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Ionization equilibria of dicarboxylic acids in dimethyl sulfoxide as studied by NMR

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ABSTRACT: The ionization equilibria of dicarboxylic acids measured by K_1/K_2 are expected to be substantially influenced by stabilization of the monoanion through intramolecular hydrogen bonding. However, except in sterically favorable cases, such as with maleic, 3,4-furandicarboxylic, 2,3-bicyclo[1.2.2]heptadienedicarboxylic and diethylmalonic acids, the K_1/K_2 values for other dicarboxylic acids, where intramolecular hydrogen bonding of the monoanion might be expected, are relatively small at ~100 in water. This research uses NMR to corroborate and extend the pioneering conductance measurements of K_1/K_2 of dicarboxylic acids by Kolthoff and coworkers with dimethyl sulfoxide (DMSO) as solvent. In extending these measurements, we have determined K_1/K_2 for 3,4-furandicarboxylic (**1**) and 2,3-bicyclo[1.2.2]heptadienedicarboxylic (**2**) acids, because these were predicted by McCoy to be especially sterically favorable for intramolecular hydrogen bonding in the form of their monoanions and, indeed, we have found K_1/K_2 values for these acids in DMSO of 1×10^{15} and 4×10^{16} respectively. In contrast, the corresponding value for succinic acid is about 10^8. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: dibasic acid ionization; NMR and acid strengths; hydrogen bonding of dibasic acids; acid strengths in DMSO; K_1/K_2 ratios

INTRODUCTION

The physical–organic chemistry of the ionizations of dicarboxylic acids can be considered to have begun in 1923, when Bjerrum[1] attempted to calculate the ratio of K_1/K_2 of such acids from the unfavorable electrostatic effect of removing the second proton from the negative carboxylate group of the monoanion at a distance r in water. The approach was not successful; the calculated K_1/K_2 values were much too small, especially for short-chain acids. Later, the K_1/K_2 problem received enormous impetus from the classical work of Kirkwood and Westheimer,[2,3] who showed that if the dicarboxylic acid was considered to be in a low dielectric constant cavity in the high dielectric constant medium of water, then the r values for a series of dicarboxylic acids were intermediate between those expected for random coils or the fully extended linear structures. This probably was the first measurement of an intramolecular distance in solution and was done well before the conception of conformational analysis.

The Kirkwood–Westheimer approach was criticized[4] for not taking account of possible internal hydrogen bonding for the monoanions of acids such as malonic and succinic, where hydrogen bonding in the monoanion should increase K_1 and decrease K_2, thus making K_1/K_2 greater than the statistical factor of four expected in the absence of the electrostatic effect on hydrogen bonding. A new round of research ensued, where Westheimer and Benfey[5] introduced the idea of measuring the proclivity for hydrogen-bond formation by comparing K_1 of the dicarboxylic acid with K_E, the ionization constant of its monomethyl ester. If K_E is half the value of K_1, then hydrogen bonding should not be a significant factor, but if $K_1 > 2K_E$ then it should be important. Perhaps surprisingly, with phthalic acid, $K_1 \approx 2K_E$, even though $K_1 > 2K_E$ for malonic acid and Hunter[6] reported K_1/K_2 values indicating hydrogen bonding for the monoanion of maleic acid, but not for fumaric acid in water. Later, Eberson and Wadso[7] showed very clearly the importance of hydrogen bonding to K_1/K_2 in racemic 2,3-di-*tert*-butylsuccinic acid.

Early NMR studies by Forsén[8] showed that the proton of the hydrogen bonds in potassium and sodium monomalonate, as well as potassium monophthalate, in dimethyl sulfoxide (DMSO) solution came into resonance at −15.0 to −15.5 ppm with reference to external water. Corrected to tetramethylsilane (TMS), the shifts are 19.9 to 20.4 ppm, essentially the same as the maximum values of 20 to 20.4 ppm recently reported by Kilway and coworkers.[9] A very productive study of

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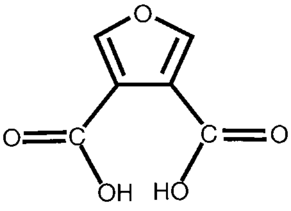
the relation of K_1/K_2 and hydrogen-bond proton shifts was provided by Eberson and Forsén[10] for *meso*- and D,L-succinic acids substituted at the 2,3-positions with isopropyl and *tert*-butyl groups. Small values of K_1/K_2 were found for the *meso* acid and quite large for the D,L-disubstituted acid, which showed the acid proton (after correction to TMS) at 19.5 ppm, again not far from the expected value. Eberson and Forsén[10] concluded that the upper limit for electrostatic effects on K_2 was 10^3. An elegant, often under-appreciated, study was made later by McCoy,[11] who investigated many different dibasic acids to find the optimum molecular geometry for intramolecular hydrogen bonding by measuring K_1/K_2 and K_E. Pioneering studies of the ionizations of dibasic acids by conductomeric procedures in polar, aprotic solvents were made by Kolthoff and Chantooni.[12,13] These workers determined that K_1/K_2 values could be quite large in such solvents and clearly recognized the importance of intramolecular hydrogen bonding in increasing K_1 and decreasing K_2.

We have been interested in the influence of the degree of ionization of short-chain dibasic and amino acids with respect to their conformational equilibria in a variety of solvents, and, like Kolthoff and Chantooni, we have used large K_1/K_2 values of dicarboxylic acids to argue for intramolecular hydrogen bonding for the monoanions, but, at the same time, have provided strong proof for this by showing that the *gauche* conformer is strongly favored in the conformational equilibria with the aid of vicinal NMR proton–proton couplings. The present paper has the purpose of extending the work of Kolthoff and Chantooni and of McCoy to larger K_1/K_2 values. The measurements of K_1/K_2 were made by an adaptation of the elegant NMR procedure of Perrin and Fabian[14] for determination of the ionization of monocarboxylic acids to measurement of K_1/K_2 of dibasic acids in DMSO. The essence of the procedure is to measure the position of equilibrium between the diacid, monoanion and dianions of interest with reference to an extensive list of acids for which a wide range of acidities have been determined and catalogued by Bordwell.[15] Some of the acids studied here are the same as those measured by Kolthoff and Chantooni[12,13] by conductance methods. These provide important cross-checks between the very different procedures.

EXPERIMENTAL

Materials

Fumaric and maleic acids were obtained from Matheson Coleman and Bell. Bicyclo[2.2.1]-2,5-heptadiene-2,3-dicarboxylic acid (**2**) was obtained from Frinton Laboratories. Trifluoroacetic and acetic acids were obtained from Mallinckrodt. DMSO-d_6 was obtained from Cambridge Isotope Laboratories. 3,4-Furandicarboxylic acid (**1**) was from the Sigma Aldrich Library of Rare Chemicals, and the other compounds used were regular Aldrich catalog products.



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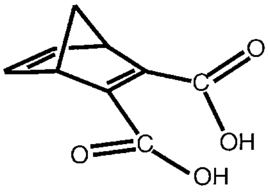

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Preparation of samples

All solutions were prepared at 0.05 M concentrations using 20–50 mg of the appropriate acid. Volumes were measured with a 250 μl syringe. To prepare the dianion solutions, the desired acid (1 equiv.) and tetrabutylammonium cyanide (Bu_4NCN, 2 equiv.) were weighed in a dry box to 0.1 mg accuracy. The sample was immediately dissolved in methanol and transferred to a flame-dried, round-bottomed flask. The methanol was removed under reduced pressure at 70 °C for 15 min, followed by an additional 45 min of heating at 70 °C to remove residual water. Alternatively, for the maleic acid, diethylmalonic acid, **1** and **2**, the desired acid (1 equiv.) and aqueous tetrabutylammonium hydroxide (40 wt.%, 2 equiv.) were weighed to 1 mg accuracy and dissolved in methanol. The methanol and water were evaporated under reduced pressure and finally heated in a round-bottomed flask for 30 min at 100 °C. The residual salt was dried at reduced pressure and dissolved in DMSO-d_6. Bu_4NCN or Bu_4NOH were used as the bases, because salts with the $(Bu_4N)^+$ counterion were more soluble in DMSO than salts with counterions such as Na^+. To prepare the monoanion solutions, the desired acid (1 equiv.) and Bu_4NCN (1 equiv.) were weighed in a dry box to 0.1 mg accuracy. The sample was immediately dissolved in DMSO-d_6 to give the desired solution. Some monoanion solutions were prepared in methanol, analogous to the dianion preparation method, in order to remove the residual HCN from the solution. When using dicarboxylic monoanions as test acids, removal of the HCN from the monoanion solution prevented unwanted protonation of the dianion solutions by HCN. To prepare the acid solutions, the acid was weighed out to 1 mg accuracy and dissolved in DMSO-d_6. To prepare the samples with the test acids, 0.5, 1, or 2 equiv. of the test acid were weighed to 1 mg accuracy and transferred to 0.5 ml of the monoanion or dianion solution.

Determination of ionization constants

The position of the equilibria between the various

Table 1. pK_a values in DMSO of test acids used to determine K_1/K_2

Acid	pK_a	Acid	pK_a
Trifluoroacetic acid	3.45[a]	Acetic acid	12.3[a]
Maleic acid	5.0[c] (pK_1)	Dibenzoylmethane	13.35[a]
2,4-Dinitrophenol	5.1[a]	Deoxybenzoin	17.65[a]
Malonic acid	7.2[b] (pK_1)	Malonic acid	18.6[b] (pK_2)
p-Nitrobenzoic acid	9.0[a]	Maleic acid	18.8[c] (pK_2)
Benzoylacetonitrile	10.2[a]	2-Phenylindene	19.4[a]
Benzoic acid	11.0[a]	Phenoxazine	21.65[a]

[a] As tabulated in Ref. 15.
[b] Ref. 12.
[c] Ref. 13.

dicarboxylic acid species and the test acids were determined by NMR. Spectra were recorded at 300 MHz, referenced to DMSO taken as 2.500 ppm.

Equations (1) and (2) were used as the basis for calculating the ionization constants.

$$\frac{K_1}{K_{HB}} = \frac{[HA^-][HB]}{[H_2A][B^-]} \tag{1}$$

$$\frac{K_2}{K_{HB}} = \frac{[A^{2-}][HB]}{[HA^-][B^-]} \tag{2}$$

$[H_2A]$, $[HA^-]$, and $[A^{2-}]$ represent dicarboxylic species, and $[HB]$ and $[B^-]$ represent the test acid species. The values for K_{HB}, the ionization constants of the test acids, are listed in Table 1. In addition, malonic and maleic acids were used as test acids when determining the ionization constants of other acids, with the aid of the data in Table 3. The observed chemical shift of the dicarboxylic species acid, δ_a, was assumed to be the weighted average shown in Eqn. (3).

$$\delta_a = \frac{\delta_{H_2A}[H_2A] + \delta_{HA}[HA^-] + \delta_A[A^{2-}]}{[H_2A] + [HA^-] + [A^{2-}]} \tag{3}$$

The chemical shifts $\delta_{H_2}A$, δ_{HA}, and δ_A in Eqn. (3) were taken from standard preparations. The observed chemical shift of the test acid, δ_b, was assumed to be the weighted average of species present in Eqn. (4).

$$\delta_b = \frac{\delta_{HB}[HB] + \delta_B[B^-]}{[HB] + [B^-]} \tag{4}$$

The chemical shifts, δ_{HB} and δ_B, in Eqn. (4) were taken from standard preparations. Equations ((1)–(4)) give Eqn. (5) after algebraic manipulation.

$$(\delta_a - \delta_A)\left(\frac{\delta_{HB} - \delta_b}{\delta_b - \delta_B}\right)\left(\frac{K_2}{K_{HB}}\right) + (\delta_a - \delta_{HA}) + (\delta_a - \delta_{H_2A})\left(\frac{\delta_b - \delta_B}{\delta_{HB} - \delta_b}\right)\left(\frac{K_{HB}}{K_1}\right) = 0 \tag{5}$$

There are two unknowns, K_1 and K_2, in Eqn. (5). Therefore, two measurements will be sufficient for solving the system to obtain K_1 and K_2 without making additional approximations.

Some variations were helpful in the actual methods used to determine the ionization constants for the acids. For all the acids, except fumaric acid, K_1/K_2 was sufficiently large, so K_2 was ignored when calculating K_1, and K_1 was ignored when calculating K_2. For a large K_1/K_2, the acid and dianion coexist to negligible extents, so either $[H_2A]$ or $[A^{2-}]$ can be set to zero provided the other species is present in larger concentration. Then, instead of using Eqn. (5), simpler equations, such as Eqns (6) and (7), were used.

$$(\delta_a - \delta_{HA}) + (\delta_a - \delta_{H_2A})\left(\frac{\delta_b - \delta_B}{\delta_{HB} - \delta_b}\right)\left(\frac{K_{HB}}{K_1}\right) = 0 \tag{6}$$

$$(\delta_a - \delta_A) + (\delta_a - \delta_{HA})\left(\frac{\delta_b - \delta_B}{\delta_{HB} - \delta_b}\right)\left(\frac{K_{HB}}{K_2}\right) = 0 \tag{7}$$

For fumaric acid, K_1/K_2 was small, so K_1 and K_2 were both likely to be important at any time, and approximations ignoring one or the other are likely to give inaccurate results. Consequently, Eqn. (5) was used in its complete form to determine K_1/K_2 for fumaric acid.

For determining K_2, Eqn. (7) was used when there was fast proton exchange between the monoanion and dianion. However, for some of the acids there was slow exchange between the monoanion and dianion, so the two species gave separate resonance peaks. Then, peak integrals were used instead of chemical shifts to determine the fractional composition of the solutions, and equations were modified accordingly using the substitution in Eqn. (8), which relates the fractional composition using chemical shifts to peak integrals:

$$\left(\frac{\delta_x - \delta_X}{\delta_{HX} - \delta_x}\right) = \left(\frac{I_{HX}}{I_X}\right) \tag{8}$$

where I_X and I_{HX} are peak integrals corresponding to the same protons on the acids species. On occasion, peak

Table 2. Chemical shifts of acidic and anionic species

Acid	Proton probed	$\delta_{H_2}A$ (ppm)	δ_{HA} (ppm)	δ_A (ppm)	δ_{HB} (ppm)	δ_B (ppm)
Dicarboxylic acids						
Fumaric	vinylic H	6.625	6.360	5.975		
Maleic	vinylic H	6.271	6.011	5.212		
Malonic	methylene H	3.243	2.668	2.531		
Diethylmalonic	methyl H	0.738	0.654	0.509		
Phthalic	aromatic H[a]	7.626	7.816	6.978		
1	vinylic H	8.415	8.021	7.070		
2	methylene H	2.145	1.967	1.881		
Monoprotic acids						
Benzoic	*ortho*-H				7.947	7.793
Benzoylacetonitrile	(*meta*-H + *para*-H)/2				7.567	7.218
2,4-Dinitrophenol	3-H				8.710	8.588

[a] Center of symmetrical coupling pattern.

integrals had to be used for the dicarboxylic acid, the test acid, or both.

Slow exchange between the monoanion or dianion and the test acids did not appear to be a factor in determining the results. The test acids did exhibit signs of slow proton exchange when the test acid itself was the monoanion of a dicarboxylic acid. Some samples were heated briefly to 60 °C, but showed no change in the position of equilibria, before or after heating. Consistency in the results from a variety of samples and test acids is the best indicator that the equilibria were established in a reliable manner.

In some cases the test acids gave poorly defined peaks, resulting from aromatic regions or other complex splittings that could not be used to determine the fractional composition directly. An alternative method was used in such cases to calculate the ionization constants. The concentration of the dicarboxylic acid was then used, where $[H_2A] + [HA^-] + [A^{2-}] = 1$. Here, $[HB]$ and $[B^-]$ were set to the concentrations of the test acid and the test acid's conjugate base, relative to the normalized concentration of the dicarboxylic acid. The integration of the test-acid peak gave a value for $[HB] + [B^-]$. When determining K_1 with the acid's monoanion, initially $[H_2A] = 0$ and $[B^-] = 0$, so at equilibrium, $[H_2A] = [B^-]$. When determining K_2 with the aid of the acid's dianion, initially $[HA^-] = 0$ and $[B^-] = 0$, so at equilibrium, $[HA^-] = [B^-]$. Eqn. (9) summarizes how the NMR data could be used to determine K:

$$K_1 = K_{HB}\frac{\left(1 - \frac{\delta_a - \delta_{HA}}{\delta_{H_2A} - \delta_{HA}}\right)\left(\frac{I_B n_A}{I_A n_B} - \frac{\delta_a - \delta_{HA}}{\delta_{H_2A} - \delta_{HA}}\right)}{\left(\frac{\delta_a - \delta_{HA}}{\delta_{H_2A} - \delta_{HA}}\right)^2} \tag{9}$$

Now, I_A and I_B represent the integrals of the dicarboxylic acid and test acid respectively, where n_A and n_B represent the number of protons corresponding to the respective integrals. For determining K_2, an equation of similar form was used when there was fast proton exchange between the monoanion and dianion. The procedure was further complicated when the preparation of the dianion could not be carried to completion. The relative amounts of the dianion and monoanion were measured for the incomplete preparation. Then, the relative amounts of the dianion and monoanion were measured after adding the test acid to determine the position of the equilibria.

RESULTS

The measured chemical shifts of the dicarboxylic acid species are listed in Table 2. Table 3 compares literature values with the average experimental values.

DISCUSSION

There are optimal conditions for accurately determining the ionization constants using the methods described here. When the optimal conditions are not met, deviations can be expected in the calculated values. An examination of how K_1 was determined from Eqn. (1) will serve as a general example for K_2 as well. In many cases, to find the terms for Eqn. (1), both chemical shifts and peak integrals were needed, as shown in Eqn. (9). This equation also shows that the calculated value for K_1 is particularly sensitive to the chemical-shift measurements. Chemical shifts can be easily measured to a high degree of accuracy. Peak integrals are generally less accurate than chemical shifts. Fortunately, in Eqn. (9), the calculated value for K_1 is less sensitive to changes to the peak integrals than changes to the chemical shifts. The most accurate values are obtained when Eqn. (6) can be used to calculate K_1, and an analogous equation can be used for K_2, because the calculations rely more heavily on the chemical shifts rather than the peak integrals.

For the dicarboxylic acids that displayed slow

Table 3. Ionization of dicarboxylic acids

	Water			DMSO		
Acid	pK_1	pK_2	K_1/K_2	pK_1[a]	pK_2[a]	K_1/K_2
Fumaric	3.03[b]	4.44[b]	26	9.0[c]	11.0[c]	
				9.9 ± 0.3	12.2 ± 0.1	2×10^2
Maleic	1.83[b]	6.07[b]	1.7×10^4	5.0[d]	18.8[d]	
				4.8 ± 0.1	20.4 ± 0.5	4×10^{15}
Malonic	2.83[b]	5.69[b]	7.2×10^2	7.2[g]	18.6[g]	
				7.3 ± 0.1	19.0 ± 0.4	5×10^{11}
Diethylmalonic	2.21[e]	7.35[e]	1.4×10^5	6.9 ± 0.3	20.4 ± 0.4	3×10^{13}
Phthalic	2.89[b]	5.51[b]	4.2×10^2	6.2[c]	16.0[c]	
				6.4 ± 0.1	17.4 ± 0.2	1×10^{11}
1	1.44[f]	7.84[f]	2.5×10^6	4.1 ± 0.1	19.1 ± 0.3	1×10^{15}
2	1.32[f]	7.77[f]	2.8×10^6	4.0 ± 0.1	20.6 ± 0.4	4×10^{16}
Succinic	4.20[g]	5.55[g]	2.2×10^1	9.5[g]	16.7[g]	
				(9.3)[h]	17.8 ± 0.6	3×10^8

[a] Errors indicated are standard deviations for raw data.
[b] Ref. 16.
[c] Ref. 17.
[d] Ref. 13.
[e] Ref. 18.
[f] Ref. 11.
[g] Ref. 12.
[h] Based on limited data.

exchange between the monoanion and dianion, chemical shifts could not be used to determine the percent protonation of the dianion by test acids. Only fumaric, succinic and malonic acids had a sufficiently fast proton exchange between the dianion and monoanion to give a single peak. For the other acids, peak integrals were used to find the terms for Eqn. (2). However, peak integrals are harder to measure accurately than chemical shifts, and are influenced by factors such as phasing and baseline irregularities. Calculated ionization constants that rely entirely on peak-integral measurements are likely to be the least accurate values. We expect to obtain the most accurate ionization constants when the relevant species can exchange protons fast enough to give a single, sharp peak and allow use of Eqn. (5). However, use of Eqn. (5) to determine ionization constants for fumaric acid turned out to show the largest discrepancy with previously reported values.[13] But the use of Eqn. (5) was only applied to a small number of data points for fumaric acid and was not fully explored, so this method may still be valid and accurate. There was also some difficulty because of problems with the test acids, benzoylacetonitrile and benzoic acid. For benzoylacetonitrile, the methylene peak did not appear in the partially deprotonated species, most likely because of line broadening associated with rapid exchange with trace water. As a result, only the aromatic proton peaks for benzoylacetonitrile and benzoic could be used in Eqn. (5). The aromatic peaks overlapped to give multiplets, making it difficult to select a peak for the measurements. Still, the calculated ratio K_1/K_2 from the results is reasonably close to the ratio obtained by Kolthoff and Chantooni.[13]

Even though chemical shifts can be measured accurately, in some cases the calculated ionization constants can still be limited by the accuracy of the shifts. Thus, when the test acid and dicarboxylic acid have ionization constants that are far apart, one acid is almost completely protonated while the other acid is almost completely deprotonated. It will be seen with Eqn. (6) or Eqn. (9) that, if all other variables are held constant, as δ_a approaches δ_{HA}, K_1 asymptotically approaches infinity, and as δ_a approaches $\delta_{H_2}A$, K_1 approaches zero. As one approaches these extreme conditions, the accuracy of measurements required to avoid the mathematical problems increases rapidly. It is easily seen that the most reliable values for K_1 are obtained when the test acid and dicarboxylic acid have similar ionization constants, and when equal equivalents of both are present. Some of the experimental variations can be explained by the limited accuracy of the chemical shifts. For example, when a test acid of $pK_a = 9$ was used to determine pK_1 of maleic acid, the average result was 5.7. When test acids with pK_a values of 5.1 and 7.2 were used, the average result was 4.8. The value 4.8 is more reliable and is the one recorded in Table 3. When the test acid's pK_a was too far from the dicarboxylic acid's pK_1, the limitations of the NMR measurements affected the accuracy of results.

In general, the calculated ionization constants had a tendency to be higher than the literature values, especially for K_2 values. Still, the ionization constants determined by the NMR method were fairly consistent with values obtained by other potentiometric and spectrophotometric methods. The K_1 and K_2 values for succinic acid were based on the smallest data set, but the results are still reasonable. The K_2 values for maleic acid, phthalic acid, diethylmalonic acid, **1** and **2** are the least reliable, because slow proton exchange between the monoanion and dianion required less accurate peak integrals to be used in place of chemical shifts. Also, the test acids used to determine K_2 included 2-phenylindene and phenoxazine. When both test acids were added to dianions, the solution would remain clear for 15 min. Then, the solution would slowly begin to turn cloudy. After a day, the previously clear solution had become virtually opaque. Perhaps the anions of 2-phenylindene and phenoxazine were slowly undergoing base-induced oxidation by air or some other reaction, which would make the results less accurate. In addition to using the test acids listed in Table 1, maleic acid, diethylmalonic acid, **1** and **2** were also useful as test acids. Thus, equilibrium amounts of monoanion and dianion were used to aid the determination of K_2, using the anchor value of $pK_2 = 18.8$ for maleic acid. Indeed, when two dicarboxylic acids were directly compared by measuring the equilibria between different dicarboxylic anions, the most precise results were obtained. The relative K_2 values are probably very accurate, but the absolute values may be slightly too high.

When a solution in DMSO of the malonic dianion and maleic monoanion was prepared, the results indicated that K_2 for malonic acid was more than one pK unit less than K_2 of maleic acid, which is consistent with other experimental results. The malonic monoanion and dianion exchange protons fast enough to allow the use of chemical shifts to determine the composition of malonic species, which is expected to be fairly accurate. However, the values reported for malonic acid and maleic acid have a difference of only 0.2 pK units between their K_2 values as determined by conductance.

In water, only dicarboxylic acids with a ratio of K_1/K_2 greater than 10^4 are likely to have significant internal hydrogen bonding.[10,11] Of the acids studied here, only maleic acid, diethylmalonic acid, **1** and **2** meet this criterion. Maleic acid has a rigid backbone and diethylmalonic acid has central steric bulk, both of which hold the carboxyl groups close together, making internal hydrogen bonding more likely. Based on McCoy's work,[11] the acids **1** and **2** have geometries particularly well suited to hydrogen bonding. Besides the proximity of the carboxyl groups, another important factor is associated with alkyl and cyclic substitutions. The influence of these substituents involves increases in the size of the low dielectric cavity through which the electrostatic effects are transmitted.[2,3]

In DMSO, the K_1/K_2 for the dicarboxylic acids we studied, other than fumaric acid, are at least 10^8 times larger in DMSO than in water. How can we rationalize that? If we take succinic acid with a K_1/K_2 of about 25 in water, the evidence is that water is a powerful enough solvator to stabilize the diacid and monoanion without recourse to aid from intramolecular hydrogen bonding.[19,20] In contrast, DMSO is not expected to be a good solvator of anions, so if the neighboring carboxyl can aid in stabilizing the monoanion by intramolecular hydrogen bonding, this will increase K_1 over what might otherwise be expected. In contrast, K_2 should be greatly decreased because, after ionization of the monoanion, DMSO would have to solvate two negative carboxylate groups without assistance provided by intramolecular hydrogen bonding. This way of looking at the K_1/K_2 increases in DMSO compared with water is supported by conformational analysis, which shows that the monoanion of succinic acid is essentially exclusively *gauche* in DMSO.[21]

Now, if we look at other diacids, we see the similar trends in K_1/K_2. Malonic acid, without a rigid backbone, still shows a dramatic increase in K_1/K_2 in DMSO. In contrast, fumaric acid, which cannot hydrogen bond intramolecularly, has K_1/K_2 only about four times as large in DMSO as in water. For fumaric acid, the change in K_1/K_2 is presumably the simple result of going to an environment of lower dielectric constant, because K_1 is not enhanced by hydrogen bonding and K_2 reflects a weaker electrostatic interaction between the anionic charges, which are held farther apart than in the other acids we have studied. Maleic acid shows one of the largest increases for K_1/K_2 in DMSO compared with water. Although the bond lengths and angles of phthalic acid are slightly different, its carboxyl groups are in similar positions to those of maleic acid. However, K_1/K_2 is smaller for phthalic acid than maleic acid, most likely because the negative charges of the phthalic dianion can be stabilized by polarization of the phenyl ring. Diethylmalonic acid also had one of the largest increases for K_1/K_2 in DMSO compared with water. Compared with malonic acid, the large K_1/K_2 for diethylmalonic acid could be the result of several effects. As mentioned earlier, the central large group could tend both to force the two carboxyl groups closer together and lower the dielectric constant of the local environment of the acidic groups, thus making hydrogen bonding more important for stabilizing the negative charge. Kolthoff and Chantooni[12] asserted that the dielectric constant may not affect the percentage of monoanion hydrogen bonding, but our experience is that the factors determining the degree of hydrogen bonding are too diverse to allow one to sort out the influence of dielectric constant alone.[21–23] The acids **1** and **2** already have the largest K_1/K_2 values in water, and they appear to have the highest ratios in DMSO as well. This result corresponds well with the predictions from McCoy's work.[11] Succinic acid has the lowest K_1/K_2 value of all the hydrogen-bonding acids we have studied in DMSO. Arguing from this, succinate monoanion would be expected to have a relatively weak hydrogen bond, possibly because its conformation is likely to be most favorable with a 70 or 80° dihedral angle between the carboxyl and carboxylate, and also because it lacks a rigid backbone to hold the carboxyls in a favorable orientation. Still, the succinic

Table 4. Aqueous ionization constants

Acid	pK_1	pK_2	pK_E	$El_1 = pK_E - \log 2$	Hb	El_2
Fumaric	3.03[a]	4.44[a]	–	3.03[b]	0.00	4.44
Maleic	1.83[a]	6.07[a]	3.08[c]	2.78	0.95	5.12
Malonic	2.83[a]	5.69[a]	3.35[c]	3.05	0.22	5.47
Diethylmalonic	2.21[a]	7.35[a]	(3.5)[d]	3.20	0.99	6.36
Phthalic	2.89[a]	5.51[a]	3.23[c]	2.93	0.04	5.47
1	1.44[a]	7.84[a]	3.75[c]	3.45	2.01	5.83
2	1.32[a]	7.77[a]	3.02[c]	2.72	1.40	6.37
Succinic	4.2[c]	5.55[c]	4.49[a]	4.19	0.00	5.55

[a] Ref. 16.

[b] Assuming $pK_E \approx pK_1$ because fumaric acid cannot form internal hydrogen bonds.

[c] Ref. 11.

[d] Estimated value.

monoanion appears to exist essentially completely in the *gauche* conformation in DMSO, which is strong evidence for hydrogen bonding.[21–23] The influence of the level of electrostatic interaction between the anionic charges on the K_2 value of succinate dianion is clouded by the uncertainty about the size of the dihedral angle in this species.[22]

When considering the magnitude of K_2, DMSO's poor ability to solvate anions suggests that a substantial degree of self-stabilization could be critical in determining the degree of acidity. Thus, the difference in K_2 between fumaric and succinic acids may result partly from self-stabilization by the double bond of fumaric acid, as mentioned above for phthalic acid.

Another consideration, when examining the high K_1/K_2 values for dicarboxylic acids, is the 5 kcal mol^{-1} cost in converting the O—H bond from the *Z* to *E* configuration. If the acids studied are unlike succinic acid[20] and form intramolecular hydrogen bonds in the diacid form, the cost of converting the O—H bond from the *Z* to *E* configuration would already be paid in advance. Also, all of the dicarboxylic acids we studied are short, so the entropy loss from intramolecular hydrogen bonding is probably not significant, although entropy contributions of the solvent molecules during ionization could be significant.

Proton transfers involving carboxylic acids are usually fast, so it was surprising that some of the monoanion and dianion species gave separate NMR peaks. Even when exchange was slow, the acidic protons of the carboxylic acids were not observed in the NMR spectra. The peaks were broadened too much by exchange to be visible at 0.05 M, although Kilway and Coworkers[9] suggest that the acidic proton of any dicarboxylic monoanion should be visible by NMR in the absence of trace amounts of water. There were traces of water in all of our DMSO samples, which would be expected to catalyze proton transfers. However, even with trace water, many of the acids showed slow exchange between their monoanions and dianions. When the diethylmalonic dianion was prepared directly in DMSO by adding a solution of Bu_4NOH in water, the resulting solution contained about 10% water. Nonetheless, the dianion and monoanion peaks exchanged slowly enough to give a broad, irregularly shaped peak. Slow proton exchange was not necessarily just a result of high pK_2 alone. Phthalic acid has a smaller pK_2 than malonic acid, but phthalic acid showed slow exchange between its monoanion and dianion whereas malonic acid did not. Intramolecular hydrogen bonding or steric effects could very well be responsible for an unusually high energy of activation in going from the monoanion to the dianion.

With p*K* values for the various acids studied, one can attempt to evaluate the relative importance of hydrogen bonding and electrostatic effects. Consider a simple approximation of the ionization processes. Let the diprotic acid H_2A be assigned an energy of zero in solution and take account of the energy changes at successive ionizations. Loss of the first proton gives the monoanion HA^-, which has an energy of $El_1 - Hb$, where Hb is the energy of the hydrogen bond that is formed and El_1 is taken to account for all other effects, which should be mainly electrostatic. Removing the second proton gives the dianion A^{2-}, which has an energy of $El_2 + El_1$. It is useful to compare the logarithm of equilibria constants with energy terms, so we approximate with $pK_1 = El_1 - Hb$ and $pK_2 = El_2 + Hb$, where El_1, El_2, and Hb are assigned appropriate units.

Before considering hydrogen bonding and electrostatic effects in DMSO, we will look at water solutions. Here, we can use values for pK_E, the ionization constant of the corresponding dicarboxylate monomethyl esters, to estimate Hb. For the monomethyl ester, $pK_E = El_1 + Hb$, but $Hb = 0$, and if we assume minimal electrostatic differences between the dicarboxylic acid and ester, we can take El_1(ester) $-\log 2 = El_1$(dicarboxylic). Then, for a dicarboxylic acid, $El_1 = p(2K_E)$, $Hb = p(2K_E) - pK_1$, and by substitution, $El_2 = pK_2 - Hb = pK_2 - p(2K_E) + pK_1$. The results are summarized in Table 4.

Now, we will correlate the water results with our DMSO observations. For notation, we add a subscript to denote the solvent, so that El_{1w} represents the electro-

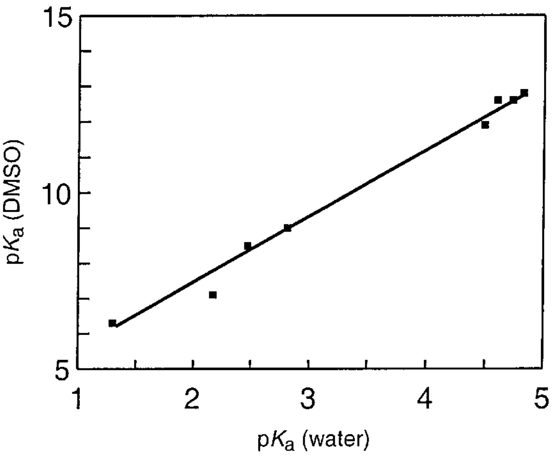

Figure 1. Linear correlation for pK_a in water and DMSO for the acids in Table 5

Table 5. Ionization constants in water and DMSO[a]

Acid	pk		
	Water	DMSO	Difference
n-Butyric	4.82	12.8	8.0
Acetic	4.73	12.6	7.9
Methyl H adipate	4.6	12.6	8.0
Methyl H succinate	4.49	11.9	7.4
$ClCH_2COOH$	2.81	9	6.2
$NCCH_2COOH$	2.47	8.5	6.0
$BrCH_2BrCHCOOH$	2.17	7.1	5.9
$Cl_2CHCOOH$	1.3	6.3	5.0

[a] Ref. 12.

static effect in water, and El_{1d} represents the effect in DMSO. If a monoanion cannot form an internal hydrogen bond, p$K_{1w} = El_{1w}$ and p$K_{1d} = El_{1d}$. Kolthoff and Chantooni[12] have compiled a list of ionization constants in water and in DMSO for acids that cannot form internal hydrogen bonds. In Figure 1, based on the data in Table 5, for simple organic acids we see a convincing linear relationship between pK_{1w} and pK_{1d}, which corresponds to a linear relationship between El_{1w} and El_{1d}. With Figure 1, we can approximate electrostatic effects in DMSO from the electrostatic effects in water for the first ionization of a dicarboxylic acid. From this estimation of El_{1d} we can approximate Hb_d using $Hb_d = El_{1d} -$ pK_{1d}. Then, we can approximate El_{2d} using $El_{2d} =$ p$K_{2d} - Hb_d$. The results are summarized in Table 6. Another significant correlation is possible from comparing Tables 5 and 6: comparison of non-hydrogen-bonding with hydrogen-bonding acids shows there is on the order of two to four pK units difference in p$K_{1w} -$ pK_{1d} for the hydrogen-bonding acids and non-hydrogen-bonding acids of comparable acid strengths. Thus, in effect, these differences provide a rough approximation to p$K_{1w} -$ pK_E.

CONCLUSIONS

Intramolecular hydrogen bonding is surely important when structurally feasible for dicarboxylic acids in DMSO. The ratio K_1/K_2 in DMSO was 10^7 to 10^{10} times the ratio in water for those acids that we studied here. Also, there was slow proton exchange between the monoanion and dianion for some of the acids. Structural variations can have significant effects on the value of K_1/K_2. As can be seen, comparisons between K_1/K_2 of malonic and diethylmalonic acids and between K_1/K_2 of fumaric and maleic acids are in accord with structural differences expected to reflect intramolecular hydrogen-bonding abilities. NMR provides a different and convenient procedure for measuring ionization constants in aprotic solvents. Experimental values obtained by these methods were generally consistent with literature values obtained by other methods.

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Table 6. Electrostatics and hydrogen bonding in DMSO

Acid	pK_{1d}	pK_{2d}	El_{1w}[a]	El_{1d}	Hb_d	El_{2d}
Fumaric	9.9	12.2	3.0	9.3	(0)	12.2
Maleic	4.8	20.4	2.8	8.9	4.1	16.3
Malonic	7.3	19	3.1	9.4	2.1	16.9
Diethylmalonic	6.9	20.4	3.2	9.7	2.8	17.6
Phthalic	6.4	17.4	2.9	9.1	2.7	14.7
1	4.1	19.3	3.5	10.1	6.0	13.3
2	4.0	20.6	2.7	8.7	4.7	15.9
Succinic	9.3	17.8	4.2	11.6	2.3	15.6

[a] From Table 4.

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REFERENCES

1. Bjerrum N. *Z. Phys. Chem.* 1923; **106**: 219.
2. Kirkwood JG, Westheimer FH. *J. Chem. Phys.* 1938; **6**: 506.
3. Westheimer FH, Kirkwood JG. *J. Chem. Phys.* 1938; **6**: 512.
4. Brown HC, McDaniel DH, Häflinger O. *Determination of Organic Structures by Physical Methods*. Academic Press: New York, 1955; 622–634.
5. Westheimer FH, Benfey OT. *J. Am. Chem. Soc.* 1956; **78**: 5309.
6. Hunter L. *Chem. Ind.* 1953; 155.
7. Eberson L, Wadso I. *Acta Chem. Scand.* 1963; **17**: 1552.
8. Forsén S. *J. Chem. Phys.* 1959; **31**: 852.
9. Brueck A, McCoy LL, Kilway KV. *Org. Lett.* 2000; **2**: 2007.
10. Eberson L, Forsen S. *J. Phys. Chem.* 1960; **64**: 767.
11. McCoy LL. *J. Am. Chem. Soc.* 1967; **89**: 1673.
12. Kolthoff IM, Chantooni JMK. *J. Am. Chem. Soc.* 1976; **98**: 5063.
13. Kolthoff IM, Chantooni JMK. *Anal. Chem.* 1978; **50**: 1440.
14. Perrin CL, Fabian MA. *Anal. Chem.* 1996; **68**: 2127.
15. Bordwell FG. *Acc. Chem. Res.* 1988; **21**: 456.
16. Weast RC (ed.). *Handbook of Chemistry and Physics*. CRC Press, Inc.: Boca Raton, FL, 1986.
17. Chantooni MK, Kolthoff IM. *J. Phys. Chem.* 1975; *79*: 1176.
18. Kortum G, Vogel W, Andrussow K. *Dissociation Constants of Organic Acids in Aqueous Solution*. Butterworths: London, 1961.
19. Lit ES, Mallon FK, Tsai HY, Roberts JD. *J. Am. Chem. Soc.* 1993; **115**: 9563–9567.
20. Price DJ, Roberts JD, Jorgenson WL. *J. Am. Chem. Soc.* 1998; **120**: 9672.
21. Petterson K. Unpublished NMR determinations in dimethyl sulfoxide, 2001.
22. Kent IV DR, Petterson KA, Gregoire F, Snyder-Frey E, Hanely LJ, Muller RP, Goddard WA, Roberts JD. *J. Am. Chem Soc.* 2002; **124**: in press.
23. Williams LN, Petterson KA, Roberts JD. *J. Phys. Chem.* 2002; **106**: in press.