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# Fascination with the Conformational Analysis of Succinic Acid, as Evaluated by NMR Spectroscopy, and Why<sup>†</sup>

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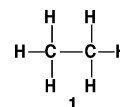
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## ABSTRACT

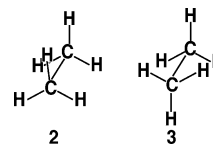
A serendipitous effort to use NMR spectroscopy to determine the conformational preferences of succinate monoanion opened a Pandora's box of unexpected uncertainties as to what influences such preferences of succinic acid in its various ionization states, not only in water but also in other less polar protic solvents, as well as a range of aprotic solvents. The dianion in aprotic solvents shows substantial gauche preferences, which give the appearance of violating Coulomb's law.

Conformations and conformational analysis have a long history, which surely began when the first ball-and-stick models were constructed, first as planar entities<sup>1,2</sup> but later three-dimensional with tetrahedral bond angles by Paterno.<sup>3,4</sup> Such models led Bischoff<sup>5–7</sup> to speculate as to which rotational angles about the C–C bonds of 1,2-substituted ethanes would be most stable in terms of “collisions” between the substituent groups. These speculations gained a solid base in the early 1950s with O. Hassel's electron-diffraction analysis of cyclohexanes,<sup>8</sup> the D.H.R. Barton studies of the reactions of substituted steroids,<sup>9</sup> and the thermodynamic work of K.S. Pitzer on ethane.<sup>10</sup>

The resulting impact on chemical research was swift and far-reaching, especially to organic chemistry, biochemistry and molecular biology. Unlike the many more arcane features of organic compounds, substituted-ethane conformations, as usually written, are simple and appeal to lay persons by their similarities to “TINKERTOYS”. In elementary organic chemistry, normally one of the first things one encounters after learning rules of valence and writing a structure for ethane, **1**, is to understand that this molecule, and many others like it, are not planar arrays of connected atoms but three-dimensional entities, with



carbon forming tetrahedrally disposed bonds with H–C–H or H–C–C bond angles of close to 109.5°, as shown by **2** and **3** (the “saw-horse” representations).



A natural question about **2**, in which the hydrogens at one end “eclipse” the hydrogens on the other end, when you look down the C–C bond axis, is the degree of allowable rotation about the central C–C bond of **2** and whether some configurations encountered in that rotation are more favorable than others. These questions lead to the showing by K. S. Pitzer<sup>10</sup> that **2** is less favorably disposed by 3 kcal/mol than the staggered arrangement **3**. Perhaps amusingly, even after the 50 or so intervening years, theoretical chemists are still arguing about the origin of this so-called barrier to rotation of ethane, although at room temperature, rotation occurs billions of times per second.<sup>11,12</sup> The preference for the staggered arrangement allows for a new dynamic stereoisomerism when there are 1,2-substituents (X, Y), on gauche and trans forms (Figure 1, in which the conformations are shown as Newman projections,<sup>13</sup> where the conformers are viewed directly along the C–C bond axis, as was also done by Bischoff<sup>6</sup> more than 100 years ago). Further, the conformations would be expected to exist in a statistical ratio of 2/1, gauche/trans, provided that the 1,2-substituents have no effect on the position of the conformational equilibria. The usual explanation for deviations from statistical equilibrium is steric hindrance between the substituent groups, which often uses the simple example of *n*-butane, where X and Y are methyl groups.<sup>14</sup> To ascribe conformational preferences generally to steric hindrance is actually a substantial oversimplification. As we will show, steric-hindrance effects are not nearly as important as commonly believed for substituted ethanes, such as **3**, unless the substituent groups, X and Y, are both large and form tetrahedral bonds.

Much experimental and theoretical work has been done on measuring the preferences and the causes of preferences in conformational analysis with compounds having conformers corresponding to the trans **3** and the gauche enantiomers, **4a,b**, or more complicated systems. The field is wonderfully summarized and critically reviewed by Ernest Eliel and co-authors.<sup>15–17</sup> The present Account has its emphasis on the conformations of highly polar and ionizable molecules as a function of solvent polarity and solute-stabilizing power of both protic and aprotic media.

<sup>†</sup> Dedicated to the memory of Christopher S. Foote, a fine chemist and a warm friend, who encouraged the preparation of this manuscript.

John D. Roberts is Institute Professor of Chemistry, Emeritus, at the California Institute of Technology. He attended the University of California at Los Angeles and received the A.B. degree in 1941, then the Ph.D. in 1944. His academic career began in 1945, as an Instructor in Chemistry at UCLA. From 1945 to 1946, he held a National Research Council Postdoctoral Fellowship and was Instructor in chemistry at Harvard. He was on the faculty at the Massachusetts Institute of Technology from 1946 to 1953. He became Professor of Organic Chemistry at the California Institute of Technology in 1953; then, in 1972, he was appointed Institute Professor of Chemistry and, in 1988, became Emeritus. His research has been concerned with the mechanisms of organic reactions, chemistry of small-ring compounds, benzyne, carbocations, and applications of nuclear magnetic resonance (NMR) spectroscopy, especially of F-19, C-13, and N-15, to organic chemistry, bioorganic chemistry, and biochemistry. His current research involves the use of NMR in conformational analysis.

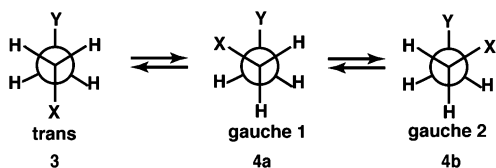
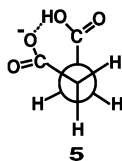


FIGURE 1. Three staggered conformations of  $X-CH_2-CH_2-Y$ .

We believe this area of conformational analysis is significant, because much of it is done in comparison between preferences in water and preferences in nonaqueous protic and aprotic solvents, the latter of which can mimic and so shed light on the interactions between polar, ionized, and hydrogen-bonded groups in the interiors of folded biochemical molecules. It seems fair to say that the overall approach provides new information and insight on one of the very basic and guiding concepts of the conformations of organic structures.

Our entry into the field of conformational analysis began many years ago, when we were first to demonstrate that rotation around the C–C bond compounds such as 1,1-difluoro-1,2-dibromo-2,2-dichloroethane could be slowed down sufficiently at around  $-60\text{ }^\circ\text{C}$  so that one could observe resonance peaks, which could be assigned to the trans and gauche conformers corresponding to **3** and **4a,b**.<sup>18,19</sup> Much later, our research on conformational analysis was revived by a desire to have a simple but interesting NMR research project for a Caltech undergraduate and a reawakened serendipitous curiosity about the Westheimer–Brown controversy regarding the importance of intramolecular hydrogen bonding with  $\alpha,\omega$ -dicarboxylic monoanions in aqueous solution. D. H. McDaniel and H. C. Brown<sup>20,21</sup> had severely criticized F. H. Westheimer's classic work to estimate the distances between the carboxylic groups by measurement of the ratio  $K_1/K_2$  for  $\alpha,\omega$ -dicarboxylic acids (throughout,  $K$  values are to be understood as macroscopic acid ionization constants).<sup>22,23</sup> To understand the problem, the conformations of monosuccinate ion **5** provide an excellent example.



Clearly, the gauche form of the monoanion **5** appears to be stereoelectronically favorable for substantial intramolecular hydrogen bonding, and it would seem difficult to dispute Brown's charge that such bonding would increase  $K_1$  and decrease  $K_2$ , possibly making  $K_1/K_2$  far from the values needed for successful use in the Kirkwood–Westheimer correlation.<sup>22,24</sup> Westheimer and Benfey's<sup>23</sup> counter was simple and compelling. They showed that  $K_1$  for phthalic acid was only just the statistical factor of 2 greater than the  $K$  of the monomethyl ester of phthalic acid. This result is inconsistent with Brown's contention that  $K_1$  should increase when intramolecular hydrogen bonding is to be expected, as it certainly should be with phthalic acid.

Despite the Westheimer and Benfey results, one wonders what the conformational preferences actually are for the monoanion, and this we investigated with water as solvent, in the following way, which is essentially standard throughout our work. After preparation of the desired solution, the proton NMR is taken at 300 or 500 MHz, at the appropriate pH values, and the vicinal H–H coupling constants are extracted from the spectrum with the aid of a modified version of LCN3<sup>25</sup> or gNMR4.<sup>26</sup> Comparison couplings for the individual conformers in the mix were estimated by the procedures of Haasnoot, Altona, and co-workers.<sup>27</sup> These were then used to estimate the fractions of the conformations by simple algebra. Usually we regard the final calculated values to be accurate to  $\pm 5\%$  or better. That the accuracy is not better, sometimes depends on the quality of the spectra, the accuracy of the Altona parameters for the comparison couplings, or both, but a more inherent flaw is that no experimental data are available for the values of dihedral angles to use in the Altona equations for the individual conformers of rapidly interconverting systems like succinic acid in solution. Many believe that even relatively simple quantum calculations should suffice to give useful dihedral angle data for the species in solution; our experience is less sanguine.<sup>28,29</sup> However, no experimental verification is available to ensure the accuracy of the calculated dihedral angles or the couplings of the conformations corresponding to them. When there is nothing better to go on, the comparison couplings were obtained assuming the average dihedral angles to be the perfect staggered values. The dihedral angle problem will be discussed in greater detail farther along.

For succinic acid,  $^{13}\text{C}$  satellites on the proton spectra were used to break the molecular symmetry and allow the vicinal H–H couplings to be measured. These were best obtained from the rather complex AA'BB'XX' spectra of succinic-2,3- $^{13}\text{C}$  acid.<sup>30</sup> To determine the conformational preferences of each of the species, the coupling constants were obtained as a function of pH from low to high values. The coupling constants for the diacid and dianion were easily obtained at the maximum and minimum pH values.<sup>30,31</sup> The monoanion was more difficult, because even at the equivalence point it is only present to the extent of 72% with equal amounts of diacid and dianion. However, enough data points were available to extract its coupling constants, calculate its conformational preference, and also check on the  $K_1$  and  $K_2$  values of the succinic acid.<sup>30</sup>

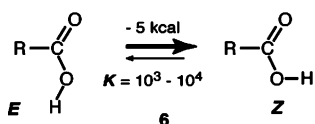
## Conformational Preferences of Succinic Acid and Its Salts in Water

What conformational preferences should we expect for the diacid in water solution? One's immediate thought might well be that steric hindrance would need to be weighed against intramolecular hydrogen bonding between the carboxylic acid groups, and of course, these effects would be anticipated to operate in opposition to one another. The diacid turned out to be  $\sim 85\%$  gauche, so we might

tentatively chalk up one for intramolecular hydrogen bonding. That steric hindrance is apparently not a large factor is probably because the carboxyl groups are planar. In other research, we have shown that while 3-(*N,N,N*-trimethylammonium)propionic acid at most shows a small steric effect, it is much larger with the corresponding ditetrahedral 3-(*N,N,N*-trimethylammonium)ethanesulfonic acid.<sup>28</sup>

Turning to the monoanion, we expect hydrogen bonding to be greatly enhanced by having one of the carboxylate groups being anionic **5**. Here, there is a surprise in that the measured preferences were for ~70% gauche, rather *less* than that for the diacid itself and not far from the 66.7% of statistical, which corresponds to no net influence at all of substituent groups. It was found that the conformational preference for the monoanion in water was unchanged within experimental error for changes in concentration and use of sodium or tetramethylammonium as the counterion, although with the lithium salt, the proportion of gauche was reduced to about 54%. The finding of less gauche with the monoanion than with the diacid was regarded as so surely incorrect by reviewers that 2 years, as well as substantially more experimentation and argumentation, were required before the results were accepted for publication.<sup>30</sup> But the fact is that it is just what would be expected from the Westheimer and Benfey results cited above. Here, quantum calculations were helpful, indicating that water was likely to be a better solvator of a non-hydrogen-bonded monosuccinate anion than a combination of water and a carboxylic acid group acting to stabilize **5**.<sup>32</sup>

Complicating factors turned up in these calculations involve the difference in energy between the *Z* and *E* forms of carboxylic acids **6**.<sup>33</sup> Clearly to form an intramolecular



hydrogen bond, the carboxylic OH group must have the *E* configuration, as seen for **5**. There seems agreement that the *E* configuration is less stable than the *Z* configuration on the order of 4–5 kcal/mol,<sup>32</sup> although its dependence on solvent is apparently not known. Jung and Gervey<sup>34</sup> have shown with the *E/Z* forms of esters that the *E* configurations become more favorable relative to *Z* as the polarity of the solvents increases. Whether the unfavorable energy of forming the *E* configuration is responsible for the lack of phthalate,<sup>23</sup> as well monosuccinate, intramolecular hydrogen bonding in water is not known. If the observed solvent dependence reported for esters holds for carboxyl groups, it should be a favorable influence rather than the reverse. However, the uncertainty in the overall change in entropy in the formation of an intramolecular hydrogen bond in water makes this sort of speculation difficult.<sup>35</sup>

Still another complicating factor is encountered when **5** is modeled to form a hydrogen bond with the *E* configuration of the hydrogen of the carboxyl OH group,

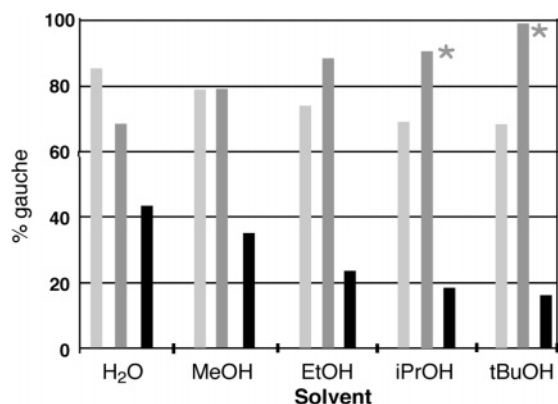
because it is seen that to attain a nearly linear O–H–O bond without changing the normal bond distances and angles cannot be easily accomplished without rotating the central C–C to give a dihedral angle between the carboxyl carbons from the usually expected 60° to at least 65–70°. The Altona procedure for estimating the vicinal coupling constants of the gauche conformers then reduces the gauche preference from ~70% to ~61%. The degree of geometrical change for phthalate monoanion when it forms a hydrogen bond should be much smaller than that for succinic acid because, except for the *Z* to *E* change, the geometry is quite stereoelectronically favorable for hydrogen bonding.

Coulombic repulsion between the negatively charged carboxylate groups of succinic dianion in water is expected to lead to a marked preference for gauche. However, the observed couplings analyzed in the same way, as with the other succinic species, leads to an estimated gauche preference of ~44%, independent of counterion and concentration. Whether this is a large or small change is almost a matter of taste, it is a reduction of only about one-third from the statistical factor of 66%, and the high dielectric constant of water would be expected to mute the repulsive interaction between the ions. However, there are theoretical reasons to expect that as unlike charges approach one another in water, there is a favorable enthalpic change but a less favorable entropic change.<sup>35,36</sup> Obviously, if the energy effects oppose one another, it can be difficult in any new situation to decide which is more important or whether they effectively cancel one another. A mystery here and actually throughout our work is the size of the solvation “sphere” around a carboxylate anion and whether as two solvated carboxylates approach each other, as in changing from trans to gauche for the succinate dianion, the solvating molecules seamlessly meld with each other with, or without, sizable enthalpic or entropic changes. So far, we have seen nothing in the way of conformational changes that we can attribute to such behavior.

In summary, the data obtained for the succinic species in water did not lead to much in the way of concrete general precepts to utilize for other compounds, except that steric effects appear to be essentially unrecognizable, intramolecular hydrogen bonding of monosuccinate anion in water is not favorable, repulsion between like-charged ions is not very powerful, and, for as yet unexplained but not hydrogen-bonding reasons, the diacid has a moderate gauche preference.

## Conformational Preferences of Succinic Acid and Its Salts in Nonaqueous Protic Solvents

Water has quite unique properties compared with other protic solvents, and it was important to see what changes would take place in less-polar protic solvents. For this purpose, we chose the rather mundane sequence of alcohols, methanol, ethanol, isopropyl alcohol, and *tert*-butyl alcohol. This sequence, including water, from left to right, offers rapidly decreasing acidity, dielectric con-



**FIGURE 2.** Conformational preferences estimated from vicinal proton–proton couplings for succinic acid species in ROH solvents. Light-gray bars are for the diacid, dark bars for monosuccinate, and black bars for succinate dianion. The bars marked with a star were calculated with dihedral angles of 70°, because 60° dihedral angles gave calculated values >100% gauche.

stant, and ability to form hydrogen bonds. Some of the metallic succinate salts are not very soluble in the less-polar solvents, and to remedy this, we normally use tetrabutylammonium as the counterion.<sup>37</sup> However, if the butyl proton resonances overlap with those of the succinate species, the tetraethylammonium or even tetramethylammonium cations can be used, although their succinate salts are not as soluble as those derived from tetrabutylammonium. The tetraalkylammonium salts were most conveniently prepared by mixing weighed amounts of the acid and tetraalkylammonium cyanide in methanol, removing the hydrogen cyanide and solvent, then dissolving the residue in the desired deuterated alcohol. There seemed to be little, if any, difference in estimated conformational preference with the cation, although this was not established rigorously. The results are shown in Figure 2.<sup>38</sup>

The estimated preferences in Figure 2 for the diacid are revealing in decisively eliminating hydrogen bonding as a possibility for its 85% gauche preference in water. This can be seen from the fact that the percentage of gauche of the diacid decreases from left to right, leveling off essentially at the statistical proportions for isopropyl and *tert*-butyl alcohols. In contrast, the proportion of gauche for the monoanion increases dramatically over the same solvent range. Similar decreases in gauche with solvent polarity have been observed for diethyl succinate<sup>39</sup> and other polar molecules.<sup>40,41</sup> This pattern of changes in preferences has been ascribed to changes in the “gauche effect”. The gauche effect was originally associated with gauche preferences where X and Y substituents of Figure 1 are strongly electronegative groups. Attributing gauche preferences to strongly electronegative groups is inconsistent with the preferences of succinonitrile.<sup>42</sup> This substance has strongly electronegative groups but is about 73% gauche in water and 55% in toluene. Experimentally, the gauche effect is especially evident with the X and Y substituents of Figure 1 being F or an OR group with R as H, alkyl, and OCR.<sup>40,43</sup> An early important example was ethylene glycol **7**, which exhibits the expected change to

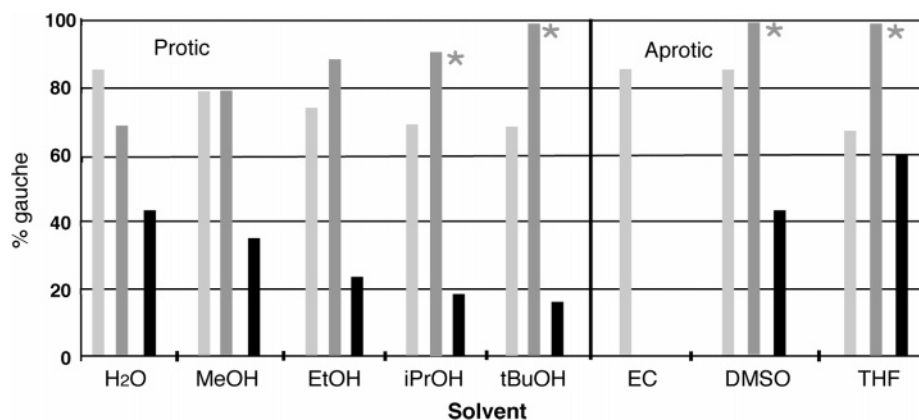
less gauche in less-polar solvents.<sup>40</sup> The discovery that 2-fluoroethanol **8** also showed a strong gauche preference has led to suggestions of intramolecular O–H–O and O–H–F hydrogen bondings to explain the gauche effect for **7** and **8**. However, that this is important seems inconsistent with data on the large dilution shifts of the OH protons of **7** and **8**.<sup>44</sup> There is, however, a very careful study of *trans*-2-fluorocyclohexanol, which supports an OH–F intramolecular hydrogen bond.<sup>45–47</sup>

An alternative explanation of some examples of increasing preference for gauche with strongly electron-attracting substituent groups is that their dipole moments generally increase as they become more gauche and are then expected to be better stabilized by more polar solvents. We might characterize this as a polar-solvent effect. Recently, there has been substantial quantum mechanical calculations to ascribe the gauche effect with OH and F as substituents to hyperconjugative interactions between the substituent and a trans hydrogen, where the hydrogen electrons are donated to the s\* orbitals of the oxygen or fluorine atoms.<sup>48,49</sup> In past eras, such interactions were formulated as H–C–C–F ↔ H<sup>+</sup> C=C F<sup>-</sup>. Inspection of the Newman projections **4a,b** shows that if both X and Y are fluorine, each will have two such H–C–C–F trans interactions.

In principle, one might be able to distinguish the hyperconjugative from the polar-solvent effect, if the hyperconjugative effect of X and Y were to be reduced to zero as the result of solvent changes. Then, if there are no other effects operating to change the preferences, the result should be a statistical mix of conformers. Thus, preferences for succinic acid in alcohols may be the result of a weak H–C–C–CO<sub>2</sub>H hyperconjugative interaction going to near zero in *tert*-butyl alcohol (see Figure 2).<sup>38</sup> It would seem unlikely that the polar-solvent effect would operate in the same way. The overall averaged dipole moment would be larger for the gauche than the trans, and going to less-polar solvent should give more trans. This scenario seems to be followed for succinonitrile where the estimated fraction of gauche is 73% gauche in water and 55% in toluene.<sup>42</sup>

Turning to the monoanion, we see from Figure 2 that as the polarity and the solvating power of the solvent decreases, the fraction of gauche dramatically increases, surely the result of hydrogen-bond formation, wherein the carboxyl group effectively solvates the anionic carboxylate group. If one maintains a 60° dihedral angle between the X and Y groups, the vicinal coupling constants for solutions in isopropyl and *tert*-butyl alcohols suggest that the estimated percentage of gauche is greater than 100%. Resetting the dihedral angle to 70° gives close to 100% gauche, which supplies strong support for our earlier supposition, based on inspection of models that indicate for good intramolecular hydrogen bonding, the dihedral angle should be increased to 65–70° for the succinate monoanion.

For the succinate dianion, Figure 2 shows the expected decrease in the fraction of gauche as the polarity of the solvent decreases, diminishing to about 16% in *tert*-butyl



**FIGURE 3.** Conformational preferences estimated from vicinal proton–proton couplings for succinic acid species in protic and aprotic solvents. Each group is displayed in decreasing order of dielectric constant from left to right. Light-gray bars are for the diacid, dark bars for monosuccinate, and black bars for succinate dianion. The bars marked with a star were calculated with dihedral angles of 70°, because 60° dihedral angles gave calculated values >100% gauche.

alcohol, as the result of increased repulsion between the negative carboxylate groups. It is uncertain whether the fraction of gauche is actually smaller than 16%, because there are almost no freely interconverting compounds with X and Y groups that can be surely predicted to be almost exclusively trans. The excellent example provided by Abraham and Gatti<sup>50</sup> of (2,2-dimethylbutyl)-*N,N,N*-trimethylammonium cation has vicinal H–H couplings in water that, when calculated by the same procedures used for the preferences in Figure 2, correspond to a 10% gauche. However, in any event, the overall rationalization of the behavior of the succinic species in the protic solvents employed here can be regarded as generally successful, despite some uncertainty about the gauche effect.

### Conformational Preferences of Succinic Acid and Its Salts in Nonaqueous Aprotic Solvents

Aprotic solvents are of special interest, because they can have a very wide range of dielectric constants, are incapable of providing donor hydrogen bonds, but may have quite reasonable to strong capabilities for forming acceptor hydrogen bonds. Our first choices have been DMSO (dimethyl sulfoxide,  $\epsilon = 45$ ) and THF (tetrahydrofuran,  $\epsilon = 7$ ). EC (ethylene carbonate,  $\epsilon = 85$ ) is potentially interesting in having a dielectric constant comparable to that of water. However, we have done little work with it, except to show that succinic acid has about the same percentage of gauche in EC, as in water. The available data on the conformational preferences of succinic species in DMSO and THF solvents are displayed in Figure 3.

For the diacid, the proportions of gauche are seen to be rather like those in protic solvents, largest with the highest dielectric constant and decreasing to essentially statistical at the lowest dielectric constant, as possibly accountable by a hyperconjugative H–C–CO<sub>2</sub>H interaction.

The monoanion appears to have a strong intramolecular hydrogen bond in all aprotic solvents, which, as in the less-polar alcohols, can be attributed to lack of power for solvating anions relative to the adjacent undissociated

carboxyl group. A very effective way of evaluating intramolecular hydrogen bonding is to determine the relative  $K_1/K_2$  values for 1,4-dicarboxylic acids in water and DMSO. The original work for DMSO was done along these lines by Kolthoff and Chantooni<sup>51,52</sup> using conductance methods. The determinations are now made much easier using NMR<sup>53,54</sup> and relative acidities in DMSO provided by Bordwell.<sup>55</sup> The resulting  $K_1/K_2$  values agree satisfactorily with those obtained by Kolthoff. With succinic acid,  $K_1/K_2$  is 25 in water and  $3 \times 10^8$  in DMSO. The reason is the same as postulated by McDaniel and Brown,<sup>20</sup> that formation of a strong hydrogen bond will increase  $K_1$  and decrease  $K_2$  by making the monoacid more difficult to ionize. The irony of the Westheimer–Brown conflict discussed earlier is that Westheimer was correct for water and Brown would have been correct if the solvent were DMSO, where the ratio of the first ionization constants of phthalic acid and monomethyl phthalate is  $10^3$ , rather than 2 as in water.<sup>23</sup>

The results with the dianion were surprising in both DMSO and THF, in which solvents it showed much more gauche than was observed in *tert*-butyl alcohol. Now, if you accept the evidence of the vicinal H–H couplings, you are confronted with the specter of like charges attracting one another in aprotic solvents. How can this be so? A possible rationalization is provided by eq 1 derived by M. Born<sup>56</sup> for stabilization of charges in dielectric media.

$$\Delta G_s = -\frac{z_i^2 e^2 N_A}{8\pi\epsilon_0 r_i} \left(1 - \frac{1}{\epsilon_r}\right) \quad (1)$$

For us, the key element of Born's formulation is that the stabilization energy of a charge of magnitude  $z$  in a dielectric, besides being a function of the dielectric constant  $\epsilon$  and physical constants, is proportional to the square of  $z$ . If we consider the trans (anti) conformation of the succinate dianion with its carboxylate groups as far apart as possible, then each would have close to an effective charge of  $-1$  and a total effect with the Born equation of  $2(-1)^2$ . However, if the carboxylates are brought close together, they may act, to at least some degree, as a composite dianion and hence have an

effective  $z^2$  term greater than two but surely less than the maximum of  $(-2)^2$ , consequently favoring a sizable fraction of gauche. This idea is supported by quantum calculations where, in effect, the energy of the succinate dianion was calculated as a function of the dihedral angle from  $0^\circ$  to  $180^\circ$  in the gas phase, THF, and water.<sup>57</sup> The results for the solvents were not surprising in that decreasing the dihedral angle was accompanied by a large increase in the polarization of the solvent. What was more surprising was that for THF there was a decrease in energy beginning at about  $112^\circ$  to give a broad minimum at about  $40^\circ$  of about 9 kcal/mol. Such a minimum would have a clearly dominate gauche-like conformation with a  $\sim 40^\circ$  dihedral angle. Unfortunately, the vicinal proton–proton couplings calculated by the Altona procedure<sup>58</sup> for a dianion with a  $40^\circ$  dihedral angle are quite close to the dianion couplings observed experimentally for THF solutions. This means that we cannot make a decision based solely on the values of the coupling constants as to what is present in THF, a single conformation with a  $40^\circ$  dihedral angle or a mixture of gauche and trans conformations with normal  $60^\circ$  and  $180^\circ$  dihedral angles. This is a situation where being able to determine the dihedral angle is of vital importance to uncovering the nature of the conformational preferences involved.

### Hope for Determination of the Dihedral Angles of Rapidly Interconverting Conformers?

Experimental measurement of dihedral angles for rapidly interconverting conformers in solution is difficult. In a worst-case scenario for  $X-CH_2-CH_2-Y$ , it would be necessary to determine not only the equilibrium concentrations of the conformers and their dihedral angles, but all of their other bond angles and bond distances. However, because changing of the backbone bond angles and distances is expected to require substantially larger energies than changing the rotational angle about the central C–C bond, it seems to be at least plausible to start by attempting to solve the rotational-preference and dihedral-angle problem by assuming the other bond angles and distances have their “normal” values.

One would hope for an NMR solution, because with proper attention to maximizing the accuracy of taking integrals, NMR is intrinsically more accurate for measuring concentrations than infrared or Raman spectra in situations when calibration spectra are not available. It would appear that the most useful NMR technique for determination of dihedral angles would be to analyze the inter-nuclear dipole–dipole splittings of conformational systems in oriented liquid-crystal or lyotropic media.

We have been engaged in a project to determine the rotational dihedral angles of rapidly equilibrating 1,2-disubstituted ethanes in solution in oriented media. Our efforts to use the liquid-crystal method were based on the work of Chidichimo and co-workers, who reported determining the dihedral angles of ethylene glycol and succinic acid, its monoanion, and its dianion in aqueous lyotropic solutions.<sup>59,60</sup> For our interests in conformer preferences

in aprotic solutions, we needed a useful nematic, aprotic liquid crystal in which the compounds of interest are soluble. This is not too hard for succinic acid but is quite difficult for succinate salts. To be sure, liquid-crystal molecules usually possess one to three polar groups, which should increase the solubility of the salts, but the influence of these groups is overwhelmed by the presence of two or more aromatic rings and saturated groups, as typified by the otherwise excellent and widely used liquid-crystalline material 4-cyano-4'-(2-pentyl)-biphenyl. Analysis of the quite often complicated NMR spectra of an oriented substance to obtain the dipolar couplings is the next problem. We have done that with succinic acid assisted by using several different  $^{13}\text{C}$ -labeled succinic acids. To proceed further requires using the dipolar couplings to evaluate not only the position of conformational equilibrium and dihedral angles of each distinct conformer but also the parameters that define the orientation of each of those conformers in the liquid crystal matrix. Unfortunately, the equations connecting all of these variables do not lead to singular solutions. The problem could be solved with an independent way to evaluate the fractions of each conformer present. Chidichimo “solved” this problem by assuming ethylene glycol, succinic acid, and its monoanion were all 100% gauche, while taking succinic dianion to be 100% trans in aqueous solution.<sup>59,60</sup> The reliability of these assumptions is questionable, because their experimental isotropic couplings for the succinic species in their lyotropic media agreed reasonably well with our values in water and are only interpretable by assuming conformational preferences far from 100% of any one conformation. Presumably, we can expect the succinate mono- and dianions to be essentially 100% in an aprotic liquid crystal, but so far, we have not surmounted the solubility problem.

Another use of NMR to determine dihedral angles of equilibrating conformations has been devised by Markley and co-workers<sup>61</sup> that calculates probabilities for conformer populations utilizing the angular dependences of each coupling constant and also the angular dependences of each internuclear distance that gives rise to a NOE. This method (“CUPID”) has been employed in an analysis of the conformations of L-leucine.<sup>62</sup> At least in principle, the liquid-crystal procedure has the advantage of not requiring knowledge of the angular dependences of the scalar coupling constants.

### Summary

The results of our work on conformational analysis of succinic acid species in a range of solvents have offered several insights, which should be of general use in rationalizing the conformational preferences of other  $X-CH_2-CH_2-Y$  systems. First is that steric hindrance, at least with carboxyl groups as X and/or Y, is not very important. Second is the apparent unimportance of intramolecular hydrogen bonding in water, but important effects are to be expected in less polar alcohols and in aprotic solvents. Third, there may be two gauche effects,

one associated with hyperconjugative stabilization for trans H-C-C-X groupings, where X is preferably OR or F but CO<sub>2</sub>R also appears to have at least some influence. The other, the “polar-solvent effect”, for which an example appears to be succinonitrile, can be associated with preference for more polar conformations in more polar solvents. Fourth, there is evidence for succinate dianions to exhibit rather surprising extents of gauche preferences in aprotic solvents.<sup>57</sup> The applications of these influences to other substituted ethane systems is covered in other publications.

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