Thermodynamics of Protonation and Hydration of Aliphatic Amides

Alessandro Bagno,* Giancarlo Lovato and Gianfranco Scorrano
Centro CNR Meccanismi Reazioni Organiche, Dipartimento di Chimica Organica, via Marzolo 1, 35131 Padova, Italy

The protonation equilibria of a series of aliphatic amides of the type R-CO-NH_2, R-CO-$NHCH_3$ and R-CO-$N(CH_3)_2$ (R = H, Me, Et, Pr^i, Bu^t) have been studied in aqueous H_2SO_4 in the temperature range 25–60 °C, thus determining the protonation (m^* and pK) and the thermodynamic parameters of the ionization equilibrium ($\Delta G°$, $\Delta H°$, $\Delta S°$). These solution data have been combined with basicities in the gas phase and energies of hydration of neutrals, thus evaluating the enthalpies and free energies of hydration of protonated amides. The structures, energies and atomic charges for the primary derivatives and their protonated forms have been calculated by *ab initio* theoretical methods. Structural and solvation effects on basicities are discussed: increased substitution around the amide group causes a decrease in the basicity at the standard state (pK) and a concurrent decrease in the solvation of BH^+ because of better charge dispersal, which is reflected in activity coefficient behaviour (m^*). The two effects counteract each other, the outcome being that generally tertiary amides are 100% protonated at lower acid concentrations than less substituted ones. The energetics of gas phase to water transfer for neutral and protonated amides are discussed and compared with other bases (particularly thioamides) and onium ions.

The basicity and solvation of aliphatic amides are intrinsically important parameters for understanding the behaviour of biochemical systems. Despite this importance, few studies have been carried out to determine the protonation behaviour of aliphatic amides, both in solution and in the gas phase. This is partly due to the fact that the UV absorption of aliphatic amides in water takes place at 190–200 nm (and undergoes a further hypsochromic shift by protonation), *i.e.* in a region where accurate measurements are difficult to carry out. Therefore, most studies in solution[1-4] have dealt with derivatives containing aromatic groups attached to either side of the amide group, for example in the determination of the H_A acidity function.[1] Such UV spectra are affected by large solvent effects, whose calculation and elimination have been the object of several studies[2,3] which are however based on assumptions, the generality of which has not been assessed. On the other hand, aliphatic derivatives can be conveniently studied by NMR spectroscopy, for which solvent effects can be adequately handled.[5] This class of compounds includes some common organic solvents (*N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidone) and is also present as a functional group in peptides (-NH-CHR^1-CO-NH-CHR^2-$)_n$, where R^1 and R^2 are alkyl or benzyl groups, but not aryl. Thus an *N*-methylamide of the type R-CH_2-CO-NH-CH_3 is a model of the amide group in a peptide.

In a previous study concerning the basicity of common organic solvents,[6] we determined aqueous pKs for *N,N*-dimethylformamide, *N,N*-dimethylacetamide and *N*-methylpyrrolidone at 25 °C. In this paper we report on measurements extended to a series of amides of the type R-CO-NH_2, R-CO-$NHCH_3$ and R-CO-$N(CH_3)_2$ (R = H, Me, Et, Pr^i, Bu^t) at various temperatures, in order to determine also all the thermodynamic parameters of the ionization equilibrium ($\Delta G°$, $\Delta H°$, $\Delta S°$).[1c] Combined with gas-phase basicity data[7] and thermodynamic functions for the hydration of the neutral species,[8,9] these eventually permit us to determine the energetics of the gas phase to water transfer for both neutral and protonated amides, and to make comparisons with analogous thioamides.[10]

Results

The protonation equilibria have been studied at ca. 25, 40 and 60 °C (for *N,N*-dimethylformamide and *N,N*-dimethylacetamide also at 80 °C) in aqueous H_2SO_4 mixtures, by monitoring the ^1H chemical shift of all signals (relative to internal trimethylammonium sulfate, TMA)[5] as a function of the acid concentration. However, the methine septet of the Pr^i proton gives a weak signal, which partly overlaps with the TMA signal at some acid concentrations, particularly for *N,N*-dimethylisobutyramide. For this signal only few data were obtained and these were not included in the averages. The chemical shift and line width of *N*-alkyl signals are strongly influenced by the varying rate of C–N rotation, which in turn is affected by temperature and acidity.[6] In some cases, upon protonation we observed the collapse of the two non-equivalent methyl peaks even at constant temperature. These signals were discarded because the chemical shift change depends on factors other than protonation. The signals of nitrogen-bound protons (R-CO-NH_2 and R-CO-N$H$$CH_3$) were never considered, for the above reasons and because these are very broad anyway (coupling with ^{14}N) and their chemical shift cannot be accurately measured.

All the amides studied were sufficiently stable under all conditions (though hydrolysis products were often visible in the spectrum) with the exception of formamide, which hydrolysed fast even at 40 °C and therefore could be studied only at 25 °C. A similar order of reactivity towards hydrolysis was previously reported.[11]

Ionization ratios ($I = [BH^+]/[B]$) are calculated as $I = (\nu - \nu_B)/(\nu_{BH^+} - \nu)$; the values of ν_B and ν_{BH^+} (chemical shift of free and protonated base, respectively) are calculated as described elsewhere.[5] The protonation parameters are determined with the excess acidity method [eqn. (1)],[12,13] where m^* expresses

$$\log I - \log c_{H^+} = m^*X + \mathrm{p}K \qquad (1a)$$

$$\log(\gamma_B\gamma_{H^+}/\gamma_{BH^+}) = m^* \log(\gamma_{B^*}\gamma_{H^+}/\gamma_{B^*H^+}) = m^*X \qquad (1b)$$

the medium dependence of the activity coefficient term pertaining to the ionization equilibrium of B, relative to the same for a base (B*) taken as reference (a nitroaniline).[12]

In most cases the chemical shift in strongly acid solutions, where the amide is completely protonated, does not reach a constant value but drifts slowly with a linear trend. This residual

Table 1 Parameters of the thermodynamics of ionization at 25 °C[a]

Compound	R	m^*	pK	%H_2SO_4[b]	$\Delta\delta^{13}C$[c]	$\Delta G°$	$\Delta H°$	$\Delta S°$
$RCONH_2$								
	H	0.43 (0.02)	−1.47 (0.03)	83	1.468	−2.01 (0.04)	—	—
	Me	0.41 (0.01)	−0.66 (0.01)	77	3.042	−0.90 (0.01)	−0.2 (0.2)	2.4 (0.5)
	Et	0.49 (0.01)	−0.86 (0.01)	74	2.715	−1.17 (0.01)	−0.1 (0.1)	3.7 (0.4)
	Pr^i	0.58 (0.02)	−1.11 (0.02)	72	2.396	−1.51 (0.03)	−0.5 (0.1)	3.4 (0.5)
	Bu^t	0.73 (0.01)	−1.49 (0.01)	69	2.377	−2.03 (0.01)	−1.7 (0.2)	1.1 (0.4)
$RCONHCH_3$								
	H	0.32 (0.01)	−1.10 (0.04)	83	−0.301	−1.50 (0.04)	0.0 (0.3)	5.0 (0.9)
	Me	0.45 (0.02)	−0.56 (0.03)	73	1.141	−0.76 (0.03)	−0.7 (0.2)	0.3 (0.6)
	Et	0.50 (0.07)	−0.70 (0.06)	72	0.668	−0.96 (0.08)	−0.8 (0.4)	0.6 (1.2)
	Pr^i	0.69 (0.04)	−1.14 (0.05)	67	0.524	−1.55 (0.06)	−1.8 (0.2)	−0.9 (0.8)
	Bu^t	0.73 (0.01)	−1.59 (0.01)	70	0.465	−2.17 (0.01)	−2.6 (0.1)	−1.6 (0.5)
$RCON(CH_3)_2$								
	H	0.67 (0.02)	−1.13 (0.02)	68	−2.714	−1.54 (0.03)	−0.9 (0.1)	2.2 (0.4)
	Me	0.62 (0.03)	−0.21 (0.02)	60	−0.993	−0.29 (0.03)	−0.6 (0.2)	−0.9 (0.7)
	Et	0.74 (0.05)	−0.56 (0.04)	59	−0.913	−0.76 (0.04)	−1.6 (0.3)	−2.9 (0.9)
	Pr^i[d]	0.98 (0.03)	−1.61 (0.04)	61	−1.597	−2.20 (0.05)	−3.2 (0.6)	−3.5 (2.2)
	Bu^t	0.92 (0.05)	−2.03 (0.09)	66	−0.970	−2.77 (0.12)	−4.1 (0.6)	−4.5 (1.9)
$RCSN(CH_3)_2$[e]								
	Me	1.67 (0.01)	−2.25 (0.01)	52	—	−3.07 (0.01)	−4.7 (0.2)	−5.4 (0.7)
	Et	1.69 (0.01)	−2.26 (0.01)	52	—	−3.09 (0.01)	−5.0 (0.2)	−6.7 (0.7)
	Pr^i	1.73 (0.03)	−2.48 (0.04)	52	—	−3.39 (0.05)	−4.3 (0.6)	−3.1 (2.0)
	Bu^t	1.78 (0.01)	−2.32 (0.02)	51	—	−3.17 (0.03)	−3.9 (0.2)	−2.2 (0.7)

[a] Energies in kcal mol^{-1} and entropies in cal mol^{-1} K^{-1}; errors from least-squares analysis follow in brackets. Average values of pK and $\Delta G°$ from an average of pKs of all signals: $\Delta H°$ and $\Delta S°$ obtained by fitting all pKs to the van't Hoff equation. [b] %H_2SO_4 value where 100% protonation is attained. [c] Chemical shift change (ppm) of carbonyl carbon between 0.01% and 98% H_2SO_4. [d] Values only from the methyl signal. [e] Ref. 10.

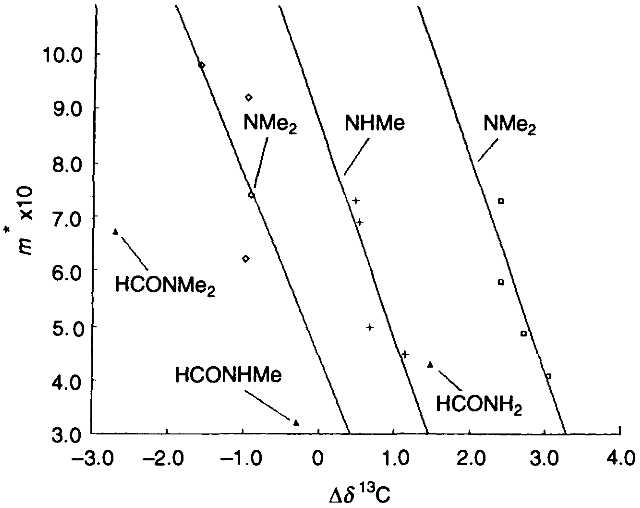


Fig. 1 Values of $\Delta\delta^{13}C$ between 0.01 and 98% H_2SO_4 plotted against m^*

solvent effect cannot be removed with any of the proposed methods;[2,3] however, those data points can be discarded because in those conditions the measurement of the ionization ratio is inaccurate anyway, and the data points corresponding to less than 5% or more than 95% ionization are not used in eqn. (1a) by the data processing program.[6,13]

The m^* and pK values obtained for each base, temperature and signal are reported in the Supplementary Material (Table S1);† in Table 1 we summarize the results at 25 °C. When different proton signals are available, the results are generally slightly outside experimental error. Because the accuracy is probably similar, all pK values were averaged to give the recommended pK and $\Delta G°$.

Table 2 *Ab initio* energies[a] and proton affinities[b] for primary amides $RCONH_2$ and their protonated forms[c]

R	E(B)	E(BH^+)	PA
H	−168.982 285 120	−169.323 341 449	214.0
Me	−208.036 668 863	−208.389 189 271	221.2
Et	−247.081 671 929	−247.436 779 972	222.8
Pr^i	−286.123 183 099	−286.483 919 343	226.4
Bu^t	−325.166 523 530	−325.527 280 892	226.4

[a] In hartrees at the HF/6-311G**//6-311G** level. [b] In kcal mol^{-1}. [c] In protonated forms, the acidic proton is *anti* with respect to the amino hydrogens and coplanar with the CONH residue. The conformation of the R group was found to be *anti*, with the carbon backbone coplanar with the CONH group except for R = Pr^i (see Fig. 2 and text).

The other thermodynamic parameters ($\Delta H°$ and $\Delta S°$)[1c,14] were determined through van't Hoff plots (pK vs. $10^3/T$). The values from each signal are collected in Table S1, whereas the averages of Table 1 result from fitting all available pK values.

The formamides have amomalous m^* and pK values compared with the other amides (see Discussion). Thus we determined the chemical shift difference of the carbonyl group between neutral and protonated form ($\Delta\delta^{13}C$), which is known to reflect changes in charge density at the carbonyl group,[15] in order to check whether such changes are substantially different from the other amides and therefore to have an independent check on m^* values. $\Delta\delta^{13}C$ values are also reported in Table 1, and plotted against m^* in Fig. 1.

In order to gain further insight into the behaviour of protonated amides, we also calculated the structures, energies and atomic charges (by fits to electrostatic potential maps, using a grid of 2 points per atomic unit) for the primary amides $RCONH_2$ and their protonated forms. The calculations were

---

† Sup. pub. No. 56947, 7 pages. For details of the supplementary publication scheme please see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 2*, 1993, issue 1.

Table 3 *Ab initio* atomic charges[a] for primary amides $RCONH_2$ and their protonated forms

	H		Me		Et		Pr^i		Bu^t	
	B	BH^+	B	BH^+	B	BH^+	B	BH^+	B	BH^+
CO	0.747	0.658	0.947	0.832	0.853	0.774	0.821	0.693	0.802	0.763
O	−0.608	−0.464	−0.658	−0.521	−0.636	−0.513	−0.655	−0.517	−0.639	−0.514
N	−0.924	−0.707	−1.050	−0.789	−1.050	−0.806	−1.035	−0.739	−1.082	−0.857
NH_2	0.798	0.906	0.843	0.909	0.838	0.905	0.844	0.876	0.870	0.934
R	−0.013	0.129	−0.082	0.089	−0.004	0.171	0.025	0.220	0.048	0.222
OH^+	—	0.477	—	0.480	—	0.468	—	0.467	-	0.452

[a] Determined from fits to electrostatic potential maps with a resolution of 2 points per atomic unit. See Tables S2 and 2 for structures and energies.

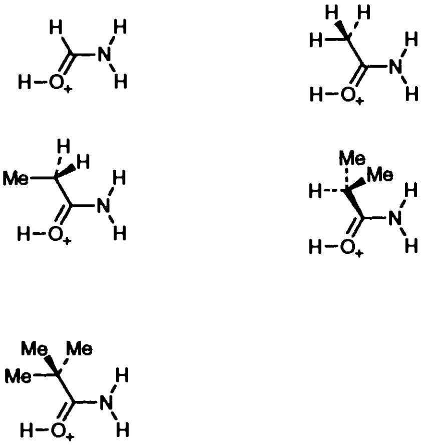
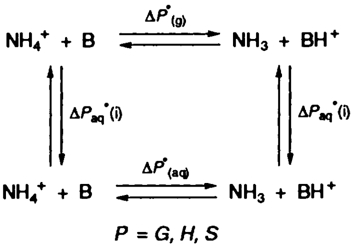


Fig. 2 Optimized structures for protonated amides

carried out at the HF/6-311G**//6-311G** level of theory with full geometry optimization. Relevant geometrical parameters are collected in Table S2 of the Supplementary Material, while energies and charges are collected in Tables 2 and 3; the optimized structures are depicted qualitatively in Fig. 2. Geometry optimization (following a preliminary conformational search using molecular mechanics) converged to structures with the carbon backbone (in an *anti* conformation) coplanar with the $CONH_2$ group in all cases except protonated isobutyramide, for which a dihedral angle of 134.9° between the β hydrogen and the nitrogen was found. The corresponding coplanar (eclipsed) structure is, however, higher in energy only by 1.3 kcal mol^{-1}.† In the protonated forms, the OH^+ hydrogen was *anti* with respect to the NH_2 group (*i.e.*, pointing towards the alkyl group) and coplanar with the $CONH_2$ group. This behaviour persists even in the most sterically congested species (protonated pivalamide), where the energy difference between the *anti* and *cis* forms was 6.1 kcal mol^{-1} in favour of the former. This finding is probably related to the large electrostatic repulsion between the OH^+ and NH_2 hydrogens, which are also positively charged (see Discussion). In all cases, the C=O distance increases considerably upon protonation (from *ca.* 1.19 to 1.28 Å), while the O^+–H distance was *ca.* 0.95 Å.

The values of $\Delta G°$ and $\Delta H°$ have been combined with literature gas-phase basicities (GB) and proton affinities (PA),[7] free energies[9] and enthalpies[8a] of hydration [$\Delta G°_{aq}(B)$ and $\Delta H°_{aq}(B)$] of neutral amides in a Born–Haber cycle (Scheme 1), whereby hydration energies for protonated amides can be determined.

This allows one to obtain energies of hydration for the neutral and protonated base, relative to NH_3 and NH_4^+ [$\delta_R\Delta P°_{aq}(B)$ and $\delta_R\Delta P°_{aq}(BH^+)$, respectively] from the following expressions:[16]



Scheme 1

$$\Delta P°_{(g)} = \Delta P°_{aq}(NH_4^+) + \Delta P°_{aq}(B) + \Delta P°_{(aq)} - \Delta P°_{aq}(NH_3) - \Delta P°_{aq}(BH^+) \quad (2)$$

$$\Delta G°_{(g)} = GB(NH_3) - GB \quad (3)$$

$$\Delta H°_{(g)} = PA(NH_3) - PA \quad (4)$$

$$\Delta G°_{(aq)} = 2.303RT[pK(NH_4^+) - pK(BH^+)] \quad (5)$$

$$\delta_{aq}\Delta P° = \Delta P°_{(g)} - \Delta P°_{(aq)} \quad (6)$$

$$\delta_R\Delta P°_{aq}(B) = \Delta P°_{aq}(B) - \Delta P°_{aq}(NH_3) \quad (7)$$

$$\delta_R\Delta P°_{aq}(BH^+) = \Delta P°_{aq}(BH^+) - \Delta P°_{aq}(NH_4^+) \quad (8)$$

$$-\delta_R\Delta P°_{aq}(BH^+) = \delta_{aq}\Delta P° - \delta_R\Delta P°_{aq}(B) \quad (9)$$

The scarce and poorly overlapping data of PA, GB, $\Delta H°_{aq}$ and $\Delta G°_{aq}$ available allow us to carry out a complete thermodynamic analysis of the ionization equilibrium only for HCONHMe, $HCONMe_2$ (enthalpies only), $MeCONH_2$, MeCONHMe and $MeCONMe_2$ (also free energies). All the available data are collected in Tables 4–6, which also report literature data[13] for other oxygen bases. The energies for BH^+ relative to NH_4^+ can be converted to absolute values introducing the (estimated) corresponding quantities for NH_4^+ (see Table 6).

Discussion

Historical Outlook.—It is not infrequent that, whenever p*K* values of weak bases are needed for other investigations, quoted values are presented as lists of numbers spanning a large range. For this reason strong doubts are raised as to their validity, thus attaching much uncertainty to such data in general. Part of this situation arises from the long and complex development that the studies of acid–base equilibria in concentrated media have experienced in the past 60 years.

The earlier work was reviewed by Arnett in 1963.[20] From his paper it can be seen that, strictly speaking, protonation studies

---

† 1 cal = 4.184 J.

Table 4 Energies of ionization in the gas phase and solution, and energies of solvation of neutrals[a]

Compound	GB[b]	PA[b]	$\Delta G^{\circ c}$	$\Delta H^{\circ c}$	$\Delta G^{\circ}_{aq}{}^{d}$	$\Delta H^{\circ}_{aq}{}^{e}$
$HCONH_2$	190.6	198.4	−2.01	—	—	−13.9
HCONHMe	198.0	205.8	−1.50	0.0	—	−15.3
$HCONMe_2$	203.6	211.4	−1.54	−0.9	—	−15.1
$MeCONH_2$	198.4	206.2	−0.90	−0.2	−7.8	−16.9
MeCONHMe	204.5	212.3	−0.76	−0.7	−8.2	−17.6
$MeCONMe_2$	209.0	216.8	−0.29	−0.6	−6.7	−17.1
$EtCONH_2$	—	—	−1.17	−0.1	−7.5	—
Me_2NH	212.8	220.6	14.7	12.0	−2.4	−12.9
Me_2O	184.3	192.1	−3.4	0.6	0.0	−9.9
Me_2S	192.8	200.6	−9.4	−6.9	0.3	−7.6
Me_2SO	203.5	211.3	−2.1	−2.3	−8.2	−17.4
Me_2CO	188.9	196.7	−4.2	0.2	−1.9	−9.9
MeCOOMe	190.0	197.8	−5.3	−4.5	−1.4	−9.6

[a] In kcal mol^{-1}. [b] Ref. 7, except MeCONHMe (GB value from ref. 17; PA calculated[18] adding 7.8 kcal mol^{-1}). [c] Values for amides from this work; see ref. 13 for the other compounds. [d] Ref. 13, except amides (ref. 9). Standard state for ΔG°_{aq} is 1 mol dm^{-3} gas phase and 1 mol dm^{-3} hypothetical aqueous solution; ref. 9 reports data in terms of the equilibrium constant $K = c_g/c_{aq}$, where concentrations are in mol dm^{-3}; therefore values of ΔG°_{aq} were referred to our standard state by $\Delta G^{\circ}_{aq} = 2.303\ RT(\log RT + \log K)$, where $\log RT$ is calculated using $R = 0.082$ atm $dm^3\ mol^{-1}\ K^{-1}$. [e] Ref. 8.

Table 5 Energies of ionization in gas phase and solution relative to NH_3, and solvent effects on the ionization reaction.[a]

Compound	$\Delta G^{\circ}_{(g)}$	$\Delta H^{\circ}_{(g)}$	$\Delta G^{\circ}_{(aq)}$	$\Delta H^{\circ}_{(aq)}$	$\delta_{aq}\Delta G^{\circ b}$	$\delta_{aq}\Delta H^{\circ b}$
$HCONH_2$	5.0	5.6	14.6	—	−9.6	—
HCONHMe	−2.4	−1.8	14.1	12.5	−16.5	−14.3
$HCONMe_2$	−8.0	−7.4	14.2	13.4	−22.2	−20.8
$MeCONH_2$	−2.8	−2.2	13.5	12.7	−16.3	−14.9
MeCONHMe	−8.9	−8.3	13.4	13.2	−22.3	−21.5
$MeCONMe_2$	−13.4	−12.8	12.9	13.1	−26.3	−25.9
$EtCONH_2$	—	—	13.8	12.6	—	—
Me_2NH	−17.2	−16.6	−2.1	0.4	−15.1	−17.0
Me_2O	11.3	11.9	16.0	11.9	−4.7	0.0
Me_2S	2.8	3.4	22.0	19.4	−19.2	−16.0
Me_2SO	−7.9	−7.3	14.7	14.8	−22.6	−22.1
Me_2CO	6.7	7.3	16.8	12.3	−10.1	−5.0
MeCOOMe	5.6	6.2	18.0	17.0	−12.4	−10.8

[a] In kcal mol^{-1}. $\Delta G^{\circ}_{(g)} = GB(NH_3) - GB$ [free energy of ionization in the gas phase, relative to NH_3; $GB(NH_3) = 195.6$]. $\Delta H^{\circ}_{(g)} = PA(NH_3) - PA$ [enthalpy of ionization in the gas-phase, relative to NH_3; $PA(NH_3) = 204$]. $\Delta G^{\circ}_{(aq)} = 2.303\ RT[pK(NH_4{}^{+}) - pK]$ [free energy of ionization in solution, relative to NH_3; $pK(NH_4{}^{+}) = 9.245\,77$]. $\Delta H^{\circ}_{(aq)} = \Delta H^{\circ}(NH_3) - \Delta H^{\circ}$ [enthalpy of ionization in solution, relative to NH_3; $\Delta H^{\circ}(NH_3) = 12.485$]. See Ref. 16 for sources of data on NH_3. [b] See eqn. (6).

of aliphatic amides are certainly not lacking. However, for example, the quoted p*K*s of CH_3CONH_2 lie between −1.44 and 0.7. If we trace the history of these measurements, as well as those for other amides, we see that they come either from potentiometric titrations with $HClO_4$ in glacial acetic acid or from UV measurements in aqueous H_2SO_4. The results obtained with the first approach cannot be directly converted to aqueous p*K*s without the aid of the energies of transfer between the two solvents of all the species involved (a complex problem in itself), or through some correlation with bases of known behaviour. However, such correlations are generally restricted to families of bases,[6] which in fact precludes any general use of them. This circumstance makes these data of little value.

Studies in aqueous acid overcome this problem, but require a correct treatment both of medium effects on the spectra and, more importantly, of the equilibrium itself by means of, *e.g.* an appropriate acidity function. All the works cited are found wanting in this respect, because: (*a*) medium effects on UV spectra were inadequately dealt with (a problem which is far from being solved even now); (*b*) the H_0 acidity function was used for the derivation of amide p*K*s. It is now well known that the intercept of $\log I$ *vs.* H_0 plots is not a thermodynamic p*K*, unless the slope is unity, which is not the case for amides.

The subsequent development was that of building an acidity function appropriate for amides (H_A). This topic has been reviewed by Cox and Yates.[21] This acidity function was defined[1a] using benzamide derivatives, and was later shown to have been misanchored.[21] Despite the wide application of this acidity function, the fairly large changes in m^* among these compounds makes this approach very inaccurate. Accurate measurements, processed with modern methods, were subsequently reported by Cox *et al.*,[3] which however comprise few aliphatic derivatives.

Therefore, much of the supposed uncertainty in the field of acid–base equilibria actually arises from the fact that several p*K* values of widely varying origin and accuracy have been accumulated over the years. As seen above, some of the previously reported data concerning aliphatic amides are totally erroneous and should not be used.

Basicity of Amides: General Features.—Among weak bases, amides are known to be the strongest.[12] In fact, we found p*K* values between −0.21 ($MeCONMe_2$) and −2.03 (Bu^tCONMe_2). Similar values for a small number of aliphatic amides commonly used as solvents were previously reported by ourselves.[6] In a systematic work, mainly concerned with aromatic amides, Cox *et al.*[3] reported p*K* values between −0.1 and −1.8.

The limiting values found in this work require a first general comment. Indeed, the order of basicity ($Bu^tCONMe_2 < MeCONMe_2$) is opposite to what one would expect on the grounds that the most electron-releasing group (Bu^t) should better stabilize the protonated form and therefore give rise to the most basic amide. This apparent discrepancy can be rationalized only by considering also the other protonation parameter (m^*), as discussed below.

The m^* parameter [eqn. (1b)] relates the solvent effect on the protonation equilibrium with that of the reference equilibrium (protonation of nitroanilines) through the activity coefficients of the species involved.[12] Low m^* values are known to imply a high solvation requirement of the protonated base relative to the anilinium ions taken as reference (typical for ions where the positive charge is largely localized on a small or non-polarizable atom, *e.g.* oxonium ions with $m^* = 0.2$). At the other end of the scale, high m^* values (up to *ca.* 2.0) are found for ions in which the positive charge is mostly delocalized (arylcarbenium ions) or resides on a polarizable atom (sulfonium ions), and interact weakly with the solvent. In fact, m^* measures the solvation requirement of BH^+, *i.e.* the extent to which the positive charge is externally dispersed by interactions with the solvent (rather than internally), especially through hydrogen bonding. More practically, m^* measures the rate of increase of $\log I$ with acidity, so that the relative extent of ionization of bases with different m^*'s may actually change sign according to the medium acidity. In the present case, because the m^*s are rather low, 100% protonation is attained only in 50–60% H_2SO_4, *i.e.* at a higher acidity than one would expect only on the basis of their p*K* values. The m^* values found in this work are also similar to those reported in the literature for amides (0.5–0.7).[1–3,12] Values in this range are typical for oxygen bases where the positive charge is partly delocalized to heteroatoms: *e.g.*

Table 6 Free energies and enthalpies of hydration of neutral and protonated amides (kcal mol^{-1})[a]

	B		BH$^+$			
Compound	$\delta_R\Delta G°_{aq}$	$\delta_R\Delta H°_{aq}$	$-\delta_R\Delta G°_{aq}$	$-\delta_R\Delta H°_{aq}$	$\Delta G°_{aq}$	$\Delta H°_{aq}$
$HCONH_2$	—	−5.5	—	—	—	—
HCONHMe	—	−6.9	—	−7.4	—	−77
$HCONMe_2$	—	−6.7	—	−14.1	—	−70
$MeCONH_2$	−5.4	−8.5	−10.9	−6.4	−66	−78
MeCONHMe	−5.8	−9.2	−16.5	−12.3	−60	−72
$MeCONMe_2$	−4.3	−8.7	−22.0	−17.2	−55	−67
$EtCONH_2$	−5.1	—	—	—	—	—
Me_2NH	0.0	−4.5	−15.1	−12.6	−62	−71
Me_2O	2.4	−1.5	7.1	1.5	−84	−85
Me_2S	2.7	0.8	−22.0	−16.7	−55	−67
Me_2SO	−5.8	−9.0	−16.8	−13.2	−60	−71
Me_2CO	0.5	−1.5	−10.6	−3.5	−66	−80
MeCOOMe	1.0	−1.2	−13.4	−9.6	−64	−74

[a] In kcal mol^{-1}. See eqns. (7)–(9) for explanation of symbols. $\Delta G°_{aq}(NH_3) = -2.409$; $\Delta H°_{aq}(NH_3) = -8.243$ (Ref. 16); $\Delta G°_{aq}(NH_4^+) = -77$; $\Delta H°_{aq}(NH_4^+) = -84$ (calculated values; Ref. 19).

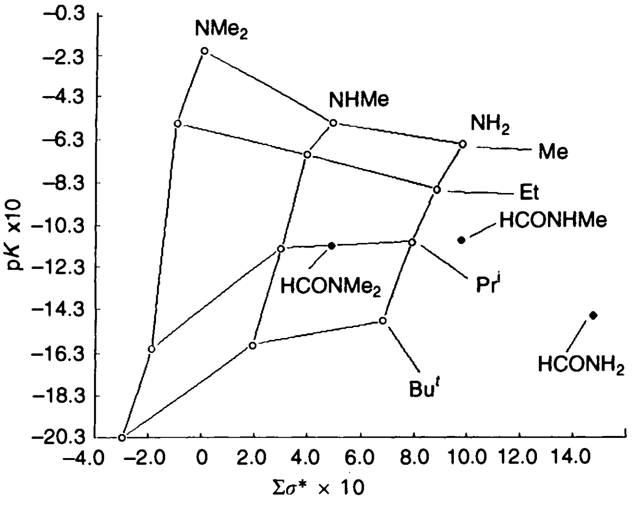


Fig. 3 Correlation between the sum of σ^* values for $R^1CONR^2R^3$ and m^*

ketones, esters and sulfoxides have $m^* = 0.3$–0.4, but those for amides are higher. These results imply a larger charge delocalization (to the nitrogen atom) with respect to the above carbonyl compounds.

Structural Effects on the Basicity of Amides.—Structural changes affect the internal and external stabilization of onium ions in opposite directions. Therefore no simple relationship can be expected between the p*K* (*i.e.* the value of the equilibrium constant at the standard state) and substituent constants. However, in order to simplify the discussion we have plotted in Fig. 3 p*K* values *vs.* the sum of σ^* for the substituents at nitrogen and carbonyl. No better results are obtained, or expected, with other choices of σ constants.

An inspection of Table 1 and Fig. 3 reveals that at constant substitution pattern at nitrogen (*i.e.* comparing primary, secondary and tertiary amides), an increase of size of the acyl moiety (Me to Bu^t) causes an increase of m^* and a decrease of p*K*. The variation is largest for tertiary amides, which span some 2 p*K* units, and progressively decreases. We can even estimate ρ^* values for the ionization of primary, secondary and tertiary amides as 2.8, 3.6 and 6.5, respectively. The formamides do not fit this scheme, with m^* values similar to the corresponding acetamides but more negative p*K*s; these compounds behave rather differently, as will be discussed below.

The trend of decreasing p*K* with increasing donor effect of the substituents has been found for other functional groups, like ketones and esters. It has been explained[12] by recalling that the positive charge in the onium ion can be dispersed internally through the substituents, thus decreasing the stabilizing interaction with the solvent through hydrogen bonding (see the m^* values). Thus the basicity as probed by p*K* (*i.e.* at the standard state, where the solvating power is a maximum) is diminished.

When we compare amides with the same acyl moiety but differing substitution at nitrogen, on going from NH_2 to NMe_2 we observe a moderate increase in m^* and a small p*K* change, which however follows different trends: p*K*s increase for R = Me, Et but decrease for Pr^i and Bu^t. In this case (going from NH_2 to NMe_2) we are changing both the number of possible hydrogen bonding sites and the internal stabilization of the ion through the electron-releasing ability of the NR_2 moiety. In all cases, going from NH_2 to NR_2 makes the interaction with the solvent less efficient, thus yielding larger m^*s. While in the Pr^i and Bu^t series this is accompanied by the usual decrease of p*K*, in the Me and Et series the internal stabilization relies to a larger extent on the electron-releasing ability of the NR_2 group: in this case, p*K* values increase.

We wish to emphasize the practical consequence of this interplay of lower p*K* associated with higher m^* by considering the actual extent of ionization. Higher m^* values imply a steeper increase of log *I* with acidity: this means that full protonation is reached at lower acid concentration for the secondary amide, despite its more negative p*K*. Indeed *N*,*N*-dimethylpropionamide is the 'strongest' amide (the one protonated at the lowest acidity) because of the favourable compromise between m^* and p*K*. The values of % H_2SO_4 needed to attain complete protonation are listed in Table 1. It can be seen that (*a*) the different behaviour of activity coefficients affects the equilibrium to the point that relative basicities predicted from p*K* values may be seriously in error or even wrong in sign when compared with the actual values in a given acid solution; (*b*) in general, more substituted amides are also more basic (in the sense given above).

Fig. 3 shows that formamides do not fit the $\Sigma\sigma^*$ correlation. The lower p*K* of formamide compared to acetamide is consistent with the difference in electron-releasing power of H and Me. However, in this case the decrease of p*K* is not accompanied by the usual increase of m^*, as occurs for the other amides; the values for formamides are in fact similar or even lower. We have attempted to gain insight into the peculiar solvation properties

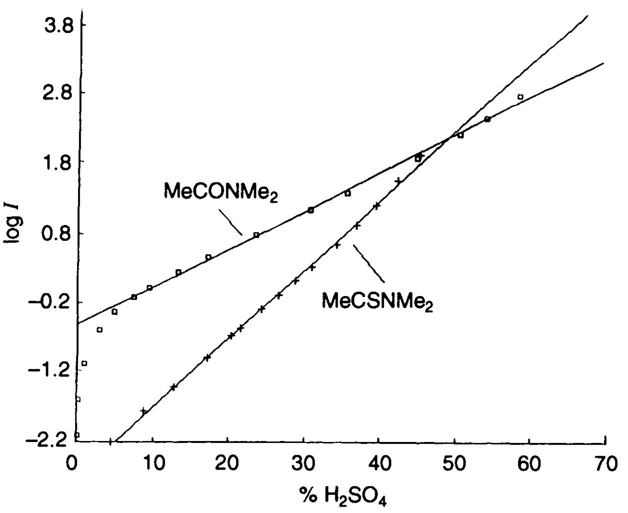


Fig. 4 Inversion of basicity between $MeCONMe_2$ and $MeCSNMe_2$. The two lines are approximate, because a linear relationship between % acid and log *I* is not expected. The lines intersect at 48% H_2SO_4.

of protonated formamides by considering the $\Delta\delta^{13}C$ values (Fig. 1) in the hope that these would show any anomalous charge density changes in these molecules. Indeed, $\Delta\delta^{13}C$ values are correlated with m^* for all compounds except formamides. However, the measured changes are *ca.* ±2 ppm, which is an order of magnitude lower than those found for ketones.[15] This is perhaps due to the larger charge delocalization taking place in protonated amides, but, in view of the small changes, the observed deviations are of little diagnostic help.

Quite interestingly, the *ab initio* charges (Table 3) show that the structural dependence of the partial positive charge on the acidic ($C{=}OH^+$) hydrogen parallels the observed changes in m^*. In fact, m^* reaches a minimum in $MeCONH_2$ (Table 1) and then steadily increases with alkyl substitution (this implies that protonated acetamide has the highest solvation requirement). Correspondingly, the charge on the acidic hydrogen in $MeC(OH)^+NH_2$ is the highest in the series of primary amides (this implies the lowest degree of charge delocalization and therefore the largest stabilization by solvation).

The other theoretical results offer some useful insight too. Upon protonation, the nitrogen atom and the amide hydrogens undergo a moderate increase (*ca.* 15%) of positive charge (Table 3), while the charges on the carbonyl carbon and oxygen increase by only 6–7%; the acyl groups experience the largest charge increase, alkyl hydrogens bearing all of the charge (the carbon actually becomes slightly more negative). The amount of change for formamide is the lowest, in agreement with the expected lower stabilizing efect of H *vs.* alkyl. The *ab initio* calculations hence show that: (*a*) the internal stabilization of the onium ion is lower in formamides than in acetamides; (*b*) the amount of charge on the acidic hydrogen is lower in acetamides than in formamides. These two effects are bound to show lower p*K* and larger m^* values for formamides than acetamides, as shown by the experimental results.

Calculated proton affinities (Table 2) show a monotonic increase with alkyl substitution, and level off for R = Pr^i and Bu^t. It is very important to note that this trend, which expresses an intrinsic basicity, does not match the trend of p*K* changes (which is not monotonic) but rather the trend of % H_2SO_4 values required for 100% protonation (Table 1). Though the match is not perfect (in particular, the levelling noted above is not found in solution) these results support our claim (see above) that, especially for weak bases, p*K* values generally do not reflect intrinsic basicities because they contain complex differential solvation effects. On the contrary, if solvation (*i.e.* m^*) is taken into account, one can calculate the above % H_2SO_4 values and obtain a 'basicity scale' referring to poorly solvated conditions which better match the gas-phase behaviour.

Relative Basicity of Amides and Thioamides.—The comparison with the corresponding thioamides is particularly interesting (Table 1). The main difference lies in the very different m^* values (1.7 *vs.* 0.7 for thioamides and amides, respectively), which reflects the low solvation of the $R\text{-}C(SH)^+\text{-}NR_2$ ions; simple sulfonium ions R_2SH^+ (m^* = 1.3) compare similarly with oxonium ions R_2OH^+ (m^* = 0.2).[12] $R\text{-}C(SH)^+\text{-}NR_2$ ions are stabilized mainly by the sulfur atom, and indeed there is almost no structural dependence of basicity[10] (m^* and p*K* are about the same) unlike amides, in which the solvent takes a decisive part in the stabilization (though less than in other carbonyl bases). These extreme m^* values (only those for carbenium ions are higher) imply a very steep increase of log *I* with acidity; in fact thioamides reach 100% protonation before the corresponding amides, despite a p*K* more negative by 1–2 units, in full analogy to what we discussed before. The situation is depicted in Fig. 4, which shows the acidity dependence of log *I* for $CH_3CON(CH_3)_2$ and $CH_3CSN(CH_3)_2$. The steeper line of the thioamide crosses the other at 48% H_2SO_4, and therefore at higher acid concentrations the thioamide is more protonated than the amide. Similar inversions of basicity and acidity are known.[12,22]

Thermodynamic Parameters.—The complete characterization of the ionization equilibria in solution afforded by enthalpies and entropies of ionization allows us to determine the relative weight that these have on the basicity of amides. However, we emphasize that, because these quantities refer to the process at the standard state (like the p*K*), all the considerations will also refer to ideal aqueous solution. Thus in this context the term 'basicity' does not mean the fractional concentration of BH^+ in an acid solution where B is measurably protonated, but only the standard-state basicity. We also remark that the estimated errors on $\Delta H°$ and $\Delta S°$ preclude the discussion of small differences.

Firstly, we note that the values of $\Delta H°$ and $\Delta S°$ (−2.4 kcal mol^{-1} and −6.3 cal mol^{-1} K^{-1}, respectively) previously obtained[14] for CH_3CONMe_2 are at variance with our own, and do not fit the general trend (see below). The values of m^* and p*K* at 25 °C (0.54 and −0.40, respectively) are not very different from ours; therefore the discrepancy probably arises from an incorrect treatment of the data obtained at higher temperatures. We wish to stress this point because such data have been the only ones hitherto available, and were used to calculate the energetics of solvation of BH^+.[16,19]

(a) *Comparison with other carbonyl compounds.* The values of $\Delta G°$ for all amides studied lie between −2.77 and −0.29 kcal mol^{-1}, and are thus greater than for other oxygen bases (aliphatic ketones and esters have values between −6 and −4 kcal mol^{-1}). The enthalpies of ionization of aliphatic ketones are generally close to zero (to be compared with −4.1–0.0 kcal mol^{-1} for amides), while those of esters are similar to those of amides or slightly more negative. The main difference lies in the entropies: for ketones and esters they are markedly positive (6–16 cal mol^{-1} K^{-1}) and give a base-weakening contribution, while those of amides are lower or negative (−4.5–3.7 cal mol^{-1} K^{-1}) and give a favourable contribution. Thus the greater basicity of amides stems from a favourable entropy of ionization, while esters are disfavoured also by the enthalpic term. We also note that, if in a family of bases the charge is better delocalized, $\Delta H°$ becomes more negative because solute–solvent interactions are relatively unfavourable. An inspection of Tables 1 and 4 shows that amides in general resemble sulfoxides rather than simple carbonyl bases.

(b) *Comparison with thiocarbonyl bases.* This is particularly interesting because it shows the sole effect of substitution with sulfur without any skeletal change. Table 1 shows that the thioamides R-CS-NMe$_2$ with R = Me, Et are less basic because of the enthalpy term, despite an entropy of ionization more favourable than for the amides. When R = Pr^i the values of $\Delta S°$ are the same, so that the difference is determined by the $\Delta H°$, while when R = Bu^t the balance is inverted and the pKs are practically equal. Thus the effect of substitution with sulfur is not constant, but depends on the whole structure. This example highlights the compensating effect of structural changes on basicities: when the charge is better delocalized into the substitutents or polarizable atoms, the ion interacts unfavourably with the solvent; this has the double effect of making the enthalpy of ionization less exothermic (base-weakening) but the entropy of ionization more negative (base-strengthening) because the solvent becomes more ordered. Obviously, these considerations apply only to structurally related compounds, where other enthalpic, and especially entropic, effects can be assumed equal.

(c) *Comparisons among amides.* Within the classes of primary, secondary or tertiary amides, if the acyl moiety becomes larger both $\Delta H°$ and $\Delta S°$ become smaller or more negative. Thus the pK is determined by two counteracting factors, as seen above, whose weight is similar for primary and secondary amides. For tertiary amides $\Delta H°$ is larger and its base-weakening effect predominates accordingly.

Energetics of the Gas Phase to Water Transfer.—The values of $\delta_{aq}\Delta G°$ and $\delta_{aq}\Delta H°$, *i.e.* the difference between the free energies and enthalpies of ionization in gas phase and solution, tend to be more negative than for other oxygen bases of similar size, particularly for the *N*,*N*-dimethylamides. This is largely due to the GB and PA values (which are higher by 8–10 kcal mol^{-1}), while the corresponding quantities in solution differ less. Thus, amides are stronger bases also in the gas phase, because the lower solvation requirement of protonated amides favours them in a non-solvating environment. This in turn agrees with the results in solution, which show that amides are favoured also in poorly solvating acidic media.

The data obtained in this work now allow us to compare the energetics of solvation of neutral and protonated amides with other onium ions and among themselves.

Firstly, we observe that the enthalpies of solvation of neutral amides are more exothermic than for the other bases listed in Table 4, except Me$_2$SO. This corresponds to the well known strong hydrogen-bonding ability of amides (and Me$_2$SO) in water. The strongly exothermic enthalpy of solvation is partly compensated for by a corresponding unfavourable entropy of solvation, as usual, but the latter remains almost constant for all species (at *ca.* -30 cal mol^{-1} K^{-1}). Thus the outcome in terms of ΔG reflects the behaviour of the enthalpies, so that the solvation of amides is also more exoergonic with respect to the other bases.

With the protonated species the situation is different, because in this case the properties of the proton-bearing site prevail. For example, the most exothermic and exoergonic solvation is displayed by the strongly hydrogen-bonded Me$_2$OH$^+$ ion, for which the entropy of solvation is close to zero, as expected from the close similarity between solute and solvent. The decreasing strength of the hydrogen bonding can be appreciated by comparing it with Me$_2$NH$_2{}^+$ and Me$_2$SH$^+$.

The behaviour of amides shows again a marked dependence on the substitution at nitrogen. Firstly, the values of $\Delta H°_{aq}$ for the two *N*,*N*-dimethylamides are less exothermic than for the others, which shows the effect of removing hydrogen-bonding sites. A more detailed analysis can be done for the three acetamides, for which the complete data set is available. As before, both $\Delta H°_{aq}$ and $\Delta G°_{aq}$ become less negative going from the primary to the tertiary one. The difference among them rests only in the enthalpies of solvation of BH$^+$, which differ by *ca.* 6 kcal mol^{-1} for each added methyl group. The values of $\Delta S°_{aq}$(BH$^+$) are thus the same (-40 cal mol^{-1} K^{-1}). This trend highlights the importance of hydrogen bonding terms in the energetics of solvation of a series of similar onium ions.

Such comparisons may not always be valid, because solvation energies contain also differing contributions due to cavity formation in the solvent, which depend on the molecular size.[16] This difficulty can be partly overcome by dissecting the observed $\Delta G°_{aq}$ (or $\Delta H°_{aq}$) into the sum of a non-electrostatic general term ($\Delta G°_{aq.ne}$, due to cavity formation and van der Waals interactions) and an electrostatic term ($\Delta G°_{aq.el}$), and making the assumption[23] that the former is equal to the value for the neutral species [$\Delta G°_{aq.ne}(BH^+) = \Delta G°_{aq}(B)$]; then the electrostatic solvation term can be estimated [eqns. (10) and (11)]

$$\Delta P°_{aq.el}(BH^+) \approx \Delta P°_{aq}(BH^+) - \Delta P°_{aq}(B) \quad (10)$$

$$\Delta P°_{aq.el}(BH^+) = \Delta P°_{aq.el}(NH_4{}^+) - \delta_{aq}\Delta P° \quad (11)$$

recalling eqn. (9). Thus under this assumption the electrostatic term differs from $\delta_{aq}\Delta P°$ by a constant [whose values are $\Delta G°_{aq.el}(NH_4{}^+) = -75$ and $\Delta H°_{aq.el}(NH_4{}^+) = -76$ kcal mol^{-1}].

For example, it can be seen that both $\Delta G°_{aq}$ and $\Delta H°_{aq}$ are equal for MeC(OH)$^+$NMe$_2$ and Me$_2$SH$^+$. However, this coincidence does not imply that the 'absolute' solvation properties are equal for the two ions, because the corresponding electrostatic terms for the sulfonium ion are much less exothermic and exoergonic than for the other, as expected. With regard to amides, Table 5 shows that our previous conclusions hold also for the electrostatic terms (solvation energies becoming less negative in the order CONH$_2$ < CONHMe < CONMe$_2$).

Conclusions

We have obtained a series of data concerning the basicity of aliphatic amides, using accurate experimental methods and modern data processing techniques. These data provide a picture of the combined influence that structural and solvation effects have on these compounds; thus we have shown that increased alkyl substitution entails two counteracting effects, in that the stability of the onium ion is increased in strongly acidic solutions but decreased at the standard state. Therefore, tertiary amides generally have more negative pKs but are more easily protonated; this effect is reflected in their m^* values, which must be taken into account if one wants to estimate the fraction of protonation taking place in a given acid solution. The combined influence of m^* and pK has also been analysed and compared to analogous thio compounds. The thermodynamic factors determining the standard state basicity of amides have also been evaluated; thus, it is shown that the greater basicity of amides with respect to ketones and esters stems mainly from more favourable entropies of ionization. The energetics of the solvation of protonated amides have been compared with onium ions derived from other bases: the main factor affecting the exothermicity of solvation is shown to be the number and strength of hydrogen bonding sites.

Experimental

All the amides studied are commercially available, except Bu^{t}CONH$_2$, Pr^{i}CONHMe, Bu^{t}CONHMe, Pr^{i}CONMe$_2$ and Bu^{t}CONMe$_2$, which were prepared by standard methods.

Preparation of sulfuric acid solutions, sample purification and handling were carried out as previously described.[6,13] NMR measurements were run unlocked on a Bruker AC 200 instrument operating at 4.7 T equipped with a variable temperature unit. 32K points were used in acquisition; the ^1H solvent peak was suppressed by gated decoupling. The temperature was checked by a sample of neat ethylene glycol.

Processing of experimental data was carried out as previously described.[13]

Ab initio calculations were carried out with the *Spartan* (V. 2.0) program running on an IBM RS/6000 workstation.

References

1 (*a*) K. Yates, J. B. Stevens and A. R. Katritzky, *Can. J. Chem.*, 1964, **42**, 1957; (*b*) J. T. Edward and S. C. Wong, *Can. J. Chem.*, 1977, **55**, 2492; (*c*) M. Liler and D. Markovic, *J. Chem. Soc., Perkin Trans. 2*, 1982, 551; (*d*) G. D. Frederick and C. D. Poulter, *J. Am. Chem. Soc.*, 1975, **97**, 1797.

2 J. T. Edward and S. C. Wong, *J. Am. Chem. Soc.* 1977, **99**, 4229.

3 R. A. Cox, L. M. Druet, A. E. Klausner, T. A. Modro, P. Wan and K. Yates, *Can. J. Chem.*, 1981, **59**, 1568.

4 P. De Maria, C. L. Barbieri, D. Spinelli, C. Dell'Erba, M. Novi, G. Petrillo and F. Sancassan, *J. Chem. Soc., Perkin Trans. 2*, 1991, 373.

5 A. Bagno, V. Lucchini and G. Scorrano, *Bull. Soc. Chim. Fr.*, 1987, 563.

6 A. Bagno and G. Scorrano, *J. Am. Chem. Soc.*, 1988, **110**, 4577.

7 S. G. Lias, J. F. Liebman and R. D. Levin, *J. Phys. Chem. Ref. Data*, 1984, **13**, 695 and updates.

8 (*a*) G. Della Gatta, G. Barone and V. Elia, *J. Solution Chem.*, 1986, **15**, 157; (*b*) V. Majer and V. Svoboda, *Enthalpies of Vaporization of Organic Compounds. A Critical Review and Data Compilation*, IUPAC Chemical Data Series No. 32, Blackwell, Oxford, 1985.

9 (*a*) R. Wolfenden, *J. Am. Chem. Soc.*, 1976, **98**, 1987; (*b*) R. Wolfenden, *Biochemistry*, 1978, **17**, 201; (*c*) R. Wolfenden, L. Andersson, P. M. Cullis and C. C. B. Southgate, *Biochemistry*, 1981, **20**, 849.

10 A. Bagno, V. Lucchini and G. Scorrano, *Can. J. Chem.*, 1990, **68**, 1746.

11 V. K. Krieble and K. A. Holst, *J. Am. Chem. Soc.*, 1938, **60**, 2976.

12 A. Bagno, G. Scorrano and R. A. More O'Ferrall, *Rev. Chem. Intermed.*, 1987, **7**, 313.

13 A. Bagno, V. Lucchini and G. Scorrano, *J. Phys. Chem.*, 1991, **95**, 345.

14 G. Zangrossi, Tesi di Laurea, Università di Padova, 1976; quoted also in ref. 16.

15 G. Scorrano and V. Lucchini, *J. Org. Chem.*, 1979, **44**, 1726.

16 R. W. Taft, J. F. Wolf, J. L. Beauchamp, G. Scorrano and E. M. Arnett, *J. Am. Chem. Soc.*, 1978, **100**, 1240.

17 M. Decouzon, O. Exner, J.-F. Gal and P.-C. Maria, *J. Org. Chem.*, 1992, **57**, 1621.

18 D. H. Aue and M. T. Bowers, in *Gas Phase Ion Chemistry*, ed. M. T. Bowers, Academic Press, New York, 1979, vol. 2.

19 R. W. Taft, *Prog. Phys. Org. Chem.*, 1983, **14**, 247.

20 E. M. Arnett, *Prog. Phys. Org. Chem.*, 1963, **1**, 223.

21 R. A. Cox and K. Yates, *Can. J. Chem.*, 1983, **61**, 2225.

22 A. Bagno, G. Scorrano and F. Terrier, *J. Chem. Soc., Perkin Trans. 2*, 1990, 1017.

23 B. Wilson, R. Georgiadis and J. E. Bartmess, *J. Am. Chem. Soc.*, 1991, **113**, 1762.

Paper 3/00829K
Received 10*th February* 1993
Accepted 15*th March* 1993