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An NMR and Quantum-Mechanical Investigation of Tetrahydrofuran Solvent Effects on the Conformational Equilibria of 1,4-Butanedioic Acid and Its Salts

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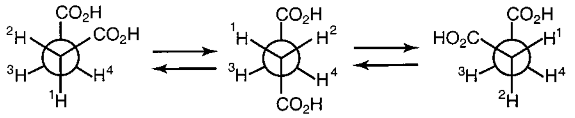
Abstract: Vicinal proton−proton NMR couplings have been used to compare the influences of water and tetrahydrofuran (THF) as solvents on the conformational equilibria of 1,4-butanedioic (succinic) acid and its mono- and dianionic salts. An earlier NMR investigation (Lit, E. S.; Mallon, F. K.; Tsai, H. Y.; Roberts, J. D. *J. Am Chem. Soc.* **1993**, *115*, 9563−9567) showed that, in water, the conformational preferences for the gauche conformations for butanedioic acid and its monoanion and dianion were, respectively, ~84%, 66%, and 43%, essentially independent of the nature of the cation or concentration. We now report the corresponding gauche percentages calculated in the same way for 0.05 M solutions in THF to be 66%, 90−100%, and 46−64%. Substantial evidence was adduced for the rotational angle between the substituents in the monoanion being ~70°. The positions of conformational equilibria of the salts in THF, particularly of the dianion, were found to be rather insensitive to concentration and temperature, but more sensitive to the amount of water present. Ab initio quantum-mechanical calculations for 1,4-butanedioate dianion indicate that, as expected for the gas phase, the trans conformation of the dianion should be heavily favored over the gauche, but, in both THF and water, the gauche conformation is calculated to predominate with rotational angles substantially less than 60°. This conclusion is, in fact, generally consistent with the experimental vicinal proton couplings, which are wholly inconsistent with the trans conformation.

Introduction

Simple 1,2-disubstituted ethanes, such as 1,4-butanedioic acid **1**, are expected to have a statistical 2:1 ratio of gauche to trans in the absence of environmental or structural influences. Structural influences can include electrostatic, steric, hydrogen-bonding, and electron-correlation effects. Conventional wisdom tells us that steric effects tend to favor the trans conformations.



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

In the gas phase, electrostatic effects arising from charged groups are found to favor trans conformations for like-charged groups and gauche conformations for oppositely charged groups. Predictions about solution-phase conformational equilibria are much more difficult, because electrostatic effects can be heavily screened by the dielectric of the solvent. Possible hydrogen bonding between the solute and the solvent, or intramolecular hydrogen bonding, as well as mutual polarization of the solvent and solute, add further degrees of complexity to the prediction of conformational equilibria in solution. It is especially significant that, in water solution, β-alanine[2] and the monoanion of butanedioic acid[1] do not show the considerable dominance of gauche conformations, which might be expected as the result of electrostatic or intramolecular hydrogen-bonding influences.[3] In fact, the monoanion of 1,4-butanedioic acid shows less preference for the gauche conformation than does the undissociated acid itself.[1] Our purpose here is to report on an extension of these studies of 1,4-butanedioic acid and its salts in tetrahydrofuran as solvent. This solvent was chosen because of the interesting studies of hydrogen bonding of 1,4-butanedioic salts reported in it by Perrin and co-workers.[4,5]

Experimental Section

Sample Preparation. Some of our attempts to synthesize tetrabutylammonium hydrogen butanedioate-2,3-$^{13}C_2$ and di(tetrabutylammonium) butanedioate-2,3-$^{13}C_2$ for use in THF solutions as described by

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(1) Lit, E. S.; Mallon, F. K.; Tsai, H. Y.; Roberts, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 9563−9567.
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Table 1. Calculated and Measured J_{HH} Coupling Constants of 1,4-Butanedioic-2,3-^{13}C Acid, Its Mono- and Di(tetrabutylammonium) Salts in Tetrahydrofuran, and Derived Conformational Preferences

species, preparations, conditions	Altona calcd J_{13}/J_{14} gauche trans[a,b]	conc, M	obsd, Hz J_{13}/J_{14}	calcd % gauche[b]	^{13}C shifts
1,4-butanedioic acid					
20 °C	8.77/3.62 3.90/14.21	0.1	6.94/6.87	65	29.186
20 °C		0.02	7.10/6.95	66	
1,4-butanedioic monoanion					
20 °C	9.01/3.76 3.87/14.54	0.05	9.85/2.22	100[c]	34.402
with added water, 20 °C		0.05	9.28/3.58	92[c]	34.464
1,4-butanedioate dianion					
20 °C with water (65.5×)[d,e,f]	10.04/2.08 3.83/14.88	0.025	5.86/10.77	36	36.616
20 °C[d,f,g]		0.05	6.38/9.58	48	37.804
20 °C[d,f,g]		0.05	6.30/9.62	46	38.279
20 °C after 15 days[d,f]		>0.05	7.12/8.46	60	36.902
2:1 $(Bu)_4N^+$ CN^-:1,4-butanedioic acid, water content (4×)[e,f]		0.005	7.07/7.57	64	37.997
2:1 $(Bu)_4N^+$ CN^-:1,4-butanedioic acid, water content (1×)[e,f]		0.005	6.37/9.05	49	38.775
4:1 $(Bu)_4N^+$ CN^-:1,4-butanedioic acid, no water[f]		0.05	6.96/8.08	60	37.813
propionate	3.87/15.22	0.05	7.57	67	

[a] In these calculations, the λ values of 0.47 and 0.29 were used respectively for CO_2H and CO_2^- following the Altona procedure.[6,7] [b] Unless otherwise noted, these calculations were made with $\theta_g = 60°$ and $\theta_t = 180°$. [c] $\theta_g = 70°$ angle used for this case. [d] The sample tubes used here were closed with plastic caps, not sealed off in vacuo. [e] Figures such as 65.5× mean 65.5 times as much water as 1,4-butanedioate dianion on a molal basis as measured by NMR integrals. [f] Reasons for the variability among the dianion preparations are considered in the Discussion section. [g] Duplicate preparations.

Perrin and co-workers[4] from solutions of 40 wt % solution of tetrabutylammonium hydroxide in water (Aldrich) and 1,4-butanedioic-2,3-$^{13}C_2$ acid (99% ^{13}C, ICON) encountered problems with insoluble carbonates and difficulties in drying the products. In general, we found it easier to use tetrabutylammonium cyanide (Aldrich) as the primary base for preparing tetrabutylammonium salts of butanedioic acid. For the mono salt, one can mix the appropriate volumes of THF solutions of tetrabutylammonium cyanide (Aldrich) and butanedioic-2,3-$^{13}C_2$ acid. The K_a of hydrogen cyanide in water is 5.2 powers of 10 less than K_1 of butanedioic acid, so it seems safe to presume that formation of the monoanion goes to completion for all practical purposes.

However, when attempts were made to prepare the dianion in THF with even a several-fold excess of tetrabutylammonium cyanide, the proton NMR spectrum was found to be essentially the same as with one equivalent. Further, the NMR spectrum of the solution was unchanged after evaporation of most of the THF solvent, followed by making up the volume with fresh THF. One possibility is that the conformation of the dianion is the same as that of the monoanion, or else, in THF as solvent, K_2 is much less than K_1, and cyanide is not a strong enough base to convert the monoanion to the dianion. To resolve this question, various ways of preparing the dianion were investigated, and the best procedure we have found is to dissolve the cyanide salt and the appropriate equivalents of acid in dry methanol, remove the hydrogen cyanide and methanol under reduced pressure, and finally dry the residue under reduced pressure in a flask equipped with an efficient liquid-nitrogen cooled coldfinger. If well-dried, a solution of this material in THF-d_8 shows no recognizable peaks of methanol or water, and its proton and ^{13}C NMR spectra are different from those of the monoanion. For the more dilute solutions of the dianion where we expected possible complications from autoxidation products of THF, a vacuum-line procedure was used very similar to that described by Perrin.[4]

For the monoanion, there remain questions as to proportions of diacid, monoanion, and dianion at the stoichiometric concentration of monoanion in THF and the degree of the influence of water or of any residual hydrogen cyanide. These actually turned out not to be a problem as we will show later.

For both the mono- and dianion in THF, there is the possibility of Hofmann elimination of 1-butene with the tetrabutylammonium cations, but the NMR spectra gave no evidence that either this reaction or that with THF to cause fragmentation to ethene and ethanal occurs to a significant extent with these anions. However, there is evidence for change in solutions contained in NMR tubes with plastic caps on standing for a day or two, when a broad complex multiplet appeared at about 2.4 ppm with an integral at most of about 15% of the methylenes of the 1,4-butanedioic acid. This seems to be an effect of oxygen, because it did not occur with samples sealed off in vacuo.

Tetrabutylammonium propionate was prepared from the hydroxide or tetrabutylammonium cyanide analogously to the dianion and dissolved at 0.05 M concentration in THF-d_8 to provide a standard for a λ value for estimating the influence of the carboxylate substituents on the coupling constants between the vicinal protons of the dianion by the procedure of Altona and co-workers.[6,7] The resulting $^3J_{H-H}$ coupling was found to be 7.57 Hz, the same as for water solutions.

NMR Spectra. Proton NMR spectra were for the most part taken with a GE QE-300 NMR spectrometer. The ^{1}H NMR peaks were referenced to TMS. For most of the samples, the ^{13}C shifts of the methylene carbons were taken immediately after the ^{1}H spectra, and these served to provide approximate checks on the degree of ionization. The values of the ^{13}C shifts of the un-ionized acid, monoanion, and dianion in 0.05 M THF solutions were about 29, 34, and 36.5−39 ppm.

Coupling-Constant Calculations. The $^3J_{HH}$ coupling constants for the various solutions of 1,4-butanedioic acid-2,3-$^{13}C_2$ and its mono- and di(tetrabutylammonium) 1,4-butanedioate-2,3-$^{13}C_2$ salts, as well as of tetrabutylammonium propionate, were extracted from the observed line positions with the aid of a much-revised Macintosh version of the LAOCN3 program of Bothner-By and Castellano[8] and gNMR 3.6.2 (Adept Scientific) and are listed in Table 1. The positions of the

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conformational equilibria were calculated with the aid of estimated coupling constants for the gauche and trans conformations obtained by the Altona procedure,[7] which derives J's between vicinal hydrogens of ethane derivatives for specific H−H dihedral angles ϕ and empirical λ values that reflect relative substituent electron-attracting powers. Independent values of the equilibria are obtained from J_{13} and J_{14}. These usually did not differ by more than ±2−3%. The possible ambiguity[2] as to which is which between J_{13} and J_{14} could be easily resolved by the fact that one way of assigning the couplings gives a much better fit than the other.

For simplicity, we assume that the ϕ dihedral angles between the vicinal protons are not different from values calculated for normal tetrahedral angles, even though, in principle, the ϕ dihedral H−H angles will depend, to at least some degree, on the nature of the substituents in groupings of the type $-CH_2X$. We will take θ as the dihedral angle between the 1,2-substituents of our 1,2-disubstituted ethanes for the rotational dihedral angle about the central C−C bond. Because the most probable value of θ may deviate differently from the perfectly staggered values for the gauche and trans conformations, we will also use θ_g and θ_t for the respective gauche and trans conformations in the subsequent discussions.

Theoretical Calculations. The quantum-mechanical calculations were made with Jaguar version 2.35 (Schrodinger, Inc.). Hartree−Fock geometry optimizations were followed by either a Hartree−Fock or an LMP2[9,10] energy calculation. LMP2 is a second-order Moller−Plesset perturbation[11] calculation using localized orbitals. No symmetry is used in any calculations. For the LMP2 calculations, Pipek−Mezey[12] localizations were employed. The cc-pVTZ basis set[13−15] was used throughout, because it is able to describe localized charges well.

Calculations for solutions[16−19] employed self-consistent solutions of the Poisson−Boltzmann equation for a molecule in a dielectric, by the PS Solve package of Jaguar with standard parameters, for water $\epsilon = 80.37$ and $R_{\text{probe}} = 1.4$ A and for THF $\epsilon = 7.58$[20] and $R_{\text{probe}} = 2.77$ A (R_{probe} for THF was calculated using the molecular mass and density of 0.780[21] as detailed in the *Jaguar User's Guide*.) The first step in this process was to calculate wave functions for the gaseous entities, and the resulting electron distributions were then fitted to atomic charges.[22,23] Next, the solvent is represented as a layer of charges on the molecular surface by the Poisson−Boltzmann Solver. This layer of charges is used in the next iteration of the quantum-mechanical calculations with the process being repeated until convergence.

The calculations for the anions were performed without cations on the perhaps unlikely assumption that the comparisons would be made with solutions of salts sufficiently dilute that the cations would be sufficiently separated from the mono- or dianion as to not influence the position of conformational equilibria. Be that as it may, the current Poisson−Boltzmann solvation model does not allow multiple cavities for a molecule in solution.

To obtain a good description of the overall conformational energetics of the butanedioate dianion, the calculations of conformers were made with torsional angles constrained to 0, 30, 60, 90, 120, 150, and 180° while minimizing the rest of the geometry. The resulting energies were interpolated using a cubic spline with periodic boundary conditions. Relative amounts of each rotamer as a function of temperature were calculated by integrating the Boltzmann distributions, given by the spline fit to the energies over the angles that we took to define a conformer. Thus, gauche was taken to be any conformer with a torsional angle between 0° and 120°, while trans was taken as any conformer with a torsional angle between 120° and 180°. All calculations were done for 300 K.

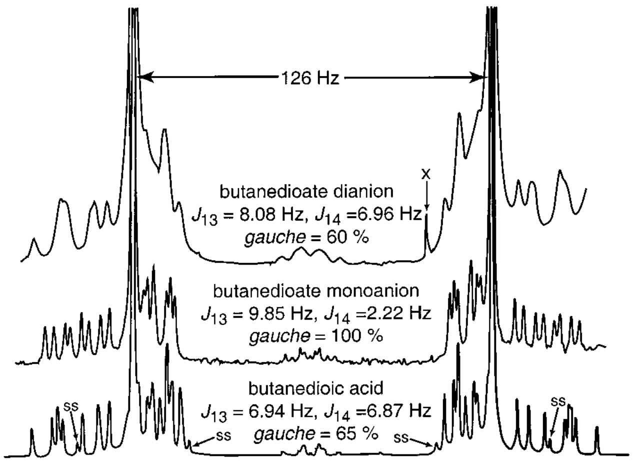

Figure 1. Proton NMR spectra of solutions of 1,4-butanedioic-2,3-$^{13}C_2$ acid (0.1 M) and its mono- and dianion $(C_4H_9)_4N^+$ salts (0.05 M) in THF-d_8; ss = spinning sideband, x = impurity.

Results and Discussion

1,4-Butanedioic-2,3-$^{13}C_2$ acid and its mono and dianion tetrabutylammonium salts were used in place of ordinary 1,4-butanedioic acid for the NMR analysis, because the ^{13}C labeling allows the J_{13} and J_{14} proton−proton couplings to be measured much more easily than for the natural-abundance ^{13}C satellites, especially at low concentrations. Typical proton spectra obtained with these substances in THF-d_8 are shown in Figure 1.

The $^3J_{HH}$ coupling constants for the acid and its salts (Table 1) were, as earlier,[1,2] assigned to particular pairs of protons so that J_{14} corresponds to the larger trans (antiperiplanar) coupling and J_{13} corresponds to the smaller (gauche) coupling of the trans conformation of a 1,2-disubstituted ethane with $\theta = 180°$, **1b**. This procedure avoids the ambiguity mentioned earlier as to whether J_{13} is J_{14} and the reverse.

To estimate the positions of conformational equilibria from the experimental J_{14} and J_{13} values in Table 1, we must have reasonably reliable estimations of what J_{14} and J_{13} should be for the separate individual conformers. For this, we have used Altona's procedure[6,7] and the observed 7.57 Hz for the $^3J_{HH}$ propionate coupling for the tetrabutylammonium salt in both water and THF-d_8 solution. The 0.29 λ value calculated for the effective electronegativity for carboxylate groups was taken from Altona,[7] as was the $\lambda = 0.47$ for the carboxyl group. In general, calculations of the positions of the conformational equilibria are rather insensitive to ±0.1 differences in λ values. In any case, we used Altona's procedure[7] to provide the respective J_{13} and J_{14} values for various conformations shown in Table 1. In the absence of definitive evidence to the contrary, we initially assumed perfectly staggered conformations, so that $\theta_g = 60°$ and $\theta_t = 180°$. The so-calculated percentages of gauche on this basis are given in Table 1.

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The relatively small differences in conformational equilibrium that we report here for water and THF suggest that intramolecular hydrogen bonding between the carboxyl groups is not important for the diacid. These small differences seem rather general for comparisons of the conformational equilibria of mono- and dicarboxylic acids in water versus other solvents we have studied, provided that the solvent is not so basic as to give significant salt formation. For THF, perhaps surprisingly, the position of conformational equilibrium for butanedioic acid is almost the same at 0.1 M as it is at 0.02 M, which means that either dimerization is small, or, if extensive, the conformation of the dimer is similar to that of the undissociated diacid in water. The substantial proportion of gauche observed in water, THF, alcohols,[24] and calculated for the gas phase[3] could be ascribed to the so-called gauche effect,[25,26] which is often associated with strong electron-attracting groups, such as carboxylic groups. However, we have shown both theoretically and experimentally that electron-attracting power alone cannot be the origin of the gauche effect.[27]

The situation for analysis of the coupling data for the monoanion is complicated, in principle, because the ratio of K_1/K_2 for 1,4-butanedioic acid is about 28 in water.[24] If the *same* ratio were to hold in THF, then the stoichiometric mix corresponding to maximum monoanion would be about 15% diacid, 70% monoanion, and 15% dianion. We could use the coupling constants for the diacid and dianion to correct the experimental values on this basis, but the fact that the spectra do not change when more than 1 equiv of tetrabutylammonium cyanide is added shows clearly that K_1/K_2 in THF is not the same as it is in water. There can be no doubt that THF is a wretched solvent for solvation of anions and certainly is not expected to solvate the dianion better than the monoanion. This will make K_1/K_2 many powers of 10 larger for THF than for water solutions, as is already known for dimethyl sulfoxide (DMSO).[28−32] Further, calculations[3] of the most favorable conformation of the butanedioate monoanion for THF, but not for water, indicate that the hydrogen-bonded gauche form is expected to have more than 10 kcal/mol greater stability than any other monoanionic species. This also strongly suggests that K_1/K_2 for THF should be much larger than that for water solution. We assume therefore essentially complete monoanion formation in the reaction of tetrabutylammonium cyanide with the diacid. Now, if we assume, as before, $\theta_g = 60°$ and $\theta_t = 180°$, the measured vicinal proton couplings for the monoanion along with the expected couplings for each conformation as predicted by the Altona procedure[7] suggest that the conformational mix is greater than 100% gauche (∼110%). However, as shown in Figure 2, if we increase θ_g to 70° as needed to form a stereoelectronically more effective hydrogen bond,[1] while θ_t is kept at 180°, then the conformational mix is calculated to be 100% gauche. It should be noted that calculations[3] suggest 80° as the proper θ angle for the gas-phase monoanion. The J_{13} and J_{14} couplings, respectively, calculated by the Altona procedure[7] for θ_g of the gauche conformer are for 70°, 9.78 and 2.09 Hz; for 80°, 10.31 and 1.10 Hz, as compared to 60°, 8.96 and 3.67 Hz. The predicted fraction of gauche for $\theta_g = 80°$ is about 92%, a value which we believe is inconsistent with the K_1/K_2 evidence.

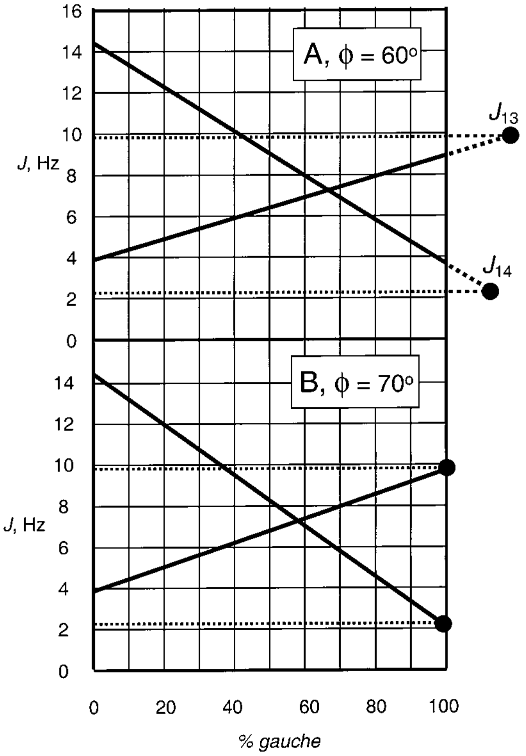

Figure 2. Changes in the calculated percentage of gauche conformation of tetrabutylammonium butanedioate in THF-d_8 solution as a function of the dihedral angle θ. The horizontal dotted lines represent the experimental values of J_{13} and J_{14}, 9.85 and 2.22 Hz, respectively.

An important consideration for us here is the degree of acidity of water in THF. Water is a very weak acid of pK 32 in DMSO,[33] and the limited ability of DMSO to solvate anions and the concentrated charge of hydroxide ion, which requires more solvation than an anion with less localized charge, must be contributing to that weakness. It may be that water is more acidic in THF than in DMSO, but it would seem much more likely that the contrary would be true, because a DMSO oxygen would be better able to hydrogen bond to hydroxide ion than would the ether oxygen of THF. Deliberate addition of water to 0.05 M monoanion in THF to the extent of 0.4 M caused a change in proportion of gauche from 100% to 92% on the assumption that θ_g remains at 70°. It is important that the ^{13}C shifts of the CH_2 groups of the anion did not change on addition of water so that it seems unlikely that water is causing conversion of the monoanion back to the diacid. Much more likely is that, as in aqueous solution,[3] hydrogen bonding of water molecules of the carboxylate group provides enough of an alternative mode of solvation to the formation of an intramolecular hydrogen bond to allow ring opening and incursion of the trans conformer. Energywise, the ring-opening process would be favored by 4−5 kcal/mol by virtue of eliminating the energy

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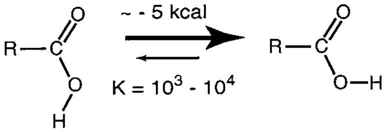
penalty for conversion of the carboxyl group of the 1,4-butanedioate monoanion to the less favorable *E*-isomer **2** to be able to form an intramolecular hydrogen bond.[3] Yet even so, the gauche conformation is highly favored.



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Our results on the conformational properties of the monoanion of butanedioic acid in THF are consistent with the elegant experiments of Perrin and co-workers,[5] which indicate that, not only does this monoanion possess a strong hydrogen bond in THF, but the hydrogen bond has the hydrogen unsymmetrically located between the carboxyl oxygens. Of course, our experiments are unable to provide any direct information as to the latter point, but they do show that the hydrogen bond is strong.

The situation for the dianion in THF is especially interesting and complex. Perrin and co-workers[4] reported difficulties in its preparation, and we have tried quite a number of possible procedures of which the most successful has been the one described in the Experimental Section. Our best evidence, that we did indeed prepare the dianion in THF, is the ^{13}C chemical shifts of the methylene carbons for which we observe successive downfield changes of about 5 ppm in the progression from diacid to monoanion to dianion, and these changes are completely congruent with earlier observations on carboxylic acids.[34] However, because we failed to use sealed NMR tubes, many of our early experimental results were vitiated by not realizing that there was a significant oxygen effect, most likely the result of attack on the THF and formation of compounds acidic enough to convert the dianion at least partially to the monoanion on standing. This, of course, was especially important in studies of the more dilute solutions, where the results were reasonably consistent provided the samples were sealed in vacuo. The values for the coupling constants and conformational equilibria of the dianion shown in Table 1 include two where the samples were allowed to stand in plastic-capped tubes for 15 days and illustrate what we believe to be oxygen degradation, as well as some solvent evaporation. All in all there is an element of variability in the percentage of gauche determined for the dianion solutions, which means that the coupling constants, J_{13} and J_{14}, for the dianion should probably not be taken to be better than ±10%. Another complication, broadening of the methylene proton lines, is also somewhat variable and seems particularly associated with the higher concentrations of dianion with the least amount of adventitious water and no, or small, excesses of tetrabutylammonium cyanide used in the dianion preparations. Line broadening is most likely to be the result of slow ionic association equilibria, the rate of which seems increased by what could be a general salt effect by adding tetrabutylammonium cyanide. Regardless of these complications, the important point here is that many experiments point to the unexpected conclusion whereby the dianion exists substantially as the gauche conformation − this despite conventional wisdom that the dianion should be exclusively trans, which would have very different vicinal proton couplings from those observed.

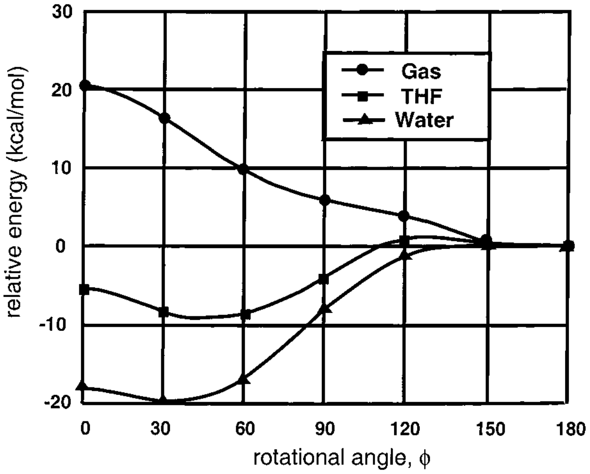

Figure 3. Quantum calculations of the relative energies of 1,4-butanedioate conformations in the gas phase and in water and in THF solutions.

The obvious question, when we wish to derive conformational equilibria from our measured coupling constants, is how do we know what to take for the values of rotational angle θ_g for the dianion in the Altona[7] procedure? One approach is through the results of the quantum-mechanical calculations shown in Figure 3, which suggest that the most favorable value of θ for the dianion in the gas phase corresponds to the trans rotamer by some 20 kcal/mol; yet, perhaps surprisingly for solutions, the most favorable calculated θ values are even less than 60°: 46° for THF and 36° for water.

What should we make of this? Despite the fact that one's confidence in the accuracy of quantum calculations for solutions as complex as this is likely to be such that they should not be regarded as more than qualitatively correct, let us assume that the gauche form with $\theta_g = 46°$ in THF is in fact approximately 9 kcal/mol more stable than the trans rotamer with $\theta_t = 180°$ as indicated by Figure 3. This energy difference corresponds to a negligible amount of trans in the mixture of rotamers, and so, if we now calculate by the Altona procedure[6] the coupling constants for a pure gauche rotamer with $\theta_g = 46°$, J_{13} comes out to be about 7.8 Hz, while J_{14} is about 6.7 Hz. These predicted values do not correlate particularly well with the average of the various experimental dianion couplings we have obtained for THF in the absence of added water (not all of which are included in Table 1), which are $J_{13} = 6.6 \pm 0.4$ Hz and $J_{14} = 8.8 \pm 0.8$ Hz, and correspond to 72% gauche with $\theta_g = 46°$ and $\theta_t = 180°$.

However, if we recall that J_{13} and J_{14} each affords an *independent* calculated conformational ratio, it will be seen that we can use J_{13} and J_{14} to determine *upper* limits on the amounts of trans rotamer that are consistent with the observed dianion coupling constants in the absence of water. We illustrate this approach with J_{14}, which has a maximum value of 9.6 Hz. With θ_t taken to be 180°, we vary θ_g from 30° to 90° in 5° steps, in the process generating a series of graphs such as Figure 2, from which the % of trans rotamer can be read off for $J_{14} = 9.6$ Hz. This procedure shows a maximum of 63% trans, which changes by less than 2% between $\theta_g = 75°$ to $\theta_g = 90°$. When we then use the minimum observed J_{13} of 6.3 Hz, we find it corresponds to a maximum of 64% trans, again almost invariant between $\theta_g = 75°$ and $\theta_g = 90°$. If now we go the other way and determine the maximum % of gauche from the minimum observed J_{14} of

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(34) Hagen, R.; Roberts, J. D. *J. Am. Chem. Soc.* **1969**, *91*, 4504−4506.

7.57 Hz, we get 100% gauche for $\theta_g = 42°$ and, from the maximum observed J_{13} of 7.12 Hz, 100% gauche for $\theta_g = 39°$.

In earlier papers,[2,27] we have mentioned the possibility of ambiguity in the assignment of particular vicinal couplings to J_{13} and J_{14}. In principle, at least, this might happen here also. However, if we apply the same kind of analysis in the preceding paragraph with reversed assignments to J_{13} and J_{14}, the discrepancies in the calculated percentages of the gauche conformer for particular pairs of J_{13} and J_{14} amount to 15−20% as compared to less than 5% for the original assignments, and the reverse assignments all lead to more gauche, rather than less.

We conclude that regardless of what is the best value between the extremes, the vicinal proton couplings indicate a very substantial proportion of the qualitatively electrostatically less-favorable gauche conformation. One argument that this is not as radical as it might first seem is offered by the quantum calculations shown in Figure 3. If one is not convinced by those numbers, the substantial proportions of gauche also accord with expectations based on the Born charging equation which shows the energy of a charged particle in a dielectric medium depends on the square of the charge.[35] The argument here is that for a dianion so constructed that, by only changing θ, its charges can be moved either far apart (180°) or brought close together (0°), the Born energy of charging the dielectric should be considered (1) as arising approximately from two separate isolated negative charges with $\theta = 180°$ or (2) from an effective composite charge approaching -2 with $\theta = 0°$. Because the ionic charge, z, in the Born equation appears as z^2, if the trans conformation of butanedioate dianion were to act like (1) and the gauche conformation like (2), the charging energy of the gauche could approach being twice as large. The argument here is just the reverse of that used earlier for the dipolar ion of β-alanine.[2]

It is important to recognize that the finding of large proportions of the gauche conformation is, so far as we have found, associated with use of aprotic solvents that can be judged to be particularly inhospitable in solvating anions. Thus, besides THF, similar behavior has been observed for the 1,4-butanedicarboxylate in DMSO.[31] In contrast, the same dianion in the less polar alcohols, such as isopropyl and *tert*-butyl alcohols, assumes nearly completely the trans conformation.[24]

It has been suggested that the high percentage of gauche conformers could be the result of formation of a distorted tetrahedral complex of the dianion oxygens and the tetrabutylammonium cations. We have no information about ionic complexes with tetrabutylammonium cations, which are certainly very reasonably expected in THF and indeed reported[30] for di(tetraethylammonium) 1,4-butanedicarboxylate in solvents of low dielectric constant. Tetrabutylammonium cations are larger than tetraethylammonium cations, and it would seem that complexes between them and the dianion would be more favorable with the dianion as the trans rotamer and the negative charges more widely separated. In any case, the quantum calculations, which do not include the influence of charged counterions, indicate a preference for gauche conformations. Consequently, it would appear that there is no strong theoretical basis for arguing that complexes of the dianion with the counterions are a necessary condition to have the gauche be favored.

Returning to the quantum calculations, the LMP2 solution-phase calculations for the dianion in water indicate a strong predominance of the gauche conformer and, in water, essentially 100% at 298 K. For water, the calculated difference in energy between θ near 30° and 180° is about 20 kcal/mol, which is in striking contrast to the experimental difference of about 0.64 kcal/mol for 41% gauche.[1] This is all the more surprising in that the corresponding calculations for the dipolar ion of β-alanine agreed reasonably well with the experimental results for the conformational equilibrium in water. However, the Poisson−Boltzmann solvation model does not take into account explicit solvation. Nor, in its present form, can it take into account any influence of positively charged counterions,[16−19] although this would seem to provide a greater difficulty with THF than with water.

Further investigations to determine the generality of these effects are in progress, but it should be clear that, from what we report here as well as earlier,[1−3,27] that body of knowledge one might call conventional wisdom regarding structural influences on conformational equilibria requires some revision. One seems to be faced with the near certainty that dianion contains more of the gauche than might reasonably be expected. Perhaps even worse, but highly interesting, is the possibility based on the quantum calculations (and certainly not ruled out by the couplings) that the dianion in THF is *exclusively* gauche with a θ substantially smaller than 60°.

One can also speculate as to what role these perhaps rather unexpected anion−anion interactions play in the nonpolar regions of protein structures and the structures of other biological molecules. For example, the degree of resolution of protein crystallography cannot easily determine whether there is actually a proton between two formally anionic oxygens that are ostensibly hydrogen-bonded. A reasonable question might be, should one assume that all such arrangements do, in fact, contain the assumed proton?

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