9672 *J. Am. Chem. Soc.* **1998,** *120,* 9672−9679

Conformational Complexity of Succinic Acid and Its Monoanion in the Gas Phase and in Solution: Ab Initio Calculations and Monte Carlo Simulations

Daniel J. Price,[†] **John D. Roberts,**[‡] **and William L. Jorgensen***,[†]

Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06520-8107, and the Gates and Crellin Laboratories of the California Institute of Technology, Pasadena, California 91125

Received April 13, 1998

Abstract: Optimized structures and relative energies for conformers of succinic acid and its monoanion in the gas phase were obtained using ab initio molecular orbital calculations at the MP2/6-311+G**//HF/6-31G* and MP2/6-311+G**//HF/6-31+G* levels, respectively. The lowest energy conformer for succinic acid, designated ZsgsZ, has a gauche conformation about the central C2−C3 bond; the lowest energy conformer with an *E*-acid group and an internal hydrogen bond is ca. 3 kcal/mol higher in energy. The lowest energy structure for the monoanion, Ecgs, does have the expected internal hydrogen bond and is 15 kcal/mol more stable than any alternative. The ab initio results were used to determine corresponding torsional-energy parameters in the OPLS all-atom force field. This allowed application of statistical perturbation theory in Monte Carlo simulations to explore the effect of hydration on the conformational equilibria. The diacid and monoanion were both computed to be ca. 80% gauche in water at 25 °C. These results are in excellent agreement with NMR data. Though the conformational results are consistent with the gauche effect, their true origin requires a detailed understanding of the potential internal hydrogen bonding and solvation. Thus, in contrast to the monoanion's striking gas-phase preference, neither the diacid nor monoanion are computed to populate *E* conformers in aqueous solution.

Introduction

The seemingly anomalous favoring of gauche conformers for $X-CH_2CH_2-Y$ molecules when X and Y are electronegative groups is referred to as the "gauche effect" or "the folding of methylene units".[1,2] There have been numerous gas-phase quantum mechanical calculations and experimental observations of this phenomenon with difunctional molecules including difluorides, diamides, diesters, and diketones.[2−5] Succinic acid (butanedioic acid) is another candidate for this effect. Though it may be expected by inference to favor a gauche conformation in the gas phase, the situation is complicated in aqueous solution by the anticipated extensive hydrogen bonding with water, which could favor less sterically crowded trans conformers. Nevertheless, when aqueous succinic acid was previously monitored with proton−proton *J*-coupling measurements, the gauche effect emerged once again.[6] The observed conformational preference of neutral succinic was ca. 80% gauche. Remarkably, a similar preference of ca. 70% gauche was also obtained for the succinate monoanion.[6] In the latter case, a potential internal hydrogen bond via an *E*-acid conformer could have been expected to yield an even higher gauche population.

It takes little reflection to realize the potential complexities for these species in view of the gauche effect, hydrogen bonding, and the *E/Z* possibilities. To elucidate the conformational energetics for this prototypical difunctional system, the present in-depth computational study was carried out. Thus, the gas-phase structures and energetics for the diacid and monoanion were first addressed with ab initio molecular orbital calculations. These results permitted development of OPLS-AA force-field parameters to reproduce the conformational energetics. The conformer populations and solvation in aqueous solution were then determined through a series of Monte Carlo simulations using Metropolis sampling[7] and statistical perturbation theory (SPT).[8] Free-energy profiles and the associated conformer populations have been obtained by perturbing the dihedral angle of interest and computing the incremental free-energy changes.[9]

There is also an important technical impetus for this study. Difficulties in parametrizing force fields for polyfunctional systems are becoming apparent, as in recent efforts on the treatment of carbohydrates.[10] The desire is to avoid making changes to the parameters for the constituent monofunctional systems. Thus, our approach is to only add the missing torsional

---

[†] Yale University.

[‡] California Institute of Technology.

(1) Wolfe, S. *Acc. Chem. Res.* **1972**, *5*, 102. Wiberg, K. B. *Acc. Chem. Res.* **1996**, *29*, 229.

(2) Alemán, C.; Puiggalí, J. *J. Org. Chem.* **1997**, *62*, 3076.

(3) Wiberg, K. B.; Murcko, M. A.; Laidig, K. E.; McDougall, P. J. *J. Phys. Chem.* **1990**, *94*, 6956.

(4) Alemán, C.; Navarro, E.; Puiggalí, J. *J. Phys. Chem.* **1996**, *100*, 16131.

(5) Alemán, C.; Navarro, E.; Puiggalí, J. *J. Org. Chem.* **1995**, *60*, 6135.

(6) Lit, E. S.; Mallon F. K.; Tsai H. Y.; Roberts, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 9563.

(7) Metropolis, N.; Rosenbluth, A. W.; Rosenbluth, M. N.; Teller, A. H.; Teller, E. J. *J. Chem. Phys.* **1953**, *21*, 1087.

(8) Zwanzig, R. W. *J. Chem. Phys.* **1954**, *22*, 1420.

(9) Jorgensen, W. L.; Buckner J. K. *J. Phys. Chem.* **1987**, *91*, 6083.

(10) Glennon, T. M.; Zheng, Y.-J.; Le Grand, S. M.; Shutzberg, B. A.; Merz, K. M. *J. Comput. Chem.* **1994**, *15*, 1019. (b) Senderowitz, H.; Parish, C.; Still, W. C. *J. Am. Chem. Soc.* **1996**, *118*, 2078. (c) Damm, W.; Frontera, A.; Tirado-Rives, J.; Jorgensen, W. L. *J. Comput. Chem.* **1997**, *18*, 1955.

S0002-7863(98)01239-6 CCC: $15.00

parameters for the polyfunctional system, if possible. In particular, redevelopment of the nonbonded parameters (charges and Lennard-Jones σ's and ϵ's) is undesirable, since they are generally assigned from lengthy consideration of gas-phase, pure liquid, and dilute solution properties of a series of monofunctional molecules.[11] The validity of this approach is further tested here for succinic acid and its monoanion.

Computational Details

Ab Initio Calculations. The conformational search utility of the BOSS program[12] was used to generate a set of starting structures. OPLS-AA parameters for carboxylic acids, carboxylates, and saturated hydrocarbons provided nonbonded and torsional parameters for the search.[11,13] The resultant energy minima with relative energies within 10 kcal/mol of the global minimum for the diacid and within 25 kcal/mol for the monoanion were used as starting points for ab initio optimizations at the HF/6-31G* and HF/6-31+G* levels, respectively. The + functions are a diffuse set of s and p orbitals on each non-hydrogen atom that aid in the description of the electronic structure of anions. To seek additional minima and to assess torsional barrier heights for the *Z*,*Z*-diacid, relaxed potential-energy scans were also performed for the C−CT−CT−C and CT−CT−C−O dihedral angles in 30° increments at the RHF/6-31G* level. Vibrational frequency calculations were performed on five optimized structures, and all were verified to be true energy minima. Subsequently, MP2/6-311+G** single-point calculations were performed on the lowest energy minima. All ab initio calculations were performed using the Gaussian 94 program[14] on an SGI Indigo2 with an R10000 processor.

Semiempirical Calculations. To obtain initial estimates of hydration effects, single-point calculations were also conducted on the ab initio energy minima using two semiempirical methods, AM1 and PM3, and the continuum solvation models, AM1/SM2 and PM3/SM3.[15] For a given conformer, subtraction of the internal energy from the total solvated energy gave an estimate of the free energy of hydration, ΔG_{hyd}. Addition of this ΔG_{hyd} to the ab initio relative energy provided a free energy in solution, ΔG_i, that can yield populations using a discrete form of the Boltzmann equation (eq 1), where S_i is the fractional population and ω_i is the degeneracy. These calculations were performed with the AMSOL package.[16]

$$S_i = \omega_i \exp(-\Delta G_i/k_{\mathrm{B}}T)/\sum_j \omega_j \exp(-\Delta G_j/k_{\mathrm{B}}T) \tag{1}$$

Force-Field Parametrization. The conformational energetics from the ab initio calculations also enabled development of the torsional parameters for the OPLS-AA force field. The force field is needed to perform the subsequent Monte Carlo simulations for the diacid and monoanion in solution. The energy function (eqs 2−5) consists of harmonic terms for bond stretching and angle bending, a Fourier series for each dihedral angle, and nonbonded interactions for which the Lennard-Jones parameters $\sigma_{ij} = (\sigma_i\sigma_j)^{1/2}$ and $\epsilon_{ij} = (\epsilon_i\epsilon_j)^{1/2}$.

$$E_{\mathrm{bond}} = \sum_i k_{\mathrm{b},i}(r_i - r_{0,i})^2 \tag{2}$$

$$E_{\mathrm{bend}} = \sum_i k_{\theta,i}(\theta_i - \theta_{0,i})^2 \tag{3}$$

$$E_{\mathrm{torsion}} = \sum_i \{V_{1,i}(1 + \cos\varphi_i)/2 + V_{2,i}(1 - \cos 2\varphi_i)/2 + V_{3,i}(1 + \cos 3\varphi_i)/2\} \tag{4}$$

$$E_{\mathrm{nb}} = \sum_i \sum_{j>i} \{q_i q_j e^2/r_{ij} + 4\epsilon_{ij}[(\sigma_{ij}/r_{ij})^{12} - (\sigma_{ij}/r_{ij})^6]\} \tag{5}$$

Atom type designations from the AMBER force field are used to facilitate specification of the bond stretching, angle bending, and torsional parameter types with the following correspondences:

CT	aliphatic carbon
HC	hydrogen on aliphatic carbon
C	carbon of carboxylate or carboxylic acid
OH	hydroxyl oxygen in carboxylic acid
HO	hydroxyl hydrogen in carboxylic acid
O	carbonyl oxygen in carboxylate or carboxylic acid

In the OPLS-AA force field there is usually a unique set of Lennard-Jones parameters for each AMBER atom type; however, the partial atomic charges are context dependent. The same nonbonded parameters have been used here as previously developed for monofunctional carboxylic acids and carboxylate ions;[11] they are summarized in the Supporting Information. The bond stretching and angle bending parameters are specified uniquely by the AMBER types; the values used here were reported previously[11] and are also provided in the Supporting Information.

Most of the torsional parameters were adopted from those for monofunctional carboxylic acids, carboxylate ions, and alkanes.[11] It should be noted that there may be different torsional parameters for a given quartet of AMBER atom types, W−X−Y−Z, in different molecules. The new parametrization focused primarily on the C−CT−CT−C torsion, and it was also found to be necessary to reoptimize the CT−CT−C−O and CT−C−OH−HO parameters for the difunctional systems. Fitting was accomplished using the program fitpar[17] in conjunction with some manual fitting to “difference profiles”. A difference profile is created by subtracting the ab initio relative energies from energies calculated using OPLS parameters with the exclusion of the torsion in question. The combination of approaches allowed an emphasis to be placed on representing low-energy conformers with higher accuracy. Furthermore, there was an additional consideration for the monoanion of succinic acid. As presented below, the standard carboxylate partial charges[11] led to overestimation of the strength of the internal hydrogen bond in the lowest energy gas-phase structure. This structure was consequently excluded from the fitting procedure, and an emphasis was placed on reproducing the

---

[11] Jorgensen, W. L.; Maxwell, D. S.; Tirado-Rives, J. *J. Am. Chem. Soc.* **1996**, *118*, 11225.

[12] Jorgensen, W. L. *BOSS Version 3.6*; Yale University: New Haven, CT, 1995.

[13] Maxwell, D. S.; Tirado-Rives J.; Jorgensen, W. L. *J. Comput. Chem.* **1995**, *16*, 984.

[14] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94, Revision B.2*; Gaussian, Inc.: Pittsburgh, PA, 1995.

[15] Cramer, C. J.; Truhlar, D. G. *J. Comput.-Aided Mol. Des.* **1992**, *6*, 629.

[16] Cramer, C. J.; Lynch, G. C.; Hawkins, G. D.; Truhlar, D. G.; Liotard, D. A. *AMSOL Version 4.0*; University of Minnesota: Minneapolis, MN, 1994.

[17] Maxwell, D. S.; Tirado-Rives, J. *Fitpar Version 1.1.2*; Yale University: New Haven, CT, 1995.

relative energies of the remaining minima. The resultant complete set of torsional parameters is summarized in the Supporting Information.

Monte Carlo Simulations. Monte Carlo statistical mechanics simulations were carried out to obtain our best estimates of the conformer populations for the diacid and monoanion in water. Free-energy perturbation (FEP) calculations were performed for changing a solute geometry from a form A to B using the Zwanzig equation (eq 6),[8]

$$\Delta G(A \rightarrow B) = -k_B T \ln\langle \exp[-(E_B - E_A)/k_B T]\rangle_A \qquad (6)$$

where $\langle\ \rangle_A$ denotes an average from sampling for the reference geometry A and E_B and E_A are the total potential energies for geometries A and B.

Two types of perturbations were performed. First, the free-energy profiles for rotation about the central CC bond in both the diacid and monoanion were computed with the acid groups initially in the *Z* conformation.[9] All internal degrees of freedom for the solutes were sampled with the exception of the C−C−C−C torsion angle, which was the reaction coordinate, and the geometry about the carboxyl carbons was kept planar. The C−C−C−C dihedral angle was perturbed from 0° to 180° in a periodic cube, which contained the single solute and 500 TIP4P water molecules.[18] The calculations were done in nine increments ("windows") with double-wide sampling;[19] therefore, each perturbation had a $\Delta\Phi$ of ±10° from the reference geometry. Both carboxyl groups were moved 5° at a time.

Second, the diacid and the monoanion were also perturbed from structures having the acids in the *Z* conformation to a structure having one *E*-acid, again with 500 TIP4P waters. The goal was to ascertain the possible population of geometries with *E*-acid groups in solution. This mutation was achieved by growing out a hydrogen in the *E* conformation concurrently with the disappearance of a hydrogen in the *Z* conformation. A hydrogen's disappearance consisted of scaling down the partial charge from 0.45*e* to zero. These calculations were carried out in 10 windows with double-wide sampling and $\Delta q = 0.0225e$. Furthermore, the O−H bond length was scaled-down concomitantly from ca. 0.94 to 0.40 Å. Since this bond is flexible, the GASP procedure was used in the simulations.[21] The opposite measures were followed for growing out a hydrogen atom. The same $Z \rightarrow E$ mutation was performed for the monoanion in a ca. 34 × 34 × 34 Å box with 267 OPLS tetrahydrofuran (THF)[20] molecules to assess the *E* population in a dipolar aprotic solvent. For the $Z \rightarrow E$ perturbations, all remaining internal degrees of freedom were sampled, so both gauche and trans conformers could contribute to the free-energy change.

All MC simulations were performed in the isothermal−isobaric (NPT) ensemble at 25 °C and 1 atm. Standard procedures were used, including Metropolis sampling, periodic boundary conditions, and preferential sampling.[7,9,19] The 10-Å cutoffs were based on the distances between non-hydrogen atoms of the solute and the oxygen of a water or THF molecule; if any distance was below the cutoff, the entire solute−water interaction energy was included. The water−water and THF−THF cutoffs were based on the O−O distances. At least 1×10^6 configurations were sampled before averaging to equilibrate the system in each FEP window. Convergence of the ΔG for each window and for the mutation as a whole was carefully monitored, as discussed below. Dihedral angle distributions for symmetrically related dihedral angles were also monitored as an indicator of convergence. For the cis → trans perturbations of the CCCC dihedral angle, 30×10^6 configurations of averaging were performed for each window. The $Z \rightarrow E$ perturbations in water and THF covered 16×10^6 and 12×10^6 configurations of averaging in each window, respectively. Reported uncertainties (±1σ) were computed with the batch means procedure.[22] Analyses of the solute−water hydrogen bonding were performed on 160 configurations, which were saved at intervals of 2.5×10^4 configurations. A hydrogen bond is defined by a donor H−acceptor distance, XH−Y, of less than 2.6 Å and a net interaction energy below −2.25 kcal/mol.

Results and Discussion

Ab Initio Calculations. The ab initio optimizations produced structures with the C−CT−CT−C torsion as either gauche or trans for all conformers. One would expect that the O−C−CT−CT torsion would favor angles of 0° (syn) and ±120° (clinal) to reflect the usual preference of eclipsing double bonds. This was also found, though in some structures the angle is closer to anti (180°). In the following, dihedral angles near 60° and −60° are designated g and G, while those near 120° and −120° are designated c and C; trans for the central dihedral is t, and anti (a) is used for the O−C−CT−CT dihedrals near 180°. Thus, conformers may be denoted according to the following example: ECGsZ refers to the diacid conformer with the central dihedral as −60° gauche, the two O−C−CT−CT dihedrals as −120° clinal and syn, and there are one *Z*- and one *E*-acid, where the *E*-acid is adjacent to the clinal O−C−CT−CT dihedral. This structure is the only conformer with an *E*-acid in Figure 1. The monoanion follows the same naming convention, less one acid descriptor. Furthermore, syn and anti for the carboxylate O−C−CT−CT torsion in the monoanion are equivalent; only syn is used.

The two lowest energy gauche conformers, two lowest energy trans conformers, and the lowest energy conformer containing an *E*-acid are illustrated in Figures 1 and 2 as a sample of the optimized structures. A total of 15 conformers for the diacid and 6 for the monoanion were optimized with the ab initio calculations. The relative energies and the results for the three central dihedral angles of each local minimum are presented in Tables 1 and 2. As in the ab initio studies of other 1,4-dicarbonyl compounds,[2,4,5] a gauche conformer of both the diacid and the monoanion is computed to be the lowest energy structure in the gas phase. Though variations in the relative energies between the HF and MP2 results are apparent, the orderings of the relative energies are quite similar. For the diacid, the ZsgsZ conformer is the global minimum with both ZstsZ and ZsgaZ about 1.3 kcal/mol higher in energy from the MP2 calculations. The electrostatic interactions are undoubtedly complicated. However, it is expected that there can be favorable interactions between the oxygens of one carboxyl group and the other carboxyl carbon when the central angle is gauche, as in the ZsgsZ and ZsgaZ conformers. There may also be electrostatic attraction between the carbonyl oxygens and the β-methylene groups in a st or ts sequence, as in the ZstsZ structure (Figure 1).

The diacid can only achieve an internal hydrogen bond by converting one acid group to the *E* geometry. The lowest energy case is the ECGsZ conformer in Figure 1, which is 3.8 kcal/

---

[18] Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L. *J. Chem. Phys.* **1983**, *79*, 926.

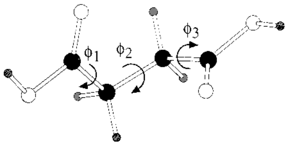
[19] Jorgensen, W. L.; Ravimohan, C. *J Chem. Phys.* **1985**, *83*, 3050.

[20] Briggs, J. M.; Matsui, T.; Jorgensen, W. L. *J. Comput. Chem.* **1990**, *11*, 958.

[21] Severence, D. L.; Essex, J. W.; Jorgensen, W. L. *J. Comput. Chem.* **1995**, *16*, 311.

[22] Allen, M. P.; Tildesley, D. J. *Computer Simulations of Liquids*; Clarendon: Oxford, England, 1987.

Table 1. Comparison of Ab Initio and OPLS-AA Gas-Phase Results for Diprotic Succinic Acid



	HF/6-31G*//HF/6-31G*				MP2/6-311+G**//HF/6-31G*	OPLS-AA				
conformer	ΔE, kcal/mol	ϕ_1	ϕ_2	ϕ_3	ΔE, kcal/mol	ΔE, kcal/mol	ϕ_1	ϕ_2	ϕ_3	μ, D
ZsgsZ	0.00	11.1	69.2	11.1	0.00	0.00	17.2	67.4	17.2	0.39
ZstsZ	0.59	0.0	180.0	0.0	1.34	1.34	0.0	180.0	0.0	0.00
ZsgaZ	1.78	0.6	62.6	−156.9	1.25	1.29	13.6	64.2	−144.0	2.91
ZstcZ	2.14	−4.4	178.7	123.4	2.06	2.12	−2.0	−179.5	111.4	2.45
ZaGaZ	3.55	163.7	−59.6	163.7	2.50	N/A	N/A	N/A	N/A	N/A
ZCtCZ	3.63	−128.5	178.5	−128.5	2.93	2.93	−116.3	177.6	−116.3	2.68
ZctCZ	3.84	123.4	180.0	−123.4	3.15	2.92	113.5	179.9	−111.6	0.03
ZCgCZ	4.08	−110.0	63.9	−110.0	2.82	0.99	−115.6	62.1	−115.6	0.85
ECGsZ	4.86	−109.0	−78.1	7.9	3.76	3.45	−106.8	−74.3	1.1	5.41
EstsZ	7.21	−0.1	180.0	−0.1	6.73	8.10	0.0	180.0	0.0	3.81
EsGaZ	8.93	−3.5	−62.9	158.1	8.93	8.52	−25.2	−63.4	150.3	5.61
ECGaZ	9.60	−101.2	−72.2	165.5	7.04	6.52	−103.0	−74.3	175.3	4.73
ECGCZ	9.77	−118.0	−94.9	−144.8	7.41	6.61	−125.1	−93.4	−131.5	4.01
EcgsE	11.08	107.3	77.8	−5.2	9.41	9.96	105.9	73.6	2.0	5.58
ZcgCZ	N/A	N/A	N/A	N/A	N/A	1.41	81.2	66.3	−110.1	2.66

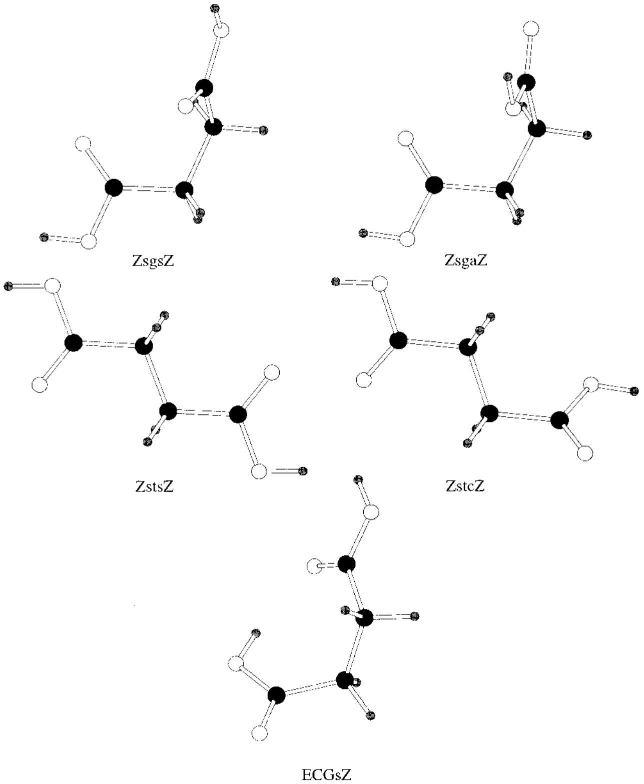

ZsgsZ ZsgaZ ZstsZ ZstcZ ECGsZ

Figure 1. Representative sample of conformers of succinic acid, optimized with HF/6-31G* calculations. The two lowest energy gauche conformers, the two lowest energy trans conformers, and the lowest energy conformer with an *E*-acid are shown.

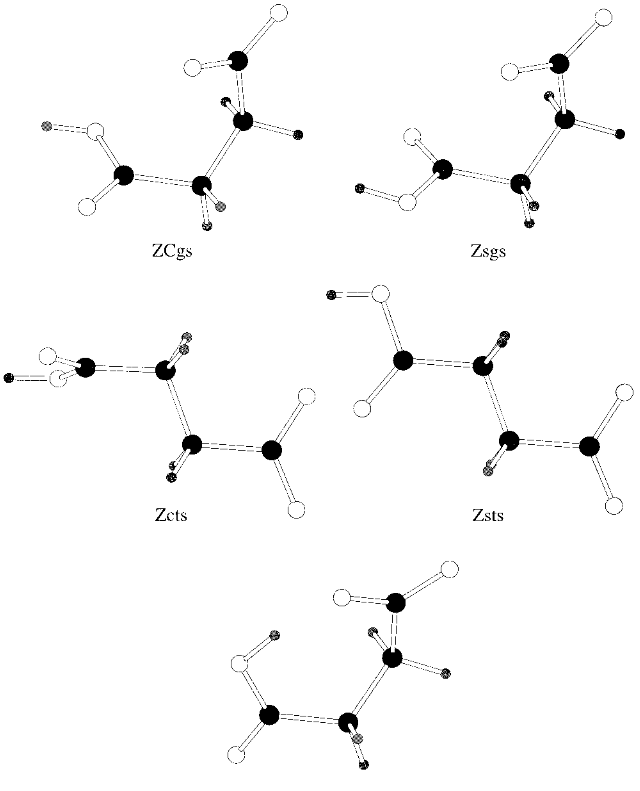

ZCgs Zsgs Zcts Zsts Ecgs

Figure 2. Representative sample of conformers of succinate monoanion, optimized with HF/6-31+G* calculations. The two lowest gauche conformers, the two lowest energy trans conformers, and the lowest energy conformer with an *E*-acid are shown.

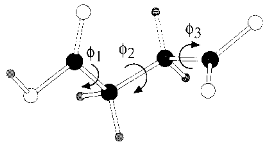
mol above the ZsgsZ structure from the MP2 calculations (Table 3). This energy difference is affected by the general *E/Z* preference at the applied level of theory. This quantity is known to be unusually sensitive to the choice of basis set and treatment of electron correlation.[23] For acetic acid, the *E/Z* energy difference decreases from 7.20 kcal/mol at the RHF/6-31G*//RHF/6-31G* level to 5.85 kcal/mol at MP3/6-311+G**//RHF/6-31G* and to 4.95 kcal/mol at the definitive G2 level.[24] The present results for the diacid are consistent with this. The RHF/6-31G*//RHF/6-31G* calculations give an energy difference of 6.62 kcal/mol between the ZstsZ and EstsZ conformers, which declines to 5.39 kcal/mol at the MP2/6-311+G**//RHF/6-31G* level. Thus, the present MP2 calculations may be overly

---

[23] Wiberg, K. B.; Laidig K. E. *J. Am. Chem. Soc.* **1987**, *109*, 5935.

[24] Rablen, P. R. Personal communication.

Table 2. Comparison of Ab Initio and OPLS-AA Gas-Phase Results for the Monoanion of Succinic Acid



	HF/6-31+G*//HF/6-31+G*				MP2/6-311+G**//HF/6-31+G*	OPLS-AA			
conformer	ΔE, kcal/mol	ϕ_1	ϕ_2	ϕ_3	ΔE, kcal/mol	ΔE, kcal/mol	ϕ_1	ϕ_2	ϕ_3
Ecgs	−12.70	128.0	80.2	−32.2	−15.44	−19.76	121.2	81.1	−25.1
ZCgs	0.93	−149.1	59.6	−10.8	0.20	0.22	−127.5	63.0	74.3
Zsgs	1.06	46.6	66.0	−13.7	0.28	0.30	56.8	67.4	10.5
Zcts	0.00	105.5	177.7	−9.3	0.00	0.00	108.7	179.9	−2.3
Zsts	0.84	−15.7	173.3	−22.0	1.17	1.10	−1.6	−179.9	0.0
Ests	4.00	0.0	180.0	0.0	3.54	3.60	0.0	180.0	0.0

Table 3. Free Energies of Hydration for Conformers of Succinic Acid from Semiempirical Calculations[a]

		AM1/SM2		PM3/SM3	
conformer	degeneracy	ΔG_{hyd}	occupancy	ΔG_{hyd}	occupancy
ZsgsZ	2	−12.24	0.85	−14.36	0.75
ZstsZ	1	−11.74	0.02	−14.45	0.04
ZsgaZ	4	−11.90	0.12	−14.30	0.16
ZstcZ	4	−11.89	0.00	−14.80	0.01
ZaGaZ	2	−11.90	0.01	−14.40	0.01
ZCtCZ	2	−11.93	0.00	−15.13	0.00
ZctCZ	2	−11.86	0.00	−14.94	0.01
ZCgCZ	2	−11.90	0.00	−14.42	0.01
ECGsZ	4	−10.86	0.00	−13.12	0.00
EstsZ	2	−12.56	0.00	−15.39	0.00
EsGaZ	4	−12.78	0.00	−14.43	0.00
ECGaZ	4	−10.62	0.00	−13.41	0.00
ECGCZ	4	−10.26	0.00	−13.22	0.00
EcgsE	4	−11.89	0.00	−14.40	0.00

[a] Free energies in kcal/mol.

disfavoring *E* structures by about 1 kcal/mol. This still places the lowest energy structure with an *E*-acid, ECGsZ, ca. 3 kcal/mol above the global minimum, ZsgsZ. Of course, an internally hydrogen-bonded structure is also expected to be less well solvated, particularly, in hydrogen-bonding solvents, than a more open structure. So, it can be concluded that conformers of succinic acid with an *E*-acid group should not be significantly populated near room temperature in the gas phase or in solution.

In contrast, the expected strong internal hydrogen bond between the *E*-acid group and the carboxylate fragment in the monoanion causes the Ecgs conformer (Figure 2) to be the global minimum with no competitors within 15 kcal/mol (Table 2). The next lowest energy conformers are a nearly isoenergetic cluster of one trans and two gauche conformers, Zcts, ZCgs, and Zsgs. In polar solvents, these more open structures should be significantly better solvated, so the conformational preferences for the monoanion in solution are unclear from the gas-phase computations. In fact, the NMR results, which revealed a ca. 2:1 gauche:trans ratio in water, imply much diminished representation by the Ecgs conformer. Another interesting point is the reduced *E*/*Z* difference, 2.37 kcal/mol, for the Ests and Zsts pair of the monoanion versus the 5.39 kcal/mol for the EstsZ and ZstsZ analogues of the diacid. This clearly reflects the shorter distance and increased electrostatic attraction between the acidic hydrogen and the carboxylate group upon flipping from Zsts to Ests in the monoanion.

Force-Field Calculations. The conformational energetics from the MP2 calculations were then used to parametrize the OPLS-AA force field. Almost all parameters are the same as for monofunctional carboxylic acids and carboxylates. It was possible to reproduce the MP2 results well by adding torsional parameters for the C−CT-CT-C angle and modifying the CT−CT−C−O and CT−C−OH−HO parameters, as summarized by the last five entries in Supporting Information Table 3. Optimizations with BOSS using the final OPLS-AA parameters produce the structural and energetic results that are summarized in Tables 1 and 2. The average energetic discrepancy between the MP2 and OPLS-AA results for the diacid is 0.5 kcal/mol, with almost no error for the conformers within 4 kcal/mol of the global minimum, ZsgsZ. The only exception is that the ZCgCZ conformer is found to be too stable by 1.8 kcal/mol. This structure has the two acid groups in a face-to-face antiparallel orientation. The problem likely stems from an electrostatic imbalance from scaling the 1,4-interactions.[10c] In addition, the ZaGaZ conformer is not an energy minimum; it optimizes to ZcGcZ, which is the same as ZCgCZ. If one uses the 6-31G* values for the three central dihedral angles and just optimizes the rest of the ZaGaZ structure with the force field, the resulting relative energy is 3.11 kcal/mol, which is not far from the MP2 result of 2.50 kcal/mol. What is most remarkable is the overall level of accord between the MP2 and OPLS-AA results in view of the limited modifications of the torsional parameters and the simplicity of the force-field model. As also seen is Table 1, the structural results are in good agreement as well; the average deviation between the 6-31G* and OPLS-AA values for the dihedral angles is only a few degrees. OPLS-AA structures are generally very similar to 6-31G* ones.[11,25]

The torsional energetics for the trans conformer are straightforward since the acid groups are well separated. The rotation about the C−CT bonds is relatively free, as expected for a nearly 6-fold barrier. When rotating from ZstsZ to ZstaZ, ZstsZ and ZstcZ (and the equivalent ZstCZ) are the only potential-energy minima. ZstsZ with $\varphi_3 = 0^\circ$ is lowest in energy. There is a small barrier with a relative energy of 0.91 kcal/mol at $\varphi_3 = 80^\circ$ leading to the shallow ZstcZ minimum at 0.77 kcal/mol with $\varphi_3 = 111^\circ$ and then to the ZstaZ maximum at 1.55 kcal/mol with $\varphi_3 = 180^\circ$. This agrees well with the ab initio results. However, the *E*/*Z* preference for ZstsZ vs EstsZ of 6.8 kcal/mol overshoots the MP2 result of 5.4 kcal/mol. This discrepancy arose from forcing the very close fit for the lowest energy *E* conformer, ECGsZ (Table 1).

The conformational energetics for the monoanion are also handled reasonably by the force field. The energies are reported in Table 2 relative to the second lowest energy conformer to clarify the quality of fit for the remaining conformers. The only problem is that the internal hydrogen bond is too strong with

---

(25) Beachy, M. D.; Chasman, D.; Murphy, R. B.; Halgren, T. A.; Friesner, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 5908.

the force field. Thus, the Ecgs conformer ends up 19.8 kcal/mol lower in energy than the next lowest alternative, Zcts (Figure 2), instead of the 15.4 kcal/mol from the MP2 calculations. Reasonable correction would require a modified set of partial charges for the monoanion. The effect of this discrepancy on the computed results in solution is considered below.

Extensive conformational searches using the force field and the BOSS program revealed only the eight energy minima listed in Table 1 for the *Z*,*Z*-diacid. For the *E*,*Z* and *E*,*E* cases, 10 and 3 minima were obtained; ECGsZ and EcgsE are the lowest energy conformers. For the monoanion, the conformational searches yielded only Ecgs and Ests as minima with the *E*-acid. For the monoanion with the acid group *Z*, five minima are found, all within 1 kcal/mol, with Zcts lowest in energy. A similar small range is found from the ab initio calculations for the *Z* conformers in Table 2; there is nearly free rotation about the HOOC−C bond for the gauche CCCC conformers of the *Z* monoanion.

Continuum Results for the Diacid. The computed free energies of hydration from the semiempirical continuum methods are listed in Table 3 for the diacid. Among the *Z*,*Z*-diacid conformers, there are only 0.3 and 0.8 kcal/mol variations in the predicted ΔG_{hyd} values with AM1/SM2 and PM3/SM3, respectively. The internally hydrogen-bonded ECGsZ conformer is predicted to be less well hydrated by about 1 kcal/mol, while EstsZ is better hydrated by a similar amount. The range of values seems small in view of the 5−6 D variation in dipole moments for the conformers (last column in Table 1) and the expected loss of two hydrogen bonds with solvent molecules in the ECGsZ conformer. With addition of the MP2 relative energies, the *E*-acid conformers remain uncompetitive and the only significantly populated conformers are ZsgsZ, ZstsZ, and ZsgaZ, as in the gas phase. The net result in Table 3 is prediction of a gauche population for the central CC bond of 92−98% in water that is dominated by the gas-phase energetics. The experimental result from the NMR measurements is 79−82% gauche.[6]

Results from the Monte Carlo Simulations. Turning to the MC results with the explicit solvent molecules, the free-energy profiles for the cis to trans perturbation of the central CC dihedral angle are shown along with the corresponding population distributions, *S*(Φ), in Figure 3. The free-energy changes are total values including the internal energetics of the solute and the differential solvation. The results for the *Z* → *E* perturbations are shown in Figure 4. The convergence behavior for the total free energy changes is illustrated in the Supporting Information. As expected, convergence for all mutations, but the cis → trans in particular, was slow, though it was achieved after about 10^7 configurations of averaging in each window. Logistically, the calculations have to be run 2−3 times longer than this before the convergence is evident. Nevertheless, even after 30×10^6 configurations, the distributions for the equivalent O−C−CT−CT dihedrals in the diacid were not identical.

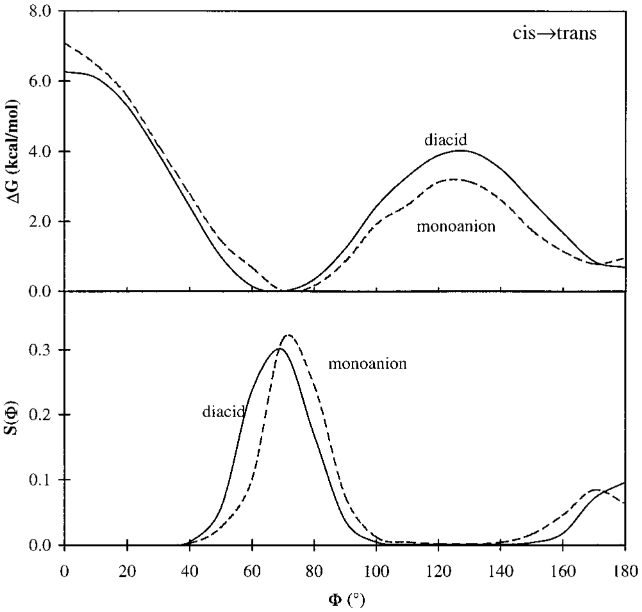


Figure 3. Computed free-energy profiles and populations for the cis to trans perturbations of succinic acid and its monoanion in aqueous solution. The abscissa is the CCCC dihedral angle.

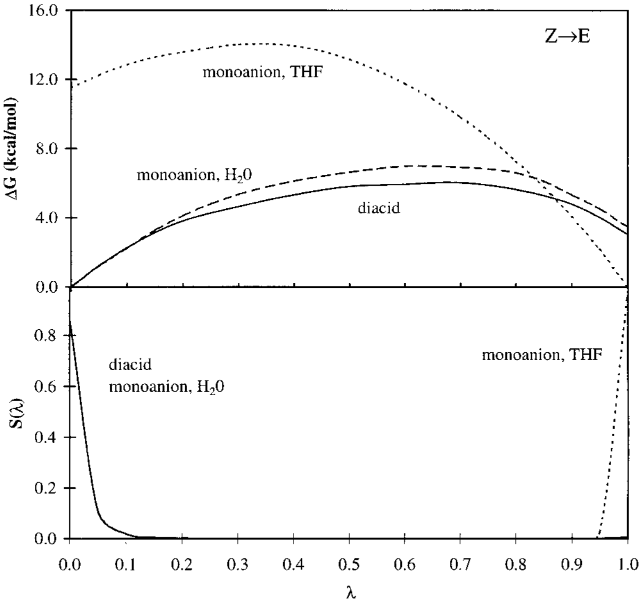


Figure 4. Computed free-energy profiles and populations for the *Z* → *E* perturbations of succinic acid and its monoanion in aqueous solution and for the monoanion in THF. The abscissa is the coupling parameter that changes from 0 for *Z* to 1 for *E*.

Hydrogen bonding of water molecules to the carboxyl groups hinders rapid sampling of the torsional space. Inspection of a random configuration from the simulation of the diacid (Figure 5), solute−solvent radial distribution functions, and hydrogen-bond analyses clearly reflect the high degree of solvent coordination. In particular, the hydrogen-bond analyses for the 70° (most gauche-like) and 170° (most trans-like) windows for the diacid revealed an average of 4.3 and 4.4 hydrogen-bonded water molecules, respectively. Each acid hydrogen acts as a hydrogen-bond donor to a water molecule, and each carbonyl oxygen is an acceptor for one hydrogen bond. In some of the configurations, one water molecule forms a hydrogen bond with both carbonyl oxygens, while hydrogen bonds to the hydroxyl oxygens of the acids are less common.

Diacid Conformations in Water. For the diacid in water, a $\Delta G(Z \rightarrow E)$ of 2.6 ± 0.1 kcal/mol was computed (Figure 4), demonstrating a rarity of *E* conformers in solution. Analysis of the $\lambda = 0.95$ (the most *E*-like) window, revealed 100% gauche structures with a preference for EsgsZ and EsgCZ conformers, neither of which contain an internal hydrogen bond. Thus, the gauche/trans ratio can be determined from the results in Figure 3 for the *Z*,*Z*-diacid. Integration of the population curve yields a gauche population of 81.1%, which is in exact accord with the experimental 79−82%.[6] From the convergence behavior, the uncertainty in the computed result is ca. ±2%.

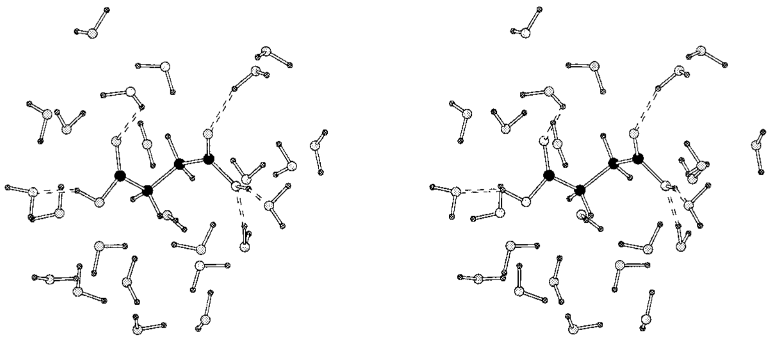


Figure 5. Stereoplot of a random configuration of succinic acid in water. Solute−water hydrogen bonds are shown by dotted lines. Only water molecules from the first solvent shell are shown. The total number of water molecules in the simulations was 500.

Special attention was taken to calculate the relative occupancy of each conformer in water, especially considering the low ZCgCZ gas-phase energy with the force field. A history of each dihedral angle was recorded throughout the simulations. Analysis of these histories reveals that the ZCgCZ conformer had a population of 4% in the 70° (gauche) window of the simulation. In fact, ZsgaZ was the most populated at 54%, ZsgsZ was next with 38%, ZCgCZ was 4%, and there was a remainder of 4% in various gauche alternatives. In view of the gas-phase energetics (Table 1), the ZsgaZ conformer is particularly stabilized in water. This is consistent with its 2.9-D dipole moment versus 0.4 D for the ZsgsZ conformer. Statistical factors are also important as seen in a similar analysis for the 170° window. The ZstcZ conformer has a statistical factor of 4 advantage over ZstsZ; the *RT* ln 4 effect on the free energy cancels the intrinsic energy difference between the two conformers (Table 1). The populations in water suggest that the greater polarity of ZstcZ also contributes a little to make it the most populated: 40% ZstsZ (0 D), 49% ZstcZ (2.5 D), 6% ZctCZ (0.3 D), and 5% other. The differential solvation from the MC simulations is greater than from the present continuum treatments. In particular, this causes the ZsgsZ conformer to be much less dominant and for there to be a substantially greater trans population than predicted by the continuum results (Table 3). Though it is reasonable that continuum calculations should have difficulties with solutes that participate in multiple hydrogen bonds,[26] there are newer continuum methods that may yield improved results.[27]

Monoanion Conformations in Solution. For the monoanion, a $\Delta G(Z \rightarrow E)$ of 3.5 ± 0.1 kcal/mol was obtained in water (Figure 4), again indicative of a dominance of the *Z*-acid conformation and particularly striking in view of the extreme gas-phase preference for the Ecgs conformer. The true difference is expected to be even more positive since the stability of the Ecgs conformer is overestimated by the force field (Table 2). Analysis of the $\lambda = 0.95$ (most *E*-like) window revealed 75% of the structures to have a trans C−CT−CT−C dihedral angle. For both the diacid and monoanion, adoption of conformations that do not feature an internal hydrogen bond clearly allows better solvation of the functional groups. Indeed, internal hydrogen bonding is found to play no role in determining the conformational preferences for these systems in aqueous solution. Of course, for the monoanion in less competitive media, the situation is expected to be very different. Thus, it was anticipated that the $Z \rightarrow E$ perturbation for the monoanion in THF would reveal the dominance of structures with an internal hydrogen bond. In fact, the Ecgs conformation was found to be nearly exclusively present in THF with a computed $\Delta G(Z \rightarrow E)$ of −11.5 ± 0.1 kcal/mol (Figure 4). NMR results support the 100% gauche assignment in THF.[28] It is interesting to note that recent computations of pK_as for succinic acid did not consider the possible population of the Ecgs conformer of the monoanion; fortunately, the calculations were for aqueous solutions.[29]

The FEP results for the cis → trans perturbation of the *Z*-monoanion (Figure 3) yield a gauche population of 78.5%. This is also in good accord with the experimental range from 61% to 78%, which reflects differences in counterion and choice of reference coupling constants.[6] It may be noted that the average dihedral angle obtained here (Figure 3) for the gauche conformer of the monoanion is 74−75°, which is somewhat larger than the assumed values of 60° or 71° in the NMR work.[6] Dihedral histories for the 70° and 170° windows were obtained again. For the 70° window, the following distribution was found: 49% Zsgs, 46% ZCgs, and 5% other. The distribution of conformers for the 170° window was 46% Zsts, 41% Zcts, and 13% other. These conformer populations are largely reflecting the similar energies of all the *Z*-monoanion conformers, which was noted above. The relatively free rotation about the HOOC−C bond for both gauche and trans leads to the intrinsic 2:1 gauche:trans bias.

Finally, the hydration of the Zsgs conformer of the monoanion is illustrated by the stereoplot of one configuration in Figure 6. The acid group typically participates in two to three hydrogen bonds, and there are an average of six to seven water molecules acting as hydrogen-bond donors to the carboxylate group, which is normal.[30] When a MC simulation is run for the monoanion locked in the Ecgs conformer, the principal change is the loss of the hydrogen bond between a water molecule and the acidic hydrogen, and the carboxylate group loses 0.5 hydrogen bond.

Conclusions

As in other ab initio studies of 1,4-dicarbonyl compounds, succinic acid is found to prefer a gauche conformation about the C2−C3 bond. The lowest energy trans and *E*-acid conform-

---

[26] Severance, D. L.; Jorgensen, W. L. In *Structure and Reactivity in Aqueous Solution*; Cramer, C. J., Truhlar, D. G., Eds.; ACS Symposium Series 568; American Chemical Society: Washington, DC, 1994; pp 243−259. Jorgensen, W. L.; Morales de Tirado, P. I.; Severance, D. L. *J. Am. Chem. Soc.* **1994**, *116*, 2199.

[27] Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027. Marten, B.; Kim, K.; Cortis, C.; Friesner, R. A.; Murphy, R. B.; Ringnalda, M. N.; Sitkoff, D.; Honig, B. *J. Phys. Chem.* **1996**, *100*, 11775. Hawkins, G. D.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **1998**, *102*, 3257.

[28] Roberts, J. D. To be published.

[29] Rajasekaran, E.; Jayaram, B.; Honig, B. *J. Am. Chem. Soc.* **1994**, *116*, 8238. Potter, M. J.; Gilson, M. K.; McCammon, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 10298. Figueirido, F.; Del Buono, G. S.; Levy, R. M. *J. Phys. Chem.* **1996**, *100*, 6389.

[30] Jorgensen, W. L.; Gao, J. *J. Phys. Chem.* **1986**, *90*, 2174. Carlson, H. A.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1996**, *118*, 8475.

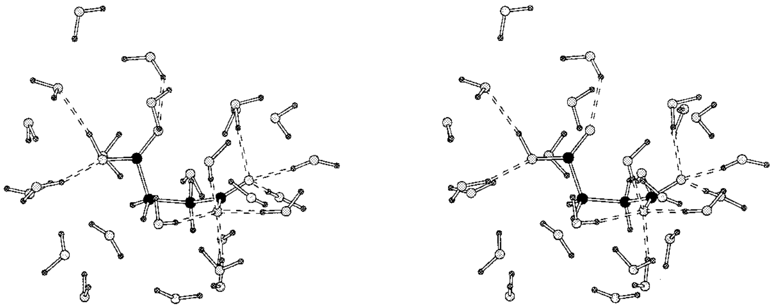


Figure 6. Stereoplot of a random configuration of succinate monoanion in water. See the caption of Figure 5 for additional details.

ers are 1.3 and 3.8 kcal/mol higher in energy from MP2/6-311+G** calculations. In contrast, the internally hydrogen-bonded Ecgs conformer of succinate monoanion is 15.4 kcal/mol more stable than any alternatives. Subsequent Monte Carlo simulations and continuum calculations predicted a strong gauche preference in aqueous solution as well. However, the Monte Carlo simulations provided the striking result that the Ecgs conformer of the monoanion is not populated in water owing to better solute−water hydrogen bonding for the open conformers. Thus, neither the diacid or monoanion is found to populate significantly structures with *E*-acid groups in water. In non-hydrogen-bonding media, the preference for the Ecgs structure reemerges, as demonstrated here for the monoanion in THF. This is an extreme example of solvent effects on a conformational equilibrium. The power of the present combination of ab initio calculations, force-field development, and liquid-state statistical mechanics simulations is apparent in the excellent accord between the computed and experimental conformer populations and in the great details on the conformational preferences and solvation that arise from the computations. In view of the potential internal and external hydrogen bonding, the origin of conformer populations can be notably complex in flexible, polyfunctional, polar molecules; it is far beyond simple, but useful, notions such as the “gauche effect”. Finally, the success of the transfer of most force-field parameters from monofunctional molecules to the difunctional ones is encouraging for extension to other polyfunctional systems.

Acknowledgment. Gratitude is expressed to Julian Tirado-Rives for helpful discussions and to the National Science Foundation for financial support.

Supporting Information Available: Tables of complete OPLS-AA parameters for carboxylic acids and carboxylate anions, a figure illustrating the convergence of the computed free-energy changes, and tables of optimized *Z*-matrices from the ab initio calculations for the lowest energy conformers of succinic acid and its monoanion (5 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA9812397