cyanamide					
Water	C*N*	−200	−	2.2	−
	NH_2	−368	−	1.1	−
1 M NaOH	$NCNH^-$ or NCN^{2-}	−306	−168; +62	3.1	0.7; 0.4
Trifluoroacetamide					
0.1 M HCl	N	−275	−	2.1	−
1 M NaOH	N	−278	−3	−	−
		−378[e]	−	2.9	−
Succinimide					
0.1 M HCl	N	−205	−	1.4	−
1 M NaOH	N	−270	−65	1.0	0.7
	N[f]	−140	−	0.5	−
Methanesulfonamide					
0.1 M HCl	N	−290	−	1.0	−
	S	−12	−	1.5	−
1 M NaOH	N	−282	+8	0.6	1.6
	S	1	+13	1.0	1.5
Benzenesulfonamide					
0.1 M HCl	N	−286	−	0.2*	−
1 M NaOH	N	−281	+5	0.4*	0.5
Hydantoin					
0.1 M HCl	N-1	−295	−	0.5	−
	N-3	−231	−	1.2	−
1 M NaOH	N-1	−293	+2	0.5	1.0
	N-3	−197	+34	0.8	1.4
Urazole					
0.1 M HCl	N-1,2; N-4	−245	−	0.5	−
	N-1,2[g]	−255.5	−	−	−
	N-4[g]	−246.7	−	−	−
1 M NaOH	N-1,2	−221	+34	0.2	−
	N-4	−246	−1	0.6	−
Urea					
H_2O	C*O*	199	−	−	−
N-Hydroxyurea					
0.1 M HCl	NH_2	−304	−	1.0	−
	NO	−239	−	0.2	−
	C*O*	184	−	−	−
	N*O*	81	−	−	−
1 M NaOH	NH_2	−313	+9	0.6	1.8
	NO	−236	+3	0.2	1.1
	C*O*	156	−28	−	−
	N*O*	[h]			

[a] Chemical shift in ppm, relative to the appropriate reference (see Experimental). The observed nucleus is in *italics*. − [b] $\Delta\delta = \delta(A^-) - \delta(AH)$. − [c] T_1's in ms. Entries marked with an asterisk report $1/\pi W_{1/2}$ rather than T_1; $W_{1/2}$'s were obtained by Lorentian fitting. Values in 1 M NaOH are not corrected for the higher viscosity. − [d] $T_1^{R} = T_1(AH)/T_1(A^-)$. − [e] Hydrolysis product (NH_3; see text). − [f] Unidentified decomposition product. − [g] ^{15}N data. − [h] Not detectable.

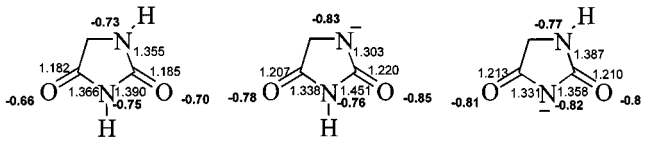
(c) Sulfonamides

The calculated NMR properties for $MeSO_2NH_2$ and $MeSO_2NH^-$ indicate very small changes, the largest variations ($\Delta\delta = +25$ ppm, $\chi_{eff}^{R} = 0.5$) being actually predicted for the sulfur atom, which is obviously not the deprotonation site. However, this long-range effect, which was previously observed in other sulfur compounds,[5] can be tested in this case, as ^{33}S spectra of sulfonyl derivatives are among the easiest to obtain.[13]

The ^{14}N signals of $MeSO_2NH_2$ and $PhSO_2NH_2$ show the expected behavior upon deprotonation, i.e. a small (5−8 ppm; calcd. +5 ppm) deshielding. The former acid undergoes a moderate T_1 shortening, and the latter a larger lengthening. In any event, the changes are rather small, in line with predictions. The ^{33}S signal of $MeSO_2NH_2$ is deshielded by 13 ppm in basic solution, in fair agreement with the calculated data. However, the expected efg change (a 50% decrease) is not well reproduced experimentally, since the T_1 values (Table 3) are not very different (the value of 1.0 ms in NaOH should be increased by 20% to 1.2 ms to account for the higher viscosity of this medium, see above).

Hydantoin

The structure of the neutral acid (**1**) and of the nitrogen anions that can be formed by deprotonation at either site (**1a**, **1b**) are depicted in Scheme 1. As it might be expected on the basis of simple resonance arguments, the most stable anion is the one deriving from deprotonation of the imido nitrogen atom (**1b**) ($\Delta E^{MP2} = 4.2$ kcal/mol). However, contrary to what was previously found for other ionic species,[12] the charge delocalization in **1b** does not bring the usual acid-weakening effect due to the decrease of solvation energy. In fact, in water (as modeled by the IPCM method) **1b** is even more stable than **1a** ($\Delta E^{IPCM} = 9.6$ kcal/mol). The combination of data according to Equation 3 yields $\Delta E_{(aq)} = 8.4$ kcal/mol favoring deprotonation at the imido N (N-1) in water as well as in the gas phase. This behavior should be compared with that previously found for [(trinitrophenyl)amino]benzoic acids,[12] which showed a clear shift of deprotonation site from N to O on going from gas phase to DMSO/water. Although in the present case one would expect a smaller effect, owing to the similarity between the two acidic sites, the lack of enhanced solvation of **1a** requires further analysis. Scheme 4 reports some relevant bond lengths and atomic charges, calculated with the Natural Bond Orbital (NBO) partition scheme,[26] for **1a−b**.



1 **1a** **1b**

Scheme 4. Bond lengths and NBO charges (in boldface) in hydantoin and its deprotonated forms

In **1b**, C-2 (or C-5)−N-1 bonds are shorter, and C−O bonds are longer, than in neutral **1**, which is consistent with participation of the whole imide system to charge delocalization. The C-2−N-3 bond is also lenghthened, indicating a slight loss of resonance in the N-3 amide system. In **1a**, the C-2−N-3 bond is shortened, and the C-2−O bond is lenghtened, as expected for an enhanced amide resonance in the anion. However, the N-1−C-5 bond also becomes shorter, and the C-5−O bond becomes longer, which clearly indicates a participation of the imide system to charge de-

localization in **1a** as well. These conclusions are reinforced by an analysis of NBO charges, which shows that in both **1a** and **1b** negative charge is developed at the oxygen atoms to a similar extent. In other words, the negative charge is delocalized to a similar extent in both anions, and solvation does not provide any differential stabilization.

Calculated NMR properties show the following trend. The two oxygen atoms (amide O-5 and imide O-2) are not equivalent, and in fact their calculated shieldings differ by ca. 100 ppm. By deprotonation O-5 is non-specifically shielded by 70−80 ppm, whereas O-2 is shielded to a different extent ($\Delta\delta = -72, -24$ ppm in **1a** and **1b**, respectively). Neither data is very informative, however, nor it refers to a deprotonation site, and no ^{17}O experiments were carried out. In **1a** (amino-deprotonated) the amino N (N-3) is deshielded by 83 ppm, whereas N-1 (imino N) is shielded by 10 ppm. In **1b** (imino-deprotonated) opposite changes take place, N-1 being now deshielded by 61 ppm, with an almost unchanged value for N-3. Hence, nitrogen shieldings should clearly differentiate the two anions; on the other hand, calculated efg′s show only modest changes.

The ^{14}N-NMR spectrum under neutral conditions shows two well-resolved signals at $\delta = -231$ and -295, which can be assigned to the imido and amido nitrogen atoms, respectively, by comparison with literature data for the solid ($\delta = -233$ and -298).[27] In the basic solution, the imide signal is deshielded by 34 ppm, whereas the amide signal is hardly affected. These data are consistent with deprotonation occurring at N-1 (imido N), in agreement with the calculated energetics seen above.

Urazole (1,2,4-Triazolidine-3,5-dione)

This compound (Scheme 2) presents both an imide (N-4) and two equivalent amide, or acyl hydrazide (N-1, N-2) sites, whose relative acidity is difficult to assess a priori.[22−24] Gas-phase MP2 calculations predict that the ion resulting from deprotonation at the imido nitrogen atom (**2b**) is less stable than the form deprotonated at the hydrazo nitrogen atoms (**2a**) by 13.3 kcal/mol. However, at the IPCM level this difference is reduced to just 2.2 kcal/mol, indicating that **2a** is significantly more stabilized in water. By applying Equation 3 one obtains $\Delta E_{(aq)} = 4.6$ kcal/mol. Hence, although the energy balance is not overturned (**2b** still less stable), there is a substantial contribution of solvation energies to the proton transfer energy; in any event, theory predicts N-1 and N-2 (the hydrazo nitrogen atoms) to be the preferred deprotonation site in both gas phase and water.

Calculations point out that the formation of **2a** causes a considerable deshielding of the deprotonated nitrogen atom ($\Delta\delta = +84$ ppm), a marked deshielding for the other hydrazo nitrogen atom ($\Delta\delta = +29$ ppm), and a small deshielding for the imido one ($\Delta\delta = +6$ ppm). If we allow for proton exchange between N-1 and N-2, the expected chemical shift change at N-1 will be averaged to +57 ppm. On the other hand, the formation of **2b** should entail opposite variations, as a major deshielding by 52 ppm is now predicted for N-4, and a very small shielding for N-1.

Efg′s at the nitrogen atoms follow a simple trend. Upon deprotonation at N-1, hydrazide nitrogen atoms undergo an average decrease of χ_{eff} by a factor of 0.6, whereas N-4 (imido nitrogen atom) is hardly affected. For deprotonation at N-4, the efg at N-4 itself is expected to decrease ($\chi_{eff}^{R} = 0.7$), and that at N-1 should remain constant. Thus, only the nitrogen atom actually being deprotonated is affected, but the changes are not large. The efg at the oxygen atom also remains constant.

This acid is not very soluble in water (at least for ^{14}N or ^{15}N NMR), and saturated solutions have been used. In acidic medium only one ^{14}N-NMR signal is found, but the corresponding ^{15}N-NMR spectrum shows the signals of the two nitrogen atoms at $\delta = -246.7$ and -255.5. Likewise, the ^{15}N-NMR spectra in water and DMSO show peaks at $\delta = -246.7, -254.2$ and $\delta = -247.0, -258.1$, respectively. However, the signals cannot be assigned from their intensities, because their ratio is not constant (this may be due to different NOEs or proton-exchange rates in the two solvents). A tentative assignment can be made by comparison with hydantoin (see above and Table 3) and acyl hydrazides R−C(O)−NH−NH_2 (NH: $\delta = -250$; NH_2: $\delta = -320$),[27] whereby one can assign the signal at $\delta = -247$ to the N-4 (imide) and that at $\delta = -254$ to -258 to the hydrazide nitrogen atoms (N-1). The assignment is confirmed by comparison with the calculated shieldings, which show that N-4 is more deshielded than N-1 by 24 ppm, in agreement with the experimental difference of 7−11 ppm. The ^{14}N-NMR spectrum is partially resolved in basic solution: the N-4 signal is essentially unaffected, while the N-1 signal is deshielded to $\delta = -221$ ($\Delta\delta = +34$ ppm), in agreement with deprotonation taking place at N-1. Owing to the lack of resolution in the spectrum of the neutral, it is impossible to analyze changes in T_1 or χ_{eff}. However, the available data allow us to pinpoint the preferred deprotonation site as the hydrazo (amido) nitrogen atoms, confirming theoretical predictions based on energetics.

Bausch and co-workers investigated the proton-transfer chemistry of urazole and related acids in DMSO and water.[22−24] Their work led to the conclusion that, while in DMSO the acid strength of N-1 and N-4 is similar, in water the N-1 protons are much more acidic. These conclusions were obtained by means of a lengthy and careful analysis of substituent effects on various urazoles and related acyl hydrazides. Our results, obtained by independent (both theoretical and experimental) means, confirm Bausch′s data. However, we wish to emphasize that the technique we adopted allows for a straightforward prediction of the deprotonation site from the data for a single compound, without assumptions concerning trends in substituent effects, or the behavior of monofunctional models.

N-Hydroxyurea

This hydroxamic acid[25,28,29] is widely used as an anticancer drug, and has recently been reported to inhibit the

replication of the HIV-1 virus.[30] Like hydroxamic acids, it may undergo deprotonation at the hydroxylamino nitrogen or oxygen atom,[11] but in this case also at the primary amido nitrogen atom, so that three deprotonation sites are available (Scheme 3); its p*K* is such that a substantial amount of ionized form may be present even at physiological pH.

Calculations predict the amide-N-deprotonated form ($^-$HN−CO−NHOH, **3a**) to be the most stable in the gas phase, by 3−6 kcal/mol. IPCM calculations overturn (albeit slightly) the balance, $H_2N-CO-N(OH)^-$ (**3b**) and $H_2N-CO-N(H)O^-$ (**3c**) being now more stable by ca. 2 kcal/mol, which highlights the stronger hydration of the latter anions. Overall, this results in $\Delta E_{(aq)}$ of −2.0 and −1.2 kcal/mol, respectively. Thus, theory predicts only a marginal difference in stability among the three anions in water, **3a** being intrinsically more stable but more weakly solvated than the other ions.

The formation of **3a** is expected to deshield the amido nitrogen atom by 41 ppm and to decrease its efg by a factor of 0.45; minor changes are calculated for the other ionization sites. Formation of **3b** should deshield the hydroxylamino nitrogen atom by more than 100 ppm with no appreciable efg change; again, essentially no change is expected at the other ionization sites. Finally, deprotonation to yield **3c** should deshield the oxygen atom by 83 ppm, and increase its efg to very high values (χ_{eff} = 419 MHz^2); the adjacent nitrogen atom should also be affected, with $\Delta\delta$ = +11 and a lower efg. Hence, deprotonation at either site is predicted to cause selective changes in the NMR properties of ^{14}N and ^{17}O. We also note that the carbonyl oxygen atom (which is not an ionization site) is calculated to undergo similar changes regardless of where proton abstraction takes place.

A 0.5 M solution in 0.1 M HCl exhibits the two expected ^{14}N-NMR signals at δ = −239 (NOH) and δ = −304 (NH_2). The former is much broader, in agreement with the observed T_1 values and calculated shieldings and efg′s (Table 2). The ^{17}O-NMR spectrum, obtained from a saturated solution in 0.1 M HCl (ca. 0.8 M) shows two signals at δ = 184 and 81, the latter being broader. These can be assigned to the carbonyl and hydroxylamino oxygen atoms, respectively, by comparison with the ^{17}O-NMR shift of urea (δ = 199)[31] and of other hydroxamic acids.[11]

The ^{14}N-NMR spectra in 1 M NaOH are slightly different, in that the chemical shift of both signals changes very little (deshielded by 3−9 ppm), whereas the relaxation of NH_2 becomes faster by a factor of 2. The ^{17}O-NMR signal of NO is broadened out of detectability (as observed for other hydroxamic acids[11] at natural abundance), and the ^{17}O-NMR signal of CO is shielded by 28 ppm.

The comparison of calculated and experimental properties allows firstly to rule out the formation of $H_2N-CO-N(OH)^-$ (**3b**) to any significant extent. Likewise, the calculated $\Delta\delta$ of +41 ppm at the amido N when it acts as deprotonation site (i.e. **3a** is formed) is inconsistent with the experimental value of +9 ppm. On the other hand, the very large line broadening found for the ^{17}O-NMR signal of NO (which in fact becomes undetectable) is fully consistent with the calculated increase by a factor of 1.6. Although the increase is not very large in itself, it acts on an already large χ_{eff} (269 MHz^2 in the neutral), and takes its value into a range where ^{17}O-NMR measurements cannot be carried out at natural abundance. Hence, the only deprotonation site reasonably consistent with all data is the hydroxylamino oxygen atom [formation of $H_2N-CO-N(H)O^-$, **3c**], as previously found for MeCONHOH and MeCON(Me)OH.[11] We note that this conclusion could not have been reached solely by calculated stabilities in water, which are remarkably similar.

Other Considerations

In a previous work,[3] we showed that shielding calculations successfully predict the absolute chemical shift range of neutrals, giving confidence also to the calculated values of the anions. Table 2 shows that deprotonation at an amide-type nitrogen acid generally causes a sizable deshielding of the deprotonated nitrogen atom, ranging from a minimum of 6 ppm for $MeSO_2NH_2$ to 80−100 ppm for CF_3CONH_2, heterocyclic compounds (hydantoin, urazole) and hydroxyurea. On the other hand, for succinimide (the only pure imide acid considered), a sizable nitrogen shielding is predicted and found. Although our experimental $\Delta\delta$ values are generally smaller than calculated $\Delta\sigma$′s, this trend is similar to that previously established by Bradamante et al.[32] and ourselves[12] for the deprotonation of other related nitrogen acids, and is also consistent with the behavior of a simple amine acid ($MeNH_2$). The nitrogen shielding in nitrogen anions was thoroughly analyzed theoretically in terms of changes in the charge distribution in the σ and π framework of appropriate systems,[33] but this falls outside the scope of the present work.

Unlike protonation, which is known to cause a very large and characteristic decrease of the electric field gradient (and a corresponding increase in T_1) at the nitrogen atom,[3] deprotonation causes much smaller changes. A 20−50% efg decrease is generally calculated, except the special case of the axially symmetric NCN^{2-} anion and CF_3CONH_2. This change in fact is the same as calculated for the deprotonation of $MeNH_2$. Owing to their small extent, such changes have not proved very useful, and the comparison of calculated and experimental shifts seems superior in general.

Summary and Conclusions

Quantum chemical calculations are a powerful tool for predicting energies and patterns of NMR properties of the acids and the anions that can be formed from deprotonation of a variety of amide-type acids. IPCM calculations in water alter the relative stability order of gas-phase ions, and hence provide a necessary complement to calculations for isolated species whenever a comparison with solution data is sought. Using this combination of exper-

imental and theoretical tools we could model the behavior of several polyfunctional acids in water, and correctly interpret NMR spectral changes in terms of (a) the structure of the preferred ion formed, and (b) the effect of solvation, and especially of hydration, on the relative stability of such ions. Thus, we demonstrated that hydantoin undergoes deprotonation at the imido nitrogen atom, urazole at the hydrazido (N-1 or N-2) nitrogen atom, and *N*-hydroxyurea at the hydroxylamino oxygen atom. The deprotonation site of hydantoin (imido rather amido nitrogen atom) agrees with expectations based on simple resonance arguments, although hydration has some unexpected effects. For urazole the preference is reversed, and the most favored deprotonation site is now the amido nitrogen atom, owing to the stabilizing effect of the α-nitrogen atom (counteracted by solvation). Hence, it appears that the relative acidity of amide and imide NH′s can be profoundly altered by structural changes. *N*-Hydroxyurea is not strictly comparable to the previous two; the stronger acidity of the OH proton agrees with previous results.

Experimental Section

All compounds studied are commercially available. − NMR measurements were run unlocked at 25°C either with Bruker AC 200 (^{15}N, 20.28 MHz), AM 400 (^{14}N, 28.92 MHz; ^{15}N, 40.56 MHz) or Avance DMX 600 (^{14}N, 43.38 MHz; ^{17}O, 81.37 MHz; ^{33}S, 46.06 MHz) instruments. 0.5−1 M solutions were employed in 5- or 10-mm tubes. ^{14}N-^{15}N, ^{17}O and ^{33}S chemical shifts were externally referenced to neat $MeNO_2$, H_2O and saturated aqueous Na_2SO_4, respectively, and are believed to be accurate to within ± 2 ppm (± 0.1 ppm for ^{15}N). ^{14}N and ^{33}S T_1 values were obtained by inversion-recovery with acoustic ringing suppression;[34] line widths were obtained from Lorentian fitting. − Calculations were carried out with the programs *Spartan* v. 4-5[35] or *Gaussian 94*,[36] running on IBM RS/6000 workstations or personal computers.

[1] R. Stewart, *The Proton: Applications to Organic Chemistry*, Academic Press, New York, **1985**.
[2] F. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456.
[3] A. Bagno, B. Bujnicki, S. Bertrand, C. Comuzzi, F. Dorigo, P. Janvier, G. Scorrano, *Chem. Eur. J.*, in press.
[4] A. Bagno, G. Scorrano, *J. Phys. Chem.* **1996**, *100*, 1536.
[5] A. Bagno, G. Scorrano, *J. Phys. Chem.* **1996**, *100*, 1545.
[6] J. Tomasi, M. Persico, *Chem. Rev.* **1994**, *94*, 2027.
[7] J. B. Foresman, T. A. Keith, K. B. Wiberg, J. Snoonian, M. J. Frisch, *J. Phys. Chem.* **1996**, *100*, 16098.
[8] A. Bagno, C. Comuzzi, G. Scorrano, *J. Chem. Soc., Perkin Trans. 2* **1993**, 283.
[9] A. Bagno, E. Menna, E. Mezzina, G. Scorrano, D. Spinelli, *J. Phys. Chem. A* **1998**, *102*, 2888.
[10] A. Bagno, S. J. Eustace, L. Johansson, G. Scorrano, *J. Org. Chem.* **1994**, *59*, 232.
[11] A. Bagno, C. Comuzzi, G. Scorrano, *J. Am. Chem. Soc.* **1994**, *116*, 916.
[12] A. Bagno, F. Dorigo, P. McCrae, G. Scorrano, *J. Chem. Soc., Perkin Trans. 2* **1996**, 2163.
[13] *Multinuclear NMR* (Ed.: J. Mason), Plenum Press, London, **1987**.
[14] *CRC Handbook of Chemistry and Physics*, 77th ed. (Ed.: D. R. Lide), CRC Press, Boca Raton, **1997**.
[15] K. Wolinski, J. F. Hinton, P. Pulay, *J. Am. Chem. Soc.* **1990**, *112*, 8251.
[16] To the best of our knowledge, the p*K* value in water is not available; however, relative acidities in water and DMSO for charge-delocalized anions (as well as the common availability of stable cyanamide salts) allow to conclude that the basic conditions needed to generate this anion are probably the same as for the other acids.
[17] T. V. Kashik, G. V. Rassolova, S. M. Ponomareva, E. N. Medvedeva, T. I. Yushmanova, V. A. Lopyrev, *Bull. Acad. Sci. USSR, Ser. Chem. (Engl. Transl.)* **1982**, *31*, 1965.
[18] R. D. Trepka, J. K. Harrington, J. W. Belisle, *J. Org. Chem.* **1974**, *39*, 1094.
[19] A. V. Willi, *Helv. Chim. Acta* **1956**, *39*, 46.
[20] E. C. Kornfeld, R. G. Jones, T. V. Parke, *J. Am. Chem. Soc.* **1949**, *71*, 150.
[21] M. Zief, J. T. Edsall, *J. Am. Chem. Soc.* **1937**, *59*, 2245.
[22] M. J. Bausch, B. David, P. Dobrowolski, V. Prasad, *J. Org. Chem.* **1990**, *55*, 5806.
[23] M. J. Bausch, D. Selmarten, R. Gostowski, P. Dobrowolski, *J. Phys. Org. Chem.* **1991**, *4*, 67.
[24] M. J. Bausch, B. David, P. Dobrowolski, C. Guadalupe-Fasano, R. Gostowski, D. Selmarten, V. Prasad, A. Vaughn, L.-H. Wang, *J. Org. Chem.* **1991**, *56*, 5643.
[25] H. Kofod, T.-Y. Huang, *Acta Chem. Scand.* **1954**, *8*, 494.
[26] A. E. Reed, L. A. Curtiss, F. Weinhold, *Chem. Rev.* **1988**, *88*, 899.
[27] M. Witanowski, L. Stefaniak, G. A. Webb, *Nitrogen NMR Spectroscopy, Ann. Rep. on NMR Spectroscopy*, Academic Press, London, **1986**.
[28] H. Kofod, *Acta Chem. Scand.* **1954**, *8*, 485.
[29] L. Bauer, O. Exner, *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 376.
[30] F. Lori, A. Malykh, A. Cara, D. Sun, J. N. Weinstein, J. Lisziewicz, R. C. Gallo, *Science* **1994**, *266*, 801.
[31] J. Jirman, P. Pech, *Collect. Czech. Chem. Commun.* **1992**, *57*, 1278.
[32] E. Barchiesi, S. Bradamante, *J. Phys. Org. Chem.* **1990**, *3*, 139.
[33] C. Gatti, A. Ponti, A. Gamba, G. Pagani, *J. Am. Chem. Soc.* **1992**, *114*, 8634.
[34] A. Bagno, *Magn. Reson. Chem.* **1992**, *30*, 1164.
[35] Wavefunction Inc., Irvine, CA.
[36] M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, *Gaussian 94, Revision E.2*, Gaussian, Inc., Pittsburgh PA, **1995**.

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