

EVALUATION OF SOLVENT EFFECTS ON THE DISSOCIATION OF ALIPHATIC CARBOXYLIC ACIDS IN AQUEOUS *N,N*-DIMETHYLFORMAMIDE MIXTURES ACCORDING TO THE SCALED PARTICLE THEORY

A. GUSTAVO GONZALEZ,* D. ROSALES AND J. L. GOMEZ ARIZA

Department of Analytical Chemistry, Faculty of Chemistry, University of Seville, 41012 Seville, Spain

AND

J. FERNANDEZ SANZ*

Department of Physical Chemistry, Faculty of Chemistry, University of Seville, 41012 Seville, Spain

The standard Gibbs energies of transfer, ΔG_i° from water to water-*N,N*-dimethylformamide mixtures for the dissociation process of several organic acids (formic, acetic, propionic, *n*-butyric, isobutyric, *n*-valeric, isovaleric, 2-methylbutyric and trimethylacetic acids) obtained from the pK_a° values are discussed in terms of the extended Scaled Particle Theory from quantum mechanical calculations in order to estimate the cavity and electrostatic contributions. The residual energy term was correlated with the hydrogen bond acceptor density and the Kamlet-Taft β parameters. The main contribution to ΔG_i° was due to dipolar and specific interactions.

INTRODUCTION

Amide-water mixtures are important polar reaction media and solvents for the interpretation of the properties of peptides in aqueous solution.¹ Aliphatic amides seem to be an optimal class of water-miscible solvents for use in studies on the interrelations between the solubility of drugs and the permittivity of the medium.² *N,N*-Dimethylformamide (DMF) has often been used as a model of the peptide linkage for a clearer understanding of the protein-denaturing ability of lithium salts^{3,4} and some biological processes are known to prefer an 'amide-like' to a 'water-like' environment.⁵

DMF appears to be a suitable cosolvent because it is aprotic and completely miscible with water. Water-DMF mixtures are strongly non-ideal and can act in the solute-solvation process according to two different solvation mechanisms: hydrophobic interaction on the polar sites at the solute molecule and preferential hydrogen bonding on the hydrophilic groups of the solute.^{6,7}

In a recent study⁸ we examined the acid-base features of formic, acetic, propionic, *n*-butyric, isobutyric *n*-valeric, isovaleric, 2-methylbutyric and trimethylacetic

acids in different water-DMF mixtures containing from 0 to 80 per cent v/v DMF regardless to its acidity constant, K_a^* , based on the standard state in the water-DMF mixture considered.

In this paper, a methodological process for the analysis of the solvent effect is given according to the scaled particle theory (SPT) model applied to the acid-base dissociation equilibria of several aliphatic carboxylic acids in water-DMF mixtures. The aim of this work was to develop procedures for the determination of the effects of the medium on dissociation. Quantum mechanical calculations were used in an attempt to overcome the problem of the evaluation of the size parameter for ionic species.

THEORETICAL METHODS

Molecular and ionic radii and charge distributions were obtained from SCF-MO theoretical calculations. All equilibrium geometries were determined by minimizing the total energy with respect to all geometrical variables. Geometrical parameters and the charge distributions of acids and their anions were estimated by means of the AM1 semi-empirical SCF-MO method⁹ using the AMPAC package.¹⁰ *Ab initio* calculations on solvents and their protonated derivatives were carried

* Authors for correspondence.

out using the GAUSSIAN 82 series of programs.¹¹ For H₂O and H₃O⁺ species, the 6-31G** split valence plus polarization basis set¹² was used, and for DMF the standard 3-21G split valence basis set.¹³ However, for DMF this level of calculation seems to furnish a strongly polarized wavefunction leading to a dipole moment (4.17 D) larger than experimental value of 3.82 D.¹⁴ The addition of polarization functions on the heavy atoms does not improve the calculated dipole moment, being 4.23 D at the 4-31G**//3-21G level.¹⁵ Because computing time restrictions prevent us from performing calculations with larger basis sets, we chose for DMF and DMFH⁺ the charge distribution obtained from AM1 semi-empirical wavefunctions. The dipole moment for DMF obtained in this way was 3.60 D, in excellent agreement with experiment. The AM1 optimized geometries are not discussed here, but are available on request.

RESULTS AND DISCUSSION

The changes in the Gibbs standard free energy accompanying the ionization of an acid HA in any mixed solvent (${}_s\Delta G^\circ$) relative to that in pure water (${}_w\Delta G^\circ$) are called the solvent effect and may be regarded as Gibbs

standard energies of the proton transfer, ΔG_i° (HA/A⁻). These values were calculated at 25 °C from the pK_a^* values reported by us⁸ using the following equation:^{16,17}

$$\Delta G_i^\circ(\text{HA/A}^-) = ({}_s\Delta G^\circ) - ({}_w\Delta G^\circ) \\ = 2.303RT(pK_a^* - pK_a^w) \quad (1)$$

For the sake of brevity, we shall use ΔG_i° rather than $\Delta G_i^\circ(\text{HA/A}^-)$ in the following. These ΔG_i° experimental values are given in Table 1.

ΔG_i° values were plotted against $1/D_s - 1/D_w$ (D = permittivity and subscripts s and w refer to mixed solvent and water, respectively) in order to establish whether or not the electrostatic effect of permittivity changes is predominant. Empirical relationships derived therefrom are given in Table 2.

$$\Delta G_i^\circ = A + B \Delta(1/D) \quad (2)$$

As can be observed, the intercept is close to zero and the slope is similar in all cases. This behaviour seems to indicate that the dielectric solvent effect contributes substantially to the dissociation processes.

According to Papanastasiou *et al.*¹⁸ it is interesting that in mixed solvents which have a low organic cosolvent content, a linear dependence exists between pK_a

Table 1. ΔG_i° exp values in kJ mol⁻¹ for the ionization of acids using various DMF-water mixtures

Acid	DMF (% _v , v/v)							
	10	20	30	40	50	60	70	80
Formic	0.399	1.426	2.739	4.279	6.105	9.186	12.210	17.117
Acetic	0.570	1.883	2.910	4.451	6.162	8.787	12.381	17.859
Propionic	0.513	1.598	2.853	4.222	6.219	8.844	12.610	17.674
<i>n</i> -Butyric	0.399	1.826	2.967	4.565	7.418	9.415	13.238	18.772
Isobutyric	0.456	1.997	2.511	5.428	7.246	9.928	13.808	19.685
<i>n</i> -Valeric	0.513	1.997	2.739	4.336	7.132	9.129	13.609	17.973
Isovaleric	0.513	1.940	2.739	4.850	6.989	9.129	13.352	18.716
2-Methylbutyric	0.456	2.111	3.766	4.565	7.646	10.556	14.721	20.199
Trimethylacetic	0.685	2.282	3.309	4.622	7.418	10.556	14.835	19.799

Table 2. Regression parameters of linear plots ΔG_i° exp = A + BΔ(1/D)

Acid	A ± s(A) ^a	B ± s(B) ^a	Correlation coefficient
Formic	0.024 ± 0.125	2514.460 ± 0.360	0.9994
Acetic	0.180 ± 0.103	2552.180 ± 0.310	0.9996
Propionic	0.011 ± 0.026	2562.450 ± 0.006	1.0000
<i>n</i> -Butyric	0.106 ± 0.177	2733.070 ± 0.006	0.9990
Isobutyric	0.068 ± 0.234	2855.340 ± 0.006	0.9998
<i>n</i> -Valeric	0.177 ± 0.171	2612.830 ± 0.006	0.9990
Isovaleric	0.032 ± 0.131	2710.860 ± 0.006	0.9990
2-Methylbutyric	0.194 ± 0.188	2945.550 ± 0.006	0.9990
Trimethylacetic	0.245 ± 0.177	2901.790 ± 0.006	0.9990

^as = Standard deviation.

values and the reciprocal of the permittivity ($1/D$). The slope of this straight line can be expressed by a relationship given by Bjerrum and Larson¹⁹ based on the Born electrostatic model²⁰:

$$\frac{dpK_a}{d(1/D)} = \frac{Ne^2}{4 \cdot 606RT} \left(\frac{1}{r_{H^+}} + \frac{1}{r_{A^-}} \right) \quad (3)$$

where r_{H^+} and r_{A^-} are the ionic radii for the species H^+ and A^- , respectively. Accordingly,

$$\frac{d\Delta G_i^\circ}{d\Delta(1/D)} = \frac{Ne^2}{2} \left(\frac{1}{r_{H^+}} + \frac{1}{r_{A^-}} \right) \quad (4)$$

Assuming that $r_{A^-} \approx r_{H_2O} = 1.4 \text{ \AA}$, the ionic radius for A^- can be estimated using the experimental value of the slope B :

$$r_{A^-} = 1/(2B/Ne^2 - 1/r_{H^+}) \quad (5)$$

In all cases the r_{A^-} values were meaningless (less than 0.33 \AA). As Sen and Adcock²¹ indicated, if a reasonable value is assumed for the solvated protons, it is possible to calculate the anionic radii. In the Born model, it is assumed that the ions are monatomic and spherical. Although it might be possible to assign a value to the lyonium ion radius, the anionic radius could be misleading, especially when the anion is polyatomic. Moreover, Reynaud²² has observed that the linear plots of ΔG_i° versus $\Delta(1/D)$ for a large amount of mixed solvent leads to absurd values for the anionic radii when equation (5) is used. It was pointed out that considering only the electrostatic Born energies is an inadequate way to describe the experimental behaviour of solute dissociation processes, even when a linear relationship was obtained. We have therefore attempted a deeper treatment of the effects of the medium on dissociation of carboxylic acids by means of the scaled particle theory (SPT). According to this theory, developed by Pierotti,²³⁻²⁵ we consider the ionization-dissociation process to consist of three steps:

1. The formation of a cavity in the solvent of suitable size to accommodate the solute.
2. The introduction into the cavity of a solute species which interacts with the solvent. The nature of interactions can be electrostatic (changes in the macroscopic dielectric constant of solvent), dipolar (ion-dipole or dipole-dipole short range interactions, deriving from the Lennard-Jones potential) or specific (hydrogen bonding, chemical equilibria, etc.)
3. Return to the standard state.

Each step can be described by a set of thermodynamic functions, and the sum gives the Gibbs standard free energy of dissociation:

$$\Delta G = \Delta G_{cav} + \Delta G_{el} + \Delta G_{dip} + \Delta G_{sp} + RT \ln(RT/V) \quad (6)$$

where the subscripts refer to the cavity formation (cav), electrostatic interactions (el), dipolar interactions (dip) and specific interaction (sp). The last term is the energy needed to return to the standard state. In this work we chose as a reference state a homogeneous mixture of water and DMF at a given composition.²⁶ The specification of the standard states of condensed phases usually includes the specification that the external pressure is 1 atm. Accordingly, a change in the pressure of the standard state could be energetically evaluated as $RT \ln(RT/V)$, where V is the molar volume of the mixed solvent.²⁷

The difference between ${}_s\Delta G$ and ${}_w\Delta G$ is the effect of the medium on the acidic system:

$$\Delta G_i^\circ = \Delta G_{i,cav}^\circ + \Delta G_{i,el}^\circ + \Delta G_{i,dip}^\circ + \Delta G_{i,sp}^\circ + RT \ln(V_w/V_s) \quad (7)$$

On the other hand, the solvent effect on the dissociation process can be expressed by²⁸

$$\Delta G_i^\circ = \Delta G_{i(H^+)}^\circ + \Delta G_{i(A^-)}^\circ - \Delta G_{i(HA)}^\circ \quad (8)$$

Estimation of $\Delta G_{i,cav}^\circ$

The partial molar Gibbs free energy for cavity formation is expressed by applying the SPT to a mixed solvent:²⁹

$$\Delta G_{cav}^\circ = RT[-\ln(1-\xi) + 3\sigma^2 Y/(1-\xi) + 3\sigma X/(1-\xi) + 9\sigma^2 X^2/2(1-\xi)^2] \quad (9)$$

where ξ is the compacity factor:

$$\xi = \pi N(x_w \sigma_w^3 + x_{DMF} \sigma_{DMF}^3)/6V_s \quad (10)$$

X and Y are given by

$$X = \pi N(x_w \sigma_w^2 + x_{DMF} \sigma_{DMF}^2)/6V_s \quad (11)$$

and

$$Y = \pi N(x_w \sigma_w + x_{DMF} \sigma_{DMF})/6V_s \quad (12)$$

σ , σ_w and σ_{DMF} are the rigid sphere diameter of the solute, water and DMF, respectively, x_w and x_{DMF} are the mole fraction of water and DMF, respectively, and V_s is the molar volume of the mixed solvent, which can be taken as

$$V_s = (x_w M_w + x_{DMF} M_{DMF})/\rho \quad (13)$$

M being the molecular weight of the solvent and ρ the density of the mixture; these data are reported in Ref. 8.

The SPT simplifies the structure of a molecule as an inelastic hard sphere with a defined diameter. We have extended the hard sphere concept to ionic species according to the Kirkwood-Westheimer model.³⁰ To determine $\Delta G_{i,cav}^\circ$ values, the values of the hard sphere

diameter for the solute, water and DMF are also needed. For a molecule, the hard sphere diameter can be obtained in several ways.³¹⁻³³

The simplest rule is to use a linear relationship between the hard sphere diameter, σ , and the density of the pure compound:³⁴

$$\sigma(\text{SPT}) = 0.9275 \sqrt{\frac{6M}{N\pi\rho}} - 0.8465 \times 10^{-8} \text{ cm} \quad (14)$$

For ionic species, the hard sphere diameter cannot be evaluated from experimental data, but it is possible to obtain a good estimation via quantum mechanical methods. The cartesian coordinates of the atoms in the different molecular and ionic species considered in this work were calculated by means of semi-empirical and *ab initio* methods. From these, the coordinates of the charge centre (x_c, y_c, z_c) were evaluated.

$$\sigma(\text{SPT}) = 2(r_{\max} + 1.5) \quad (15)$$

where r_{\max} is the distance in ångströms between the charge centre and the outer atom and 1.5 is a correction parameter for the spherical model.³⁰

The results obtained are given in Table 3 and they agree reasonably well with the results obtained from equation (14).

Once the hard sphere diameter of species is known, the energy of the cavity is easily calculated by using equation (9).

Table 3. Hard sphere diameters (σ) and Hiromi parameters (L) from quantum mechanical calculation for several neutral and ionic species

Species	σ (Å)	L
Formic acid	3.60	0.798
Formate	3.66	1.520
Acetic acid	4.94	0.917
Acetate	5.00	1.312
Propionic acid	6.60	0.488
Propionate	6.50	1.266
<i>n</i> -Butyric acid	7.92	0.543
<i>n</i> -Butyrate	7.82	1.398
Isobutyric acid	6.20	0.666
Isobutyrate	6.18	1.460
<i>n</i> -Valeric acid	9.34	0.575
<i>n</i> -Valerate	9.26	1.506
Isovaleric acid	6.78	0.895
Isovalerate	6.70	1.755
2-Methylbutyric acid	7.82	0.597
2-Methylbutyrate	7.78	1.440
Trimethylacetic acid	6.06	0.911
Trimethylacetate	6.00	1.655
H ₂ O ^a	2.42	0.789
H ⁺ (H ₂ O) ^a	2.50	2.232
DMF	5.64	0.500
H ⁺ (DMF)	5.80	1.169

^a From *ab initio* calculations.

For the sake of correctness, it is necessary to indicate the limitations of the SPT model in the calculation of cavitation energies in liquids. Langlet *et al.*³⁵ pointed out (in the case of pure liquids) the need for a more exact description of the solute shape and suggested describing the solute molecule as the union of intersecting atomic spheres. Moreover, the Van der Waals radii of these spheres were taken as structure dependent. These problems become greater in a complex mixture such as water-DMF. According to the difficulties that arise when using this modified version of SPT and despite all possible drawbacks, we utilized the equations corresponding to Pierotti's formulation because at present there is no cavity model which permits a better treatment of such a complex system.

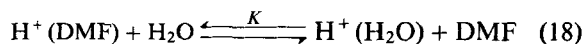
The Gibbs free energy of transfer for the cavity formation is given by

$$\Delta G_{\text{cav}}^{\circ} = {}_s\Delta G_{\text{cav}}^{\circ} - {}_w\Delta G_{\text{cav}}^{\circ} \quad (16)$$

and according to equation (8)

$$\Delta G_{\text{t cav}}^{\circ} = \Delta G_{\text{t cav}(\text{H}^+)}^{\circ} + \Delta G_{\text{t cav}(\text{A}^-)}^{\circ} - \Delta G_{\text{t cav}(\text{HA})}^{\circ} \quad (17)$$

For the H⁺ ion, the $\Delta G_{\text{t cav}}^{\circ}$ value was obtained in a different way. Since the hard sphere diameter of the H⁺ ion is not computable, and in fact the proton does not exist free in solution, we estimated its cavitation energy of transfer as the difference between the transfer energy of cavity formation for the solvated proton and the corresponding energy for a molecule of solvent. Unfortunately, it cannot be assumed that the proton is solvated only by water and hence we took into consideration the hydrated proton H⁺(H₂O) and the proton solvated by DMF, H⁺(DMF). The relative proton affinity between water and DMF is given by the reaction



From the proton affinity data in the gas phase,³⁶ the equilibrium constant K can be obtained assuming there are no entropy changes in the process:

$$K = \frac{a_{\text{H}^+(\text{H}_2\text{O})} a_{\text{DMF}}}{a_{\text{H}^+(\text{DMF})} a_{\text{H}_2\text{O}}} = 0.97 \quad (19)$$

Assuming the same value in solution and taking the activities of water and DMF as equal to the mole fractions, we have

$$\frac{a_{\text{H}^+(\text{DMF})}}{a_{\text{H}^+(\text{H}_2\text{O})}} = 0.97 \frac{x_{\text{H}_2\text{O}}}{x_{\text{DMF}}} = \frac{z}{1-z} \quad (20)$$

where z is the fraction of solvated proton which exists as the hydrated form H⁺(H₂O).

The Gibbs free energy of transfer for lyonium cavity formation is given by

$$\Delta G_{\text{t cav}(\text{H}^+)}^{\circ} = z\{\Delta G_{\text{t cav}[\text{H}^+(\text{H}_2\text{O})]}^{\circ} - \Delta G_{\text{t cav}(\text{H}_2\text{O})}^{\circ}\} + (1-z)\{\Delta G_{\text{t cav}[\text{H}^+(\text{DMF})]}^{\circ} - \Delta G_{\text{t cav}(\text{DMF})}^{\circ}\} \quad (21)$$

Table 4. $\Delta G_{i\text{cav}}^{\circ}$ values in kJ mol^{-1} for the ionization of acids using various DMF-water mixtures

Acid	DMF (% v/v)							
	10	20	30	40	50	60	70	80
Formic	0.068 (17.0) ^a	0.150 (10.5)	0.279 (10.2)	0.447 (10.4)	0.692 (11.2)	1.045 (11.4)	1.563 (12.8)	2.414 (14.1)
Acetic	0.077 (13.5)	0.170 (9.0)	0.313 (10.7)	0.500 (11.2)	0.764 (12.4)	1.155 (13.1)	1.723 (13.9)	2.624 (14.7)
Propionic ^b	-0.037 (-7.2)	-0.127 (-7.9)	-0.127 (-4.4)	-0.170 (-4.0)	-0.196 (-3.2)	-0.215 (-2.4)	-0.167 (-1.3)	0.034 (0.2)
<i>n</i> -Butyric ^b	-0.059 (-14.8)	-0.120 (-6.6)	-0.207 (-7.0)	-0.300 (-6.6)	-0.396 (-5.3)	-0.485 (-5.2)	-0.547 (-4.1)	-0.496 (-2.6)
Isobutyric	0.011 (2.4)	0.030 (1.5)	0.063 (2.5)	0.110 (2.0)	0.204 (2.8)	0.365 (3.7)	0.633 (4.6)	1.134 (5.8)
<i>n</i> -Valeric ^b	-0.055 (-10.7)	-0.112 (-5.6)	-0.187 (-6.8)	-0.280 (-6.4)	-0.356 (-5.0)	-0.445 (-4.9)	-0.477 (-3.5)	-0.356 (-2.0)
Isovaleric ^b	-0.035 (-6.8)	-0.069 (-3.6)	-0.117 (-4.3)	-0.160 (-3.3)	-0.186 (-2.7)	-0.195 (-2.1)	-0.147 (-1.1)	-0.074 (-0.4)
2-Methylbutyric	0.021 (4.6)	0.041 (1.9)	0.067 (1.8)	0.080 (1.8)	0.076 (1.0)	0.045 (0.4)	0.083 (0.6)	0.364 (1.8)
Trimethylacetic ^b	-0.011 (-1.6)	-0.018 (-0.8)	-0.027 (-0.8)	-0.020 (-0.4)	0.014 (0.2)	0.095 (0.9)	0.253 (1.7)	0.614 (3.1)

^a Values in parentheses refer to the contribution of $\Delta G_{i\text{cav}}^{\circ}$ to $\Delta G_{i\text{exp}}^{\circ}$.

^b In these cases, negative values of the cavitation energy of transfer were found.

and the total Gibbs free energy of transfer for the cavity formation, $\Delta G_{i\text{cav}}^{\circ}$, is calculated from equation (17). The results are given in Table 4.

It should be noted that the use of gas-phase data in calculations involving solvent effects is questionable, but this has been the only possibility owing to the lack of experimental data in solution, the purpose of this rough approximation being to take into consideration the 'preferential salvation' of H^+ ion.

Estimation of $\Delta G_{i\text{el}}^{\circ}$

As was discussed above, the Born model led to meaningless results when applied to the systems studied. Very similar situations have been reported by some workers^{37,38} when ionic radii were calculated from the slope of experimental plots [$\Delta G_{i\text{el}}^{\circ}$ or $\Delta \text{p}K_{\text{a}}$ versus $\Delta(1/D)$]. Evidently, when non-electrostatic effects occur, it is expected that the Born model cannot explain the behaviour of the system. However, this model could provide a good estimate of electrostatic effects caused by a change in the permittivity of medium.^{39,40}

However, in the Born model it is assumed that ions are monoatomic and spherical and the parameter r is regarded as the crystallographic radius of the corresponding ion, which are very questionable premises for evaluating solvent effects. In order to overcome all these drawbacks, a number of workers have made considerable efforts within this framework.

In 1956, Laidler and Landskroener⁴¹ proposed a more general theory of medium effects. They utilized

the Kirkwood model, assuming a spherical solute and considering the charge distribution on reagents and transition states. This theory was successfully applied but only in cases of charges very close to the sphere surface. This restriction was overcome 4 years later when Hiromi⁴² presented a modified theory also based on the Kirkwood equations but with a substantial theoretical improvement which we shall not discuss here (cf. Refs 22 and 42). Moreover, an interesting feature of Hiromi's theory is that the solute may be regarded as a rigid sphere and therefore the σ (SPT) values calculated formerly can be utilized in the calculations.

In a similar way to the cavitation energies, other more complicated theories taking into account the shape of the solute species have been developed more recently, but cannot be applied to a system as complex as water-DMF mixtures according to the SPT model.

We have therefore used Hiromi's approach in order to evaluate the electrostatic contribution to $\Delta G_{i\text{el}}^{\circ}$. Accordingly, the Gibbs energy of transfer for a solute species due to permittivity changes is given by

$$\Delta G_{i\text{el}}^{\circ} = \frac{Ne^2L}{\sigma} \left(\frac{1}{\epsilon_s D} - \frac{1}{\epsilon_w D} \right) \quad (22)$$

where σ is the hard sphere diameter of the solute and L the Hiromi parameter which is a function of the charge distribution on the solute. The parameter L can be obtained by

$$L = \sum_{k=1}^M q_k^2 f_{kk} + \sum_{k=1, l > k}^M q_k q_l g_{kl} \quad (23)$$

Table 5. $\Delta G_{\text{el}}^{\circ}$ value in kJ mol^{-1} for the ionization of acids using various DMF–water mixtures

Acid	DMF (% v/v)							
	10	20	30	40	50	60	70	80
Formic	0.207 (51.9) ^a	0.633 (44.4)	1.072 (39.1)	1.600 (37.4)	2.262 (36.7)	3.095 (33.7)	4.097 (33.6)	5.228 (30.5)
Acetic	0.175 (30.7)	0.532 (28.2)	0.898 (30.8)	1.332 (29.9)	1.869 (30.3)	2.534 (28.8)	3.304 (26.7)	4.116 (23.0)
Propionic	0.187 (36.4)	0.570 (35.7)	0.963 (33.7)	1.432 (33.9)	2.016 (32.4)	2.744 (31.0)	3.601 (28.6)	4.533 (25.6)
<i>n</i> -Butyric	0.184 (46.1)	0.561 (30.7)	0.948 (31.9)	1.409 (30.9)	1.982 (26.7)	2.695 (28.6)	3.532 (26.7)	4.435 (23.6)
Isobutyric	0.189 (41.4)	0.578 (28.9)	0.976 (38.8)	1.452 (26.8)	2.045 (28.2)	2.786 (28.0)	3.661 (26.5)	4.616 (23.4)
<i>n</i> -Valeric	0.181 (35.3)	0.553 (27.7)	0.934 (34.1)	1.388 (32.0)	1.951 (27.4)	2.650 (29.0)	3.469 (25.5)	4.348 (24.2)
Isovaleric	0.189 (36.8)	0.578 (29.8)	0.977 (35.7)	1.454 (30.0)	2.048 (29.3)	2.789 (30.6)	3.666 (27.4)	4.623 (24.7)
2-Methylbutyric	0.184 (40.4)	0.560 (26.5)	0.946 (25.1)	1.406 (30.8)	1.978 (25.9)	2.690 (25.5)	3.525 (23.9)	4.462 (22.1)
Trimethylacetic	0.188 (27.4)	0.574 (25.2)	0.971 (29.3)	1.443 (31.2)	2.033 (27.4)	2.768 (26.2)	3.636 (24.5)	4.581 (23.1)

^a Values in parentheses refer to the contribution (%) of $\Delta G_{\text{el}}^{\circ}$ to $\Delta G_{\text{el}}^{\circ}$.

where q_k and q_l are the charges on the k and l atom or the solute molecule or ion, M is the number of atoms of solute species and f_{kk} and g_{kl} are given by

$$f_{kk} = 2/(1 - x_{kk}) + (1/x_{kk}) \ln(1 - x_{kk}) \quad (24)$$

$$g_{kl} = 2/(1 - 2\alpha_{kl}x_{kl} + x_{kl}^2)^{1/2} + (1/x_{kl}) \ln \left[\frac{1 - \alpha_{kl}}{(1 - 2\alpha_{kl}x_{kl} + x_{kl}^2)^{1/2} + x_{kl} - \alpha_{kl}} \right] \quad (25)$$

$$x_{kk} = (2r_k/\sigma)^2 \quad (26)$$

$$x_{kl} = r_k r_l / (\sigma/2)^2 \quad (27)$$

r_k and r_l are the distances of atomic positions to the charge centre ω and α_{kl} is the cosine angle $\theta_{kl} = q_k \omega q_l$.

The total electrostatic free energy of transfer is given by

$$\Delta G_{\text{el}}^{\circ} = \Delta G_{\text{el}}^{\circ}(\text{H}^+) - \Delta G_{\text{el}}^{\circ}(\text{A}^-) - \Delta G_{\text{el}}^{\circ}(\text{HA}) \quad (28)$$

The $\Delta G_{\text{el}}^{\circ}(\text{H}^+)$ value was evaluated from the equation

$$\Delta G_{\text{el}}^{\circ}(\text{H}^+) = z \{ \Delta G_{\text{el}}^{\circ}[\text{H}^+(\text{H}_2\text{O})] - \Delta G_{\text{el}}^{\circ}(\text{H}_2\text{O}) \} + (1 - z) \{ \Delta G_{\text{el}}^{\circ}[\text{H}^+(\text{DMF})] - \Delta G_{\text{el}}^{\circ}(\text{DMF}) \} \quad (29)$$

Combination of equations (22), (28) and (29), followed by rearrangement, gives

$$\Delta G_{\text{el}}^{\circ} = Ne^2 \{ z [L_{\text{H}^+}(\text{H}_2\text{O})/\sigma_{\text{H}^+}(\text{H}_2\text{O}) - L_{\text{H}_2\text{O}}/\sigma_{\text{H}_2\text{O}}] + (1 - z) [L_{\text{H}^+}(\text{DMF})/\sigma_{\text{H}^+}(\text{DMF}) - L_{\text{DMF}}/\sigma_{\text{DMF}}] + L_{\text{A}^-}/\sigma_{\text{A}^-} + L_{\text{HA}}/\sigma_{\text{HA}} \} \Delta(1/D) \quad (30)$$

The σ values and the charge atomic distribution for the evaluation of L were obtained by means of semi-empirical and *ab initio* methods of calculation (Table 3).

The energy values obtained from equation (30) for the carboxylic acids in the water–DMF mixtures are given in Table 5.

Estimation of other energy terms

The determination of $\Delta G_{\text{el}}^{\circ}$ dip is possible only with a prior knowledge of the solvation number.⁴³ The Van der Waals interactions (Keesom, Debye and London interactions) can be estimated.⁴⁴ The free energy due to specific interactions is not predictable at all. Therefore, instead of setting an estimate of this quantity, the energy term $\Delta G_{\text{el}}^{\circ}$ res, which is defined by

$$\Delta G_{\text{el}}^{\circ} \text{ res} = \Delta G_{\text{el}}^{\circ} \text{ dip} + \Delta G_{\text{el}}^{\circ} \text{ sp} \quad (31)$$

can be deduced from a crude consideration based on the difference obtained by rewriting equation (7):

$$\Delta G_{\text{el}}^{\circ} \text{ res} = \Delta G_{\text{el}}^{\circ} \text{ exp} - \Delta G_{\text{el}}^{\circ} \text{ cav} - \Delta G_{\text{el}}^{\circ} \text{ el} - RT \ln (V_w/V_s) \quad (32)$$

The residual energy contains both dipolar and specific interactions (Table 6). These residual values were examined for their relationship to solvent polarity indices for each solute. Values for the polarity indices of solvent mixtures P_m , were estimated using a linear combination rule, and assuming the solvatochromic

Table 6. $\Delta G_{\text{res}}^{\circ}$ values in kJ mol^{-1} for the ionization of acids using various DMF-water mixtures

Acid	DMF (% v/v)							
	10	20	30	40	50	60	70	80
Formic	0.308 (77.2) ^a	1.011 (70.9)	1.987 (72.5)	3.070 (71.7)	4.252 (69.6)	6.450 (70.2)	8.309 (68.0)	11.677 (68.2)
Acetic	0.503 (88.2)	1.549 (82.3)	2.298 (79.0)	3.457 (77.7)	4.630 (75.1)	6.502 (74.0)	9.113 (73.6)	13.321 (74.6)
Propionic	0.547 (106.6) ^b	1.468 (91.9)	2.616 (91.7)	3.798 (90.0)	5.000 (80.4)	7.719 (87.3)	10.935 (86.7)	15.209 (86.0)
<i>n</i> -Butyric	0.458 (114.8)	1.753 (96.0)	2.825 (95.2)	4.294 (94.1)	6.933 (93.5)	8.609 (91.4)	12.012 (90.7)	17.035 (90.7)
Isobutyric	0.440 (96.5)	1.757 (88.0)	2.071 (82.5)	4.754 (87.6)	6.098 (84.2)	8.181 (82.4)	11.274 (81.6)	16.137 (82.0)
<i>n</i> -Valeric	0.571 (111.3)	1.924 (96.3)	2.591 (94.6)	4.066 (93.8)	6.638 (93.1)	8.328 (91.2)	11.776 (86.5)	16.183 (90.0)
Isovaleric	0.543 (105.8)	1.799 (92.7)	2.478 (90.5)	4.394 (90.6)	5.744 (82.2)	7.983 (87.4)	11.592 (86.8)	16.220 (86.7)
2-Methylbutyric	0.477 (104.6)	1.960 (92.8)	3.486 (92.6)	4.077 (89.3)	6.845 (89.5)	9.315 (88.2)	12.872 (87.4)	17.611 (87.2)
Trimethylacetic	0.692 (101.0)	2.094 (91.8)	2.964 (89.6)	4.036 (87.3)	6.472 (87.2)	9.097 (86.2)	13.705 (92.4)	16.806 (84.9)

^a Values in parentheses refer to the contribution (%) of $\Delta G_{\text{res}}^{\circ}$ to $\Delta G_{\text{exp}}^{\circ}$.

^b Values exceeding 100 may occur when $\Delta G_{\text{el}}^{\circ} < -\Delta G_{\text{cav}}^{\circ} - RT \ln(V_w/V_s)$.

excess to be zero:⁴⁵

$$P_m(f)P_s + (1-f)P_w \quad (33)$$

Where P is the particular polarity scale being calculated, f is the volume fraction of cosolvent and the subscripts s and w refer to cosolvent and water, respectively. The indices employed were the Hildebrand solubility parameter,⁴⁶ the polarity π^* index,⁴⁷ the hydrogen-bond acceptor group density HBA⁴⁸ and the Kamlet-Taft β values,⁴⁹ the last two reflecting the hydrogen-bond donor accepting ability of the mixed solvent. Good correlations above 0.99 were observed with HBA and β . The use of an additional term describing the hydrogen-bond ability did not improve the correlation. In general, the HBA- β scale was superior in predicting non-electrostatic effects than were the other polarity scales. This feature is probably due to the greater prevalence of solvent-associated complexes which have been postulated to occur in partially aqueous solvents.⁵⁰ The ability of cosolvent to associate with both the dissociated and undissociated forms of the solute would frequently occur (with the exception of the basic protonation of cosolvent) via hydrogen bonding, and the activity of each solute species would probably be related to these properties of the solvent. On the other hand, the similar negative intercept values indicate that a negative specific overlap effect would exist which does not act via hydrogen bonding. The explanation of this probably resides in the increase in the solvent basicity caused by adding DMF, with the corresponding stabilization of solvated protons and

hence the appearance of a negative solvent effect on lyonium ion.⁵¹

CONCLUSIONS

The linear relationship obtained by plotting $\Delta G_{\text{exp}}^{\circ}$ versus $\Delta(1/D)$ does not imply that the electrostatic solvent interactions play the main role in the dissociation of carboxylic acids in water-DMF mixtures.

The main contribution to $\Delta G_{\text{exp}}^{\circ}$ is due to dipolar and specific interactions, followed by the electrostatic interactions. The cavity term is moderately high for formic and acetic acid, but very low for the other acids. This fact makes the prediction $\Delta G_{\text{el}}^{\circ}$ for the dissociation of carboxylic acids in the medium studied impossible because the dipolar and specific contributions cannot be estimated theoretically. Nevertheless, from an empirical point of view $\Delta G_{\text{el}}^{\circ}$ may be expanded as a function on the mole fraction of DMF, x_{DMF} . When $\Delta G_{\text{el}}^{\circ}$ is plotted versus x_{DMF} , a straight line is obtained:

$$\Delta G_{\text{el}}^{\circ} = (42.11 \pm 0.51)x_{\text{DMF}} - (0.68 \pm 0.11) \\ (n = 72, r = 0.994)$$

Accordingly, an empirical interpolation may be carried out within the range 0.025-0.454 mole fraction of DMF with a maximum absolute error of ± 0.3 unit.

The scaled particle theory in conjunction with the evaluation of hard sphere diameter and charge distributions from quantum mechanical calculations have proved to be a useful tool for the evaluation of electrostatic and cavity energies. However, owing to all the

limitations and approximations in the proposed procedure, the results obtained should be treated with caution and only in an approximate sense.

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APPENDIX

In order to illustrate how the calculations of the different energetic terms were made, we develop here our procedure for the formic-formate pair at 50% v/v of DMF.

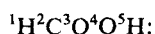
Preliminary data

The input data needed for further calculations are as follows.

Physico-chemical parameters related to the water-DMF mixture taken from Ref. 8:

DMF (% v/v)	DMF (mole fraction)	Permittivity <i>D</i>	Density (g ml ⁻¹)	p <i>K</i> _a of the HA-A ⁻ pair
0	0	78.54	0.9971	3.68
50	0.182	65.95	0.9950	4.75

Geometrical parameters and charge distribution (*q_i*) for the species HCOOH and HCOO⁻ form the printout of AMPAC (bond lengths *r_{ij}* in Å, bond angles \widehat{ijk} in degrees).

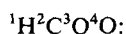


$$r_{12} = 1.103; r_{23} = 1.230; r_{24} = 1.357; r_{45} = 0.971$$

$$\widehat{123} = 130.159; \widehat{124} = 112.203; \widehat{245} = 110.657$$

$$q_1 = 0.1793; q_2 = 0.2606; q_3 = -0.3569;$$

$$q_4 = -0.3247; q_5 = 0.2418$$



$$r_{12} = 1.134; r_{23} = r_{24} = 2.057$$

$$\widehat{123} = \widehat{124} = 117.973$$

$$q_1 = -0.0556; q_2 = 0.2808; q_3 = q_4 = -0.6126$$

The physico-chemical parameters are involved in a number of calculations in the proposed procedure.

Intermediate data

Hard sphere diameters and Hiromi parameters

From the geometrical parameters and charge distribution, the charge centres for HA and A⁻ species

are obtained and then the σ (SPT) value for each is calculated from equation (15).

Once σ_{HA} and σ_{A^-} are known, the Hiromi *L* parameters are calculated taking into account the charge distribution according to equation (23). On the other hand, the σ and *L* values for the solvent species H₂O, DMF, H⁺ (H₂O) and H⁺ (DMF) should also be known. These values are obtained in an analogous way from *ab initio* instead of AMI calculations (see Theoretical Methods section). The results obtained are as follows:

Species	σ (SPT)	<i>L</i>
HCOOH	3.60	0.798
HCOO ⁻	3.66	1.520
H ₂ O	2.42	0.789
H ⁺ (H ₂ O)	2.50	2.232
DMF	5.64	0.500
H ⁺ (DMF)	5.80	1.169

Parameter *z*

The value of the fraction of solvated proton which exists as H⁺ (H₂O), *z*, is calculated from equation (20) taking into account that in this example $x_{\text{DMF}} = 0.182$ and $x_{\text{H}_2\text{O}} = 0.818$. Thus, a value $z = 0.81$ is obtained.

Calculation of energetic terms

Cavitation terms

The values of $\Delta G_{\text{cav}}^{\circ}$ are obtained from equation (17) once the corresponding free standard cavitation energies of transfer for HA, A⁻ and H⁺ have been computed. Values for HA and A⁻ species are easily obtained by computing previously the cavitation energy for each species in water and in the water-DMF mixture according to equation (9) and then applying equation (16). The $\Delta G_{\text{cav}}^{\circ}(\text{H}^+)$ value is calculated in a different way (see text) by using equation (21), which takes into account the value of *z*.

The result obtained from this example is $\Delta G_{\text{cav}}^{\circ} = 0.692$ kJ mol⁻¹.

Electrostatic terms

The total electrostatic free energy of transfer can easily be calculated taking into account the parameters σ , *L* and *z* together with the permittivity values for pure water and the water-DMF mixture. In the present instance the value obtained is $\Delta G_{\text{el}}^{\circ} = 2.262$ kJ mol⁻¹.

Return to the standard state

This energetic term is calculated from the value $RT \ln (V_w/V_s) = -1.101$ kJ mol⁻¹.

Residual energetic term

This value is obtained from equation (32) once $\Delta G_{\text{t exp}}^{\circ}$, $\Delta G_{\text{t cav}}^{\circ}$, $\Delta G_{\text{t el}}^{\circ}$ and $RT \ln(V_w/V_s)$ have been calculated.

The experimental free standard energy of transfer is obtained from the pK_a values in the mixed solvent and in water by using equation (1), which gives

$$\Delta G_{\text{t exp}}^{\circ} = 5 \cdot 706(4 \cdot 75 - 3 \cdot 68) = 6 \cdot 015 \text{ kJ mol}^{-1}$$

Thus,

$$\begin{aligned} \Delta G_{\text{t res}}^{\circ} &= 6 \cdot 105 - 0 \cdot 692 - 2 \cdot 262 + 1 \cdot 101 \\ &= 4 \cdot 252 \text{ kJ mol}^{-1} \end{aligned}$$

for the case of the formic acid-formate system when the transfer is from water to 50% v/v water-DMF.

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