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Quantification of Solvent Effects on the Acidities of *Z* and *E* Esters from Fluid Simulations

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Abstract: Solvents effects on the acidities of *Z* and *E* esters have been investigated using Monte Carlo simulations with statistical perturbation theory. The differences in free energies of hydration for (*Z*)- and (*E*)-methyl acetate and for the corresponding *Z* and *E* anions in both acetonitrile and water have been computed. Ab initio molecular orbital calculations with the 6-31+G(d) basis set were used to develop the necessary anion−water potential functions for the liquid simulations. The Monte Carlo simulations predict a preferential stabilization of the less stable *E* ester by 3.0 ± 0.2 kcal/mol in water and by 2.7 ± 0.1 kcal/mol in acetonitrile. The free energies of solvation of the *E* anion are also predicted to be more favorable than for the *Z* form by 2.3 ± 0.2 kcal/mol in water and 1.5 ± 0.2 kcal/mol in acetonitrile. The gas-phase rotational barriers between the *Z* and *E* isomers are computed to be 14.1 and 5.0 kcal/mol for the ester and anion. These results are compared to experimental observations on the unusual acidity of Meldrum's acid, and with the solvent effects on intramolecular Diels−Alder reactions involving ester tethers.

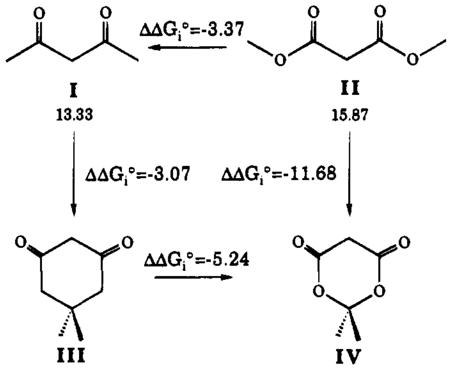
Introduction

The *Z* conformers of esters are usually more stable than the *E* isomers.[1] There have been several reports of either structural or environmental factors which alter this preference.[2−5] Our interest in this subject originated from the attribution of the anomalously high acidity of Meldrum's acid to conformational effects,[2] and was further aroused by reports of solvent effects on the rates of intramolecular Diels−Alder reactions involving ester tethers.[4]

These phenomena have been explained qualitatively by gas-phase calculations on (*Z*)- and (*E*)-methyl acetate and related species.[2b,c] The *E* conformer is considerably more polar than the *Z* conformer. Solvation should reduce differences due to polarity, because the more polar species is likely to be better solvated than the less polar species. In order to prove this quantitatively, statistical perturbation theory was applied in Monte Carlo simulations to compute the differences in free energies of solvation for (*Z*)- and (*E*)-methyl acetate, and for the corresponding anions in water and acetonitrile.

Background

Arnett and Harrelson reported the pK_a values for several 1,3-dicarbonyl compounds. These include acetylacetone (**I**) and dimethyl malonate (**II**), along with their corresponding cyclic analogues dimedone (**III**) and Meldrum's acid (**IV**).[2] The differences in free energies of ionization ($\Delta\Delta G_i^\circ$) and pK_a values of interest are given below.



The cyclization of a β-diester to a bislactone (**III** → **IV**) has a dramatic effect on acidity; the standard free energy of ionization, ΔG_i°, is reduced by 11.68 kcal/mol in going from dimethyl malonate (pK_a = 15.87) to Meldrum's acid (pK_a = 7.32). In contrast, the difference between the acidities of a cyclic β-diketone (**I** → **III**) and an acyclic diketone is much smaller. As illustrated, the difference in the free energy of ionization of acetylacetone (pK_a = 13.33) and dimedone (pK_a = 11.24) is only 3.07 kcal/mol. Therefore, Meldrum's acid is more than 8 kcal/mol more acidic than expected from the diketone system. Arnett and Harrelson attributed most of the remarkable $\Delta\Delta G_i^\circ$ to a 3−4 kcal/mol lowering of ionization energy for each *E* ester linkage in Meldrum's acid. A cyclization effect of 3 kcal/mol was also assigned on the basis of the behavior of the β-diketones.

Later, Houk and Wiberg independently used ab initio molecular orbital theory to elucidate the origin of the especially high acidity of Meldrum's acid.[2b,c] The quantum mechanical calculations predicted an enhancement of the *E* ester acidity by

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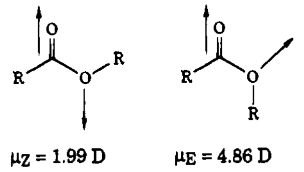
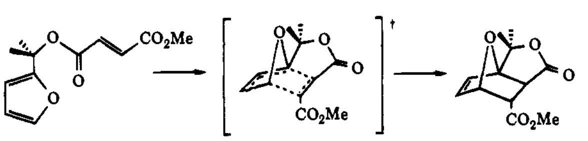
ca. 5 kcal/mol relative to the *Z* ester in the gas phase. The conversion of two *Z* esters in **II** to two *E* esters in bislactone **IV** then accounts for 10 kcal/mol of the 12 kcal/mol measured acidity difference between Meldrum's acid and dimethyl malonate. The destabilization of the *E* relative to the *Z* conformation for the ester was attributed to electrostatic (dipole–dipole) repulsion effects, which are greatly reduced in the corresponding anions.



Electrostatic considerations have been applied by Jung and Garvay to the remarkable solvent effects observed for the intramolecular Diels–Alder reaction of 2-furfuryl methyl fumarates.[4] Rate enhancements as large as 3200 were found in polar solvents. Since the ester must achieve the *E* conformation to complete the intramolecular cyclization, enhanced solvent polarity facilitates attainment of this more polar conformation in the transition state.



Computational Procedure

Quantum Mechanics. The GAUSSIAN 88 program[6] was employed in the development and testing of the ester–water and anion–water potential functions for the fluid simulations. The split-valence 6-31G(d) basis set[7] was used for methyl acetate, and the 6-31+G(d) basis[8] was used for the anion. The diffuse functions are known to be important for properly describing the electronic structures of anions[9] and hydrogen bonding with anions[10–12] and for obtaining accurate gas-phase acidities, ΔG_{gas}.[12–14]

Statistical Mechanics. The BOSS program, version 2.4, was used for the liquid simulations.[15] The procedure employed for the statistical mechanics simulations follows from earlier work where evaluation and testing of Monte Carlo and OPLS functions delineates systematic and statistical errors.[16–19] The differences in free energies of solvation for (*Z*)- and (*E*)-methyl acetate and its enolate ion were obtained from separate Monte Carlo simulations in water and acetonitrile. Previous testing of the OPLS parameters involved pure liquid simulations for methyl acetate[16] and acetonitrile.[20] The computed heats of vaporization and densities are in close agreement with experimental values.[16,20] The present dilute solution simulations were carried out for methyl acetate plus either 215 TIP4P water molecules[21] or 128 acetonitrile molecules.[20] The simulation for the anion involved 215 TIP4P waters or 126 acetonitrile molecules. All fluid simulations were carried out in a cubic box with periodic boundary conditions using Metropolis and preferential sampling in the isothermal–isobaric (NPT) ensemble at 25 °C and 1 atm.[22]

A general theoretical approach for the computation of relative pK_a values for organic compounds in solution has been reported.[17] This is based on the thermodynamic cycle below,

$$\begin{tikzcd}
AH \arrow[r, "\Delta G_{gas}"] \arrow[d, "\Delta G_{sol}(AH)"] & A^- \arrow[d, "\Delta G_{sol}(A^+)"] & + & H^+ \arrow[d, "\Delta G_{sol}(H^+)"] \\
AH \arrow[r, "\Delta G_{sol}"'] & A^- & + & H^+
\end{tikzcd}$$

which illustrates that the free energy of ionization, ΔG_{sol}, is composed of the gas-phase acidity, ΔG_{gas}, and the difference in free energies of solvation for the acid, $\Delta G_{sol}(AH)$, and the ions, $\Delta G_{sol}(A^-)$ + $\Delta G_{sol}(H^+)$ (eq 1).

$$\Delta G_{sol} = \Delta G_{gas} + \Delta G_{sol}(A^-) + \Delta G_{sol}(H^+) - \Delta G_{sol}(AH) \quad (1)$$

Quantum mechanical calculations can reliably compute the gas-phase acidities,[2] and Monte Carlo statistical mechanics can be used to compute the necessary free energies of hydration. However, improved precision and accuracy can be obtained by calculating the differences in free energies of ionization between two acids, AH and BH, according to eq 2.[17] The first term is computed with quantum mechanics, and the last two terms require two separate simulations which mutate A^- into B^- and AH into BH in the solvent of interest.

$$\Delta\Delta G_{sol} = \Delta\Delta G_{gas}(BH-AH) + \Delta\Delta G_{sol}(B^- - A^-) - \Delta\Delta G_{sol}(BH-AH) \quad (2)$$

For the present problem, AH and BH correspond to (*E*)- and (*Z*)-methyl acetate. The calculations can provide a breakdown of the intrinsic and solvation effects associated with the pK_a change. The free energy changes, $\Delta\Delta G_{sol}$, were obtained by applying statistical perturbation theory[23] to mutate the *Z* conformation of the ester or anion to the *E* form by perturbing the O═COC dihedral angle in 10° increments.[18,19] Double wide sampling was performed so that each step in the simulation spanned 20°. Thus, nine separate simulations were carried out in all cases. Each simulation had an equilibration phase of *ca.* 1.0×10^6 (neutral) or 1.5×10^6 (anion) configurations followed by averaging over an additional 1.0×10^6 or 1.5×10^6 configurations in each case. Spherical cutoffs based roughly on the centers-of-mass separation were used to truncate the intermolecular interactions at 9.0 Å. The ranges for attempted translations and molecular rotations were ±0.20 Å and ±20.0°. The attempted volume changes had a range of ±180 Å^3 and occurred every 700 configurations.

Intermolecular Potential Functions. The intermolecular potential functions used the standard Coulomb plus Lennard-Jones function:

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Table 1. Potential Function Parameters for Methyl Acetate and TIP4P Water

site	q (e$^-$)	σ (Å)	ϵ (kcal/mol)
carbonyl oxygen	−0.45	2.96	0.210
ester oxygen	−0.40	3.00	0.170
carbonyl carbon	0.55	3.75	0.105
α-methyl (united)	0.05	3.91	0.160
methyl (united)	0.25	3.80	0.170
TIP4P oxygen	0.00	3.15365	0.1550
TIP4P hydrogen	0.52	0.0	0.0
TIP4P dummy	−1.04	0.0	0.0

Table 2. Potential Function Parameters for Methyl Acetate Anion

site	q (e$^-$)	σ (Å)	ϵ (kcal/mol)
carbonyl oxygen	−0.695	2.96	0.210
ester oxygen	−0.455	3.10	0.170
carbonyl carbon	0.740	3.80	0.115
anionic carbon (explicit)	−1.075	3.91	0.300
hydrogen (explicit *syn* CO)	0.175	2.50	0.050
hydrogen (explicit *anti* CO)	0.255	2.50	0.050

$$\Delta E_{\mathrm{ab}} = \sum_{i}^{a} \sum_{j}^{b} (q_i q_j e^2/r_{ij} + A_{ij}/r_{ij}^{12} - C_{ij}/r_{ij}^{6}) \qquad (3)$$

The molecular systems are represented as a collection of interaction sites that have associated charges, q_i, and Lennard-Jones parameters, σ_i and ϵ_i. The combining rules yield the following relationships for A_{ij} and C_{ij}: $A_{ii} = 4\epsilon_i\sigma_i^{12}$, $C_{ii} = 4\epsilon_i\sigma_i^6$, $A_{ij} = (A_{ii}A_{jj})^{1/2}$, and $C_{ij} = (C_{ii}C_{jj})^{1/2}$.

The OPLS parameters (Table 1)[16] and experimental geometry were used for methyl acetate with a united atom representation for both methyl groups.[24] The ester methyl group fo the enolate ion was also treated as a united atom. The geometry of the methyl acetate anion was taken from ab initio 6-31+G(d) calculations. Consistent with earlier work on anions,[17] it was necessary to define explicitly the hydrogens at the anionic carbon to provide charge distributions capable of reproducing the ab initio results. The Lennard-Jones parameters from the OPLS library[15] were used throughout this study (Tables 1 and 2), except that σ and ϵ for the anionic site were modified slightly. The principal effort in parameterization was to define the partial charges for the anion and to verify the appropriateness of the partial charges for both the *E* and *Z* isomers. No lone-pair-type interaction sites were required to fit the ab initio data.

Up to five monohydrated structures were calculated for each conformation. For methyl acetate, the experimental geometries for the ester[24] and water[21] were held rigid while a few of the key intermolecular geometrical parameters were optimized using the 6-31G(d) basis set. In most cases, linear hydrogen bonds (O–H–O) were enforced, and the distance and angle between the substrate and water were optimized. The release of additional degrees of freedom had little energetic consequence. Recent advances in spectroscopic techniques have revealed small deviations from hydrogen bond linearity which are dependent on the molecular system.[25] For example, the OC–HF complex is linear, whereas OC–HOH is 12° from linearity.[26] This structural accuracy is difficult to attain with the molecular mechanical functions used in this study. We have focused on the energetics and heavy nuclei separation. The optimized 6-31+G(d) geometry of the anion was also held constant in the development of the anion–water interaction potentials. It has been reported that monohydration has insignificant effects on the geometries of such anions.[27] The interaction energies, charges at each of the atomic sites, and geometries of the bimolecular complexes then provide a basis in the development of the intermolecular potential functions.

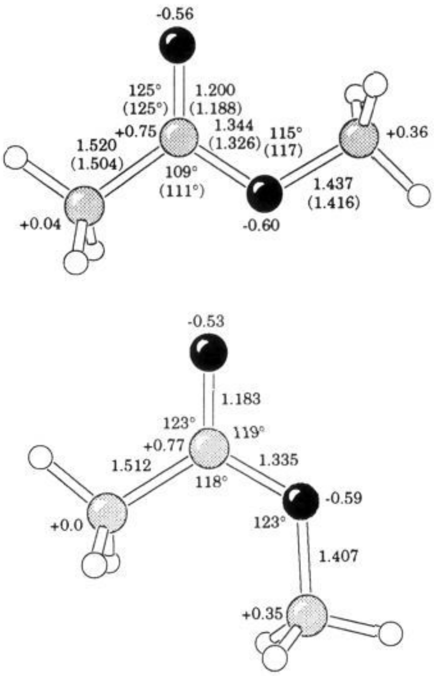

Figure 1. Experimental and 6-31G(d), in parentheses, geometries of (*Z*)-methyl acetate and optimized 6-31G(d) geometry of (*E*)-methyl acetate. The charges from a Mulliken population analysis are shown next to each atom.

Table 3. Charge Distributions from Mulliken Population Analyses for (*Z*)- and (*E*)-Methyl Acetate with the 6-31G(d) Basis Set[a]

	6-31G(d)[b]		6-31G(d)[c]		
methyl acetate	*Z*	*E*	*Z*	*E*	OPLS
carbonyl oxygen	−0.57	−0.54	−0.56	−0.53	−0.45
carbonyl carbon	0.76	0.80	0.75	0.77	0.55
ester oxygen	−0.63	−0.62	−0.60	−0.59	−0.40
ester methyl	0.39	0.38	0.36	0.35	0.25
α-methyl	0.05	−0.02	0.04	0.00	0.05

[a] Charges reported in electrons. [b] Obtained when using the experimental geometry. The *E* rotamer was generated by rigid rotation about the C–O bond. [c] Obtained with the fully optimized structure.

Results and Discussion

Gas-Phase Energetics. The geometries for (*Z*)- and (*E*)-methyl acetate were optimized in C_s symmetry; the 6-31G(d) results are shown in Figure 1. Both ester conformations are true ground-state minima, which is verified from frequency calculations. The predicted and microwave structures for (*Z*)-methyl acetate are in good accord. The 6-31G(d) bond distances are 1% shorter than reported by experiment.[24] The charges from a Mulliken population analysis are essentially the same in the *Z* and *E* conformers. A comparison of the computed charges is given in Table 3. The calculated transition states for the isomerization between (*E*)- and (*Z*)-methyl acetate and the enolate are shown in Figure 2. The energy barrier is computed as 14.1 kcal/mol for the *Z* ester and 5.0 kcal/mol for the *Z* enolate at the MP2/6-31G(d)//6-31G(d) and MP2/6-31+G(d)//6-31+G(d) levels, respectively (Table 4). The *Z* to *E* energy differences at this level of computation are 8.8 and 2.8 kcal/mol for the ester and enolate. It is of interest to note the effect of diffuse functions between the 6-31G(d) and 6-31+G(d) basis sets on the energy difference for the enolate. The MP2/6-31G(d) value of 3.9 drops to 2.8 kcal/mol when diffuse functions are included in the calculation. Wiberg and Laidig report the energy differences as 8.7 and 4.0 kcal/mol at the MP3/6-31G**//6-31G* level of theory.[2c] Thus, the *E* ester is predicted

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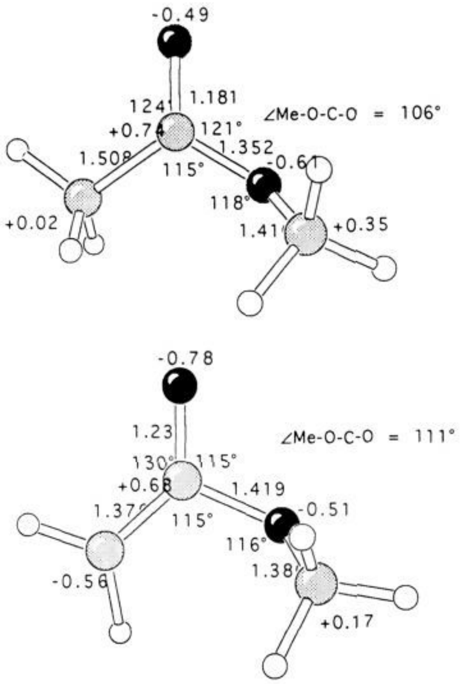

Figure 2. 6-31G(d) transition structures for isomerizations of methyl acetate and the enolate anion (6-31+G(d)). The charges from a Mulliken population analysis are shown next to each atom.

Table 4. Energies[a] (hartrees) of the Computed Stationary Points for Methyl Acetate, Enolate Anion, the Isomerization Transition Structure (TS), and Meldrum's Acid

system	3-21G	6-31G(d)	MP2/6-31G(d)
(*Z*)-methyl acetate	−265.347 43	−266.836 83	−267.569 63
(*E*)-methyl acetate	−265.332 05	−266.821 85	−267.555 56
isomerization TS	−265.327 97	−266.815 56	−267.547 11
(*Z*)-methyl acetate anion[b]	−264.711 72	−266.222 30	−266.980 79
(*E*)-methyl acetate anion[b]	−264.702 59	−266.216 31	−266.976 30
isomerization anion TS[b]	−264.699 38	−266.212 12	−266.972 77
Meldrum's acid model	−450.725 83	−453.268 18	

[a] Energies evaluated at the same level of theory as geometry optimizations. [b] Diffuse function added in basis set, 6-31+G(d).

to be 6.0 kcal/mol (MP2) or 4.7 kcal/mol (MP3) easier to deprotonate than the *Z* ester.

Ester−Water Complexes. Hydrogen-bonded forms of three different complexes of water with (*Z*)-methyl acetate and five different complexes with (*E*)-methyl acetate were examined and are illustrated in Figures 3 and 4. The optimized intermolecular geometrical parameters and interaction energies (kcal/mol) from the OPLS potential functions are given in parentheses along with the 6-31G(d) predictions. The low-energy geometries were selected for examination, since these are heavily sampled in the simulations.

The Cambridge Crystallographic Data File was previously searched by Murray-Rust and Glusker for intermolecular distances less than 3.0 Å in an attempt to analyze the directionality of hydrogen bonding to oxygen atoms.[28] In the systems searched, the largest concentration of hydrogen-bonded complexes for Z esters are in-plane and in the direction of the carbonyl oxygen lone pair on the side of the α-methyl group. The *E* ester shows a double maximum with high concentrations located in the direction generally ascribed to the lone pairs on both the carbonyl and the ester oxygens.

Table 5. Calculated and Experimental Dipole Moments for (*Z*)- and (*E*)-Methyl Acetate[a]

system	OPLS	6-31G(d)[b]	6-31G(d)[c]	exptl
(*Z*)-methyl acetate	1.44	2.34	1.99	1.72[d]
(*E*)-methyl acetate	4.18	5.02	4.86	4.18,[e] 4.12[f]

[a] Dipole moments in debyes. [b] Dipole moments computed for the experimental geometry given in ref 23. [c] Dipole moments computed for the fully optimized geomtries with the 6-31G(d) basis set. [d] Reference 28. [e] For β-propiolactone, ref 29. [f] Reference 30.

The computed results for the neutral complexes show geometries and interaction energies in reasonable accord with the crystallographic data and previous calculations on similar systems. The hydrogen bond lengths generated by the OPLS potentials are typically shorter by *ca.* 0.1−0.2 Å than those predicted by 6-31G(d) calculations.[17] The OPLS interaction energies are consistently more positive than those of the 6-31G(d) optimizations by *ca.* 0.2−0.6 kcal/mol for methyl acetate. No differential bias between the OPLS potentials and quantum mechanics is displayed for the *E* or *Z* isomer. Therefore, the use of the same OPLS parameters for both isomers is justified.

The interactions with the *Z* isomer, on the average, are not as attractive as computed for (*E*)-methyl acetate. The strongest interaction for the *Z* form is shown in Figure 3A. Hydration at the ester oxygen (Figure 3C) is computed to be less favorable.

Although linear hydrogen bonds normally provide the maximum energy stabilization,[29] the *E* conformation of an ester provides the possibility of a bent double hydrogen bond interaction between one water and both ester oxygens. Therefore, the O⋯H−O angle was released, as well. However, little energetic difference was found between the linear and uncontrained singly hydrogen-bonded systems in Figure 4A,D, or when both protons of a water hydrogen bond to the two oxygens of the ester (Figure 4B).

The charges chosen for the OPLS force field were used to compute the dipole moments for both the *Z* and *E* rotamers (Table 5). While the predicted OPLS dipole moment is slightly lower than the experimental result for the *Z* rotamer (1.44 D vs 1.72 D[30]), the predicted dipole moment of the *E* conformer (4.18 D) is in good accord with the observed value of 4.18 D for β-propiolactone,[31] and 4.12 D for γ-butyrolactone.[32] Another notable point from Table 3 is that the largest difference in the 6-31G(d) charges between the *Z* and *E* isomers is only 0.07 from the Mulliken analysis. Overall, the previously reported OPLS parameters for *Z* esters appear to perform well for both the *E* and *Z* forms.[16]

Ester Anion−Water Complexes. The geometries for the anions of (*Z*)- and (*E*)-methyl acetate were optimized in C_s symmetry; the 6-31+G(d) results are shown in Figure 5. Frequency calculations reveal that both anions are true minima. The computed charge distributions are given in Table 6. Four low-energy water complexes of (*Z*)- and two of (*E*)-methyl acetate anion were optimized. These are shown in Figures 6 and 7. The optimized intermolecular geometries and interaction energies (kcal/mol) from the derived OPLS potential functions are given in parentheses along with the 6-31+G(d) ab initio predictions.

The geometric and energetic results for the anions complexed with water are consistent with those for the neutral methyl acetate as well as other systems previously investigated. The intermolecular bond lengths produced from the OPLS parameters are usually up to 0.2 Å smaller than predicted by 6-31+G(d) calculations, while the interaction energies are in good

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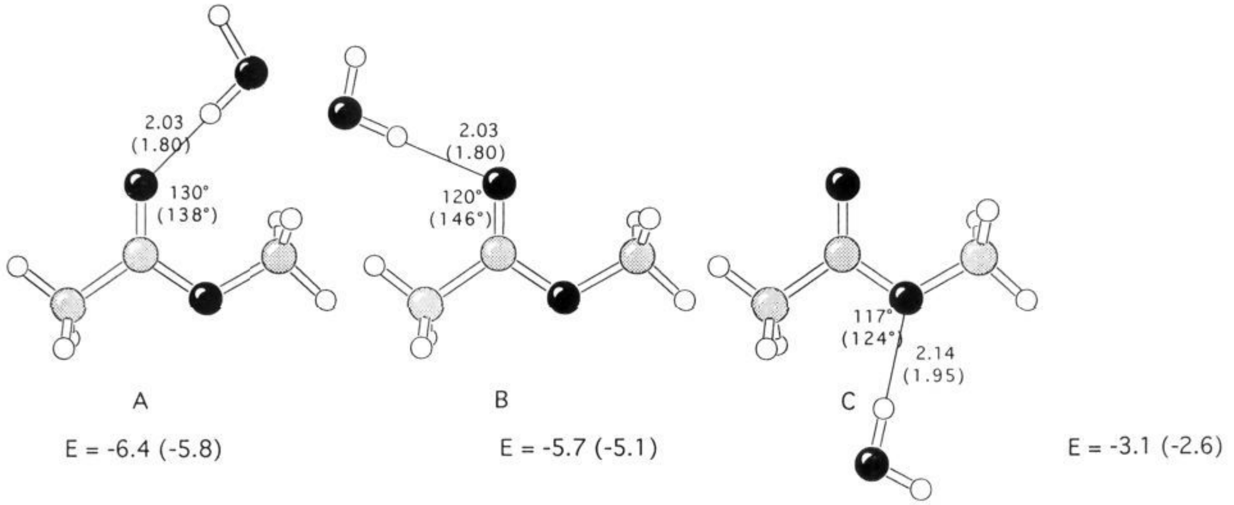

Figure 3. Optimized geometries of methyl acetate–water complexes from 6-31G(d) and OPLS (in parentheses) calculations. Methyl acetate and water geometries are from experiment. Energies are reported in kilocalories per mole and distances in angstroms.

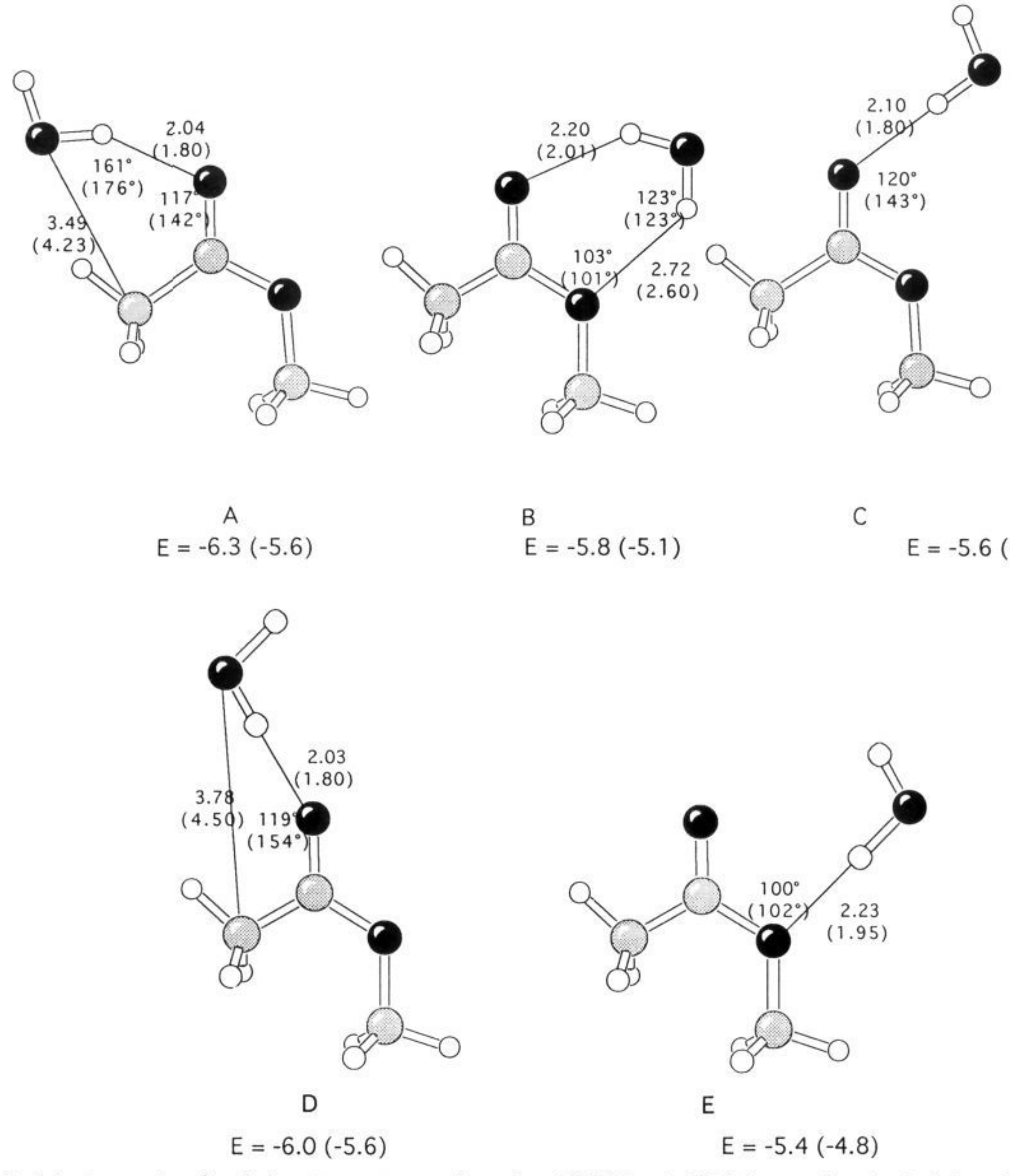

Figure 4. Optimized geomtries of methyl acetate–water complexes from 6-31G(d) and OPLS (in parentheses) calculations. Methyl acetate and water geometries are from experiment. Energies are reported in kilocalories per mole and distances in angstroms.

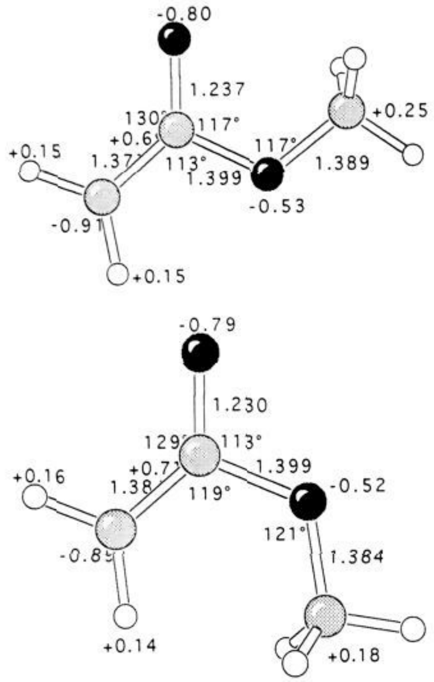

Figure 5. Optimized 6-31+G(d) geometries of (*Z*)- and (*E*)-methyl acetate anions. The partial charges from Mulliken population analyses are also given.

Table 6. Charge Distributions from Mulliken Population Analyses for (*Z*)- and (*E*)-methyl Acetate Anion with the 6-31+G(d) Basis Set[a]

	6-31+G(d)[b]		
methyl acetate anion	*Z*	*E*	OPLS
carbonyl oxygen	−0.80	−0.79	−0.695
carbonyl carbon	0.69	0.71	0.740
ester oxygen	−0.53	−0.52	−0.455
ester methyl[c]	0.25	0.18	0.250
anionic carbon	−0.91	−0.89	−1.075
hydrogen (*syn* CO)	0.15	0.16	0.175
hydrogen (*anti* CO)	0.15	0.14	0.255

[a] Charges reported in electrons. [b] Obtained with the fully optimized structure. [c] Atomic charge with hydrogens summed into the heavy atom.

accord. Typically the interaction energies are underestimated by 0.6 kcal/mol; only one configuration yields a deviation of 1 kcal/mol.

Our-of-plane interactions are particularly important at the anionic site for the enolate ion, and two such configurations of (*Z*)-methyl acetate anion with water were computed. Two additional hydrated configurations (in-plane) were computed for (*Z*)-methyl acetate anion. The first involves water with both protons facing the carbonyl oxygen and anionic center (Figure 6C). Figure 6D shows the second configuration with the water hydrogens facing the ester oxygen and anionic carbon.

Two water (*E*)-methyl acetate anion configurations were also used in the parameterization (Figure 7). A double interaction is possible when the water hydrogens face the carbonyl and ester oxygens simultaneously, as illustrated in Figure 7B. The hydrogen bond distances are typical of these systems, and the OPLS parameters yield a stabilization of −14.9 kcal/mol whereas the 6-31+G(d) calculations give −15.1 kcal/mol.

Simulations of Methyl Acetate in Solution. The results of the simulations in acetonitrile and water are tabulated in Tables 7 and 8. The differences between the free energies of solvation of the *Z* and *E* isomers are computed to be −2.7 ± 0.1 and −3.0 ± 0.2 kcal/mol in acetonitrile and water, respectively. The reported statistical uncertainties are ±σ, as obtained from the fluctuations in separate averages over blocks of (1−2) × 10^5 configurations during the Monte Carlo simulations; experience with multiple runs indicates that the uncertainties obtained via the "batch means" procedure are within a factor of 2 of the true values.

As expected, the more polar *E* isomer is preferentially stabilized for both solvent systems, and the difference in solvation is larger in the more polar solvent. In the gas phase, the *Z* ester is more stable then the *E* ester. This 8.8 kcal/mol difference is predicted to be reduced to 6.1 kcal/mol in acetonitrile and 5.8 kcal/mol in water. Wiberg and Wong have also investigated the effect of solvation on the *E*/*Z* energy difference for methyl formate and methyl acetate.[33] They used the Onsager reaction field, a continuum model, in conjunction with *ab initio* calculations. At the MP2/6-31G**//6-31G* level,

Table 7. Computed Relative Free Energies of Solvation in CH_3CN for the Interconversion of (*Z*)- to (*E*)-Methyl acetate Using the OPLS Force Field[a]

Φ_i	Φ_j	$i \rightarrow j$	$\Delta G_{\text{total}}(\Phi_i)$
0	10	0.03 ± 0.02	0.0
10	20	−0.01 ± 0.01	0.03
20	30	−0.06 ± 0.02	0.02
30	40	−0.09 ± 0.02	−0.04
40	50	−0.20 ± 0.02	−0.13
50	60	−0.19 ± 0.03	−0.33
60	70	−0.21 ± 0.03	−0.52
70	80	−0.22 ± 0.03	−0.73
80	90	−0.24 ± 0.03	−0.95
90	100	−0.26 ± 0.03	−1.19
100	110	−0.21 ± 0.02	−1.45
110	120	−0.22 ± 0.02	−1.66
120	130	−0.20 ± 0.02	−1.88
130	140	−0.19 ± 0.03	−2.08
140	150	−0.18 ± 0.02	−2.27
150	160	−0.11 ± 0.02	−2.45
160	170	−0.09 ± 0.03	−2.56
170	180	−0.06 ± 0.03	−2.65
180			−2.71 ± 0.10

[a] Angle Φ is the Me—O—C═O dihedral angle in degrees. Free energies are reported in kilocalories per mole. The error bars (±1σ) were obtained from separate averages over blocks of 10^5 configurations during the Monte Carlo simulations.

Table 8. Computed Relative Free Energies of Hydration for the Interconversion of (*Z*)- to (*E*)-Methyl Acetate Using the OPLS Force Field[a]

Φ_i	Φ_j	$i \rightarrow j$	$\Delta G_{\text{total}}(\Phi_i)$
0	10	0.03 ± 0.05	0.0
10	20	−0.03 ± 0.04	0.03
20	30	−0.13 ± 0.05	0.00
30	40	−0.12 ± 0.04	−0.13
40	50	−0.22 ± 0.03	−0.25
50	60	−0.26 ± 0.04	−0.47
60	70	−0.23 ± 0.04	−0.73
70	80	−0.17 ± 0.05	−0.96
80	90	−0.22 ± 0.05	−1.13
90	100	−0.24 ± 0.05	−1.35
100	110	−0.37 ± 0.05	−1.59
110	120	−0.34 ± 0.04	−1.96
120	130	−0.24 ± 0.05	−2.30
130	140	−0.20 ± 0.04	−2.54
140	150	−0.11 ± 0.04	−2.74
150	160	−0.05 ± 0.04	−2.85
160	170	−0.11 ± 0.03	−2.90
170	180	−0.02 ± 0.02	−3.01
180			−3.03 ± 0.18

[a] Angle Φ is the Me—O—C═O dihedral angle in degrees. Free energies are reported in kilocalories per mole. The error bars (±1σ) were obtained from separate averages over blocks of 10^5 configurations during the Monte Carlo simulations.

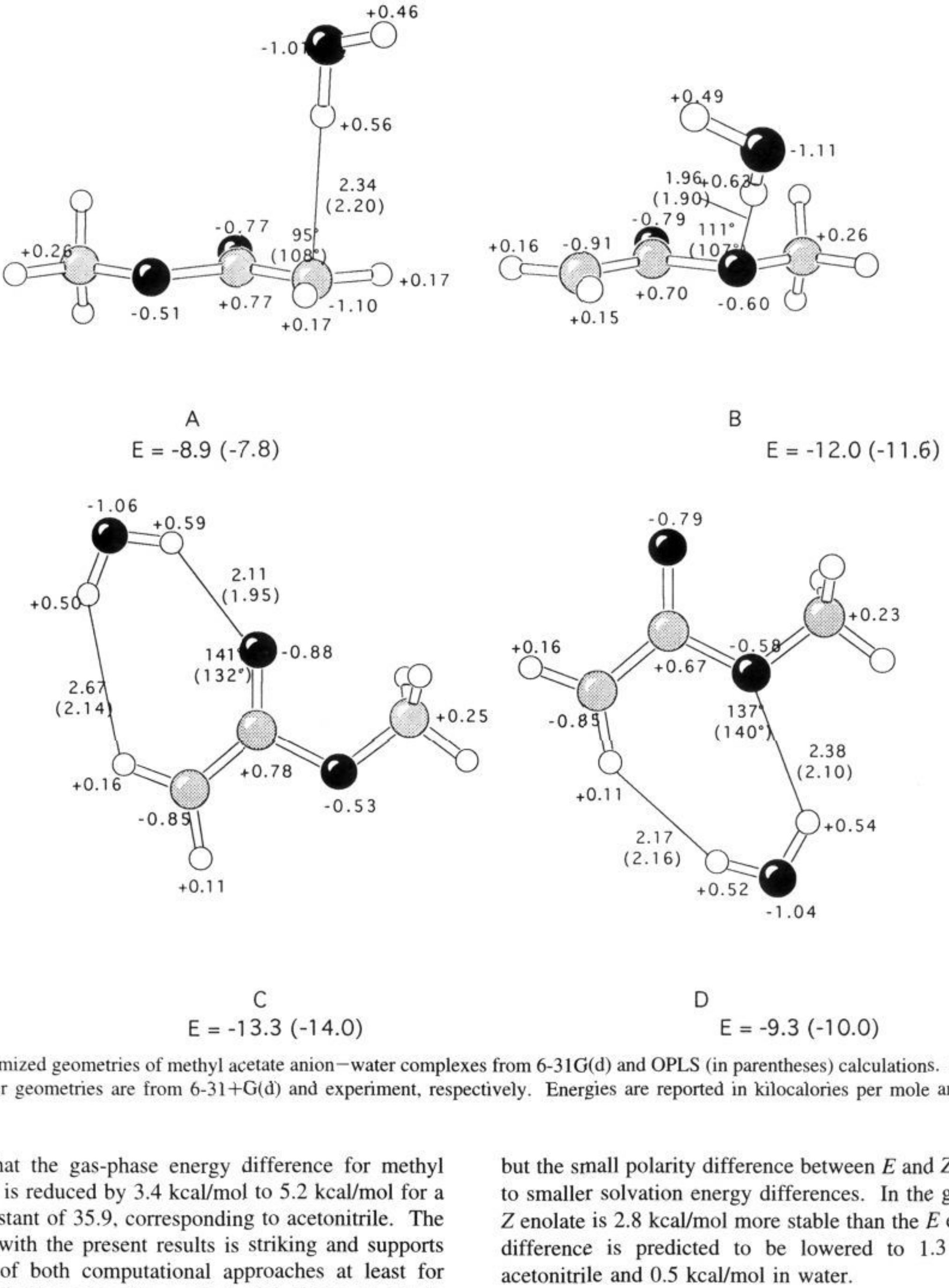

Figure 6. Optimized geometries of methyl acetate anion−water complexes from 6-31G(d) and OPLS (in parentheses) calculations. Methyl acetate anion and water geometries are from 6-31+G(d) and experiment, respectively. Energies are reported in kilocalories per mole and distances in angstroms.

they found that the gas-phase energy difference for methyl acetate of 8.6 is reduced by 3.4 kcal/mol to 5.2 kcal/mol for a dielectric constant of 35.9, corresponding to acetonitrile. The close accord with the present results is striking and supports the viability of both computational approaches at least for conformational processes with a substantial change in dipole moment in a polar, aprotic solvent. Wiberg and Wong also found that the inclusion of corrections for the zero-point vibrational energy changes affected these results for methyl acetate by less than 0.1 kcal/mol.[33a] Additional computational studies on related systems have been reported since this work was completed.[33b]

Simulations of Methyl Acetate Anion in Solution. The results of the simulations for the enolate anions derived from methyl acetate are tabulated in Tables 9 and 10. The computed differences between the free energies of solvation of the *Z* and *E* isomers are −1.5 ± 0.2 and −2.3 ± 0.2 kcal/mol in acetonitrile and water, respectively.

Once again there is preferential solvation of the *E* isomer, but the small polarity difference between *E* and *Z* anions leads to smaller solvation energy differences. In the gas phase, the *Z* enolate is 2.8 kcal/mol more stable than the *E* enolate. This difference is predicted to be lowered to 1.3 kcal/mol in acetonitrile and 0.5 kcal/mol in water.

Comparison to Experiment. (*Z*)-Methyl acetate is 8.8 kcal/mol more stable than (*E*)-methyl acetate in the gas phase.[2] This difference is reduced to 2.8 kcal/mol for the enolate anions.[2c] The energy to deprotonate the *E* ester is 6.0 kcal/mol less than the energy to deprotonate the *Z* conformer.

The free energy of hydration of (*E*)-methyl acetate is predicted to be 3.0 ± 0.2 kcal/mol greater than for (*Z*)-methyl acetate. Hydration is 2.3 ± 0.2 kcal/mol more favorable for the *E* conformer of the ester enolate ion than for the *Z* conformer. Thus, the difference in acidities has been reduced by 0.7 kcal/mol at room temperature due to the effect of hydration. In aqueous solution, the energy of deprotonation of the *E* ester is 5.3 kcal/mol less than that of the *Z* ester. These results along with those for acetonitrile are tabulated below. The important point is that solvation is not found to have a large differential effect on the acidities of the *Z* and *E* esters. It diminishes the

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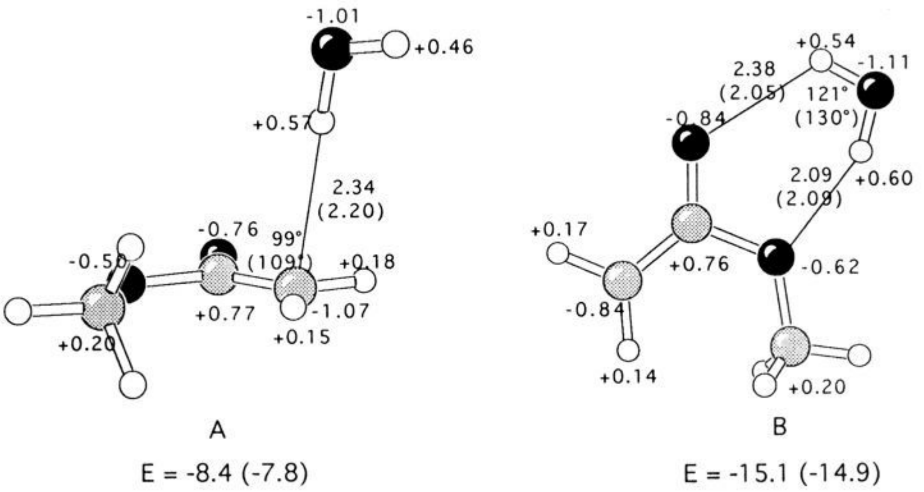


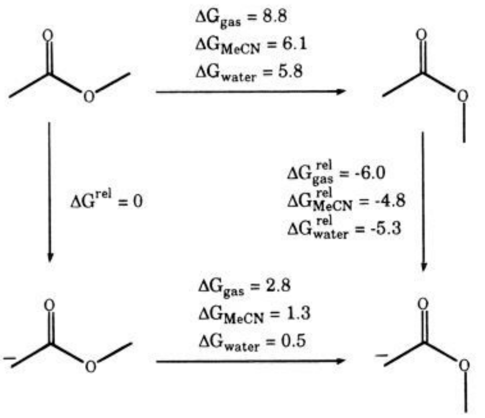
Figure 7. Optimized geomtries of methyl acetate anion−water complexes from 6-31G(d) and OPLS (in parentheses) calculations. Methyl acetate anion and water geometries are from 6-31+G(d) and experiment, respectively. Energies are reported in kilocalories per mole and distances in angstroms.

Table 9. Computed Relative Free Energies of Solvation in CH_3CN for the Interconversion of (*Z*)- to (*E*)-Methyl Acetate Anion[a]

Φ_i	Φ_j	$i \rightarrow j$	$\Delta G_{\text{total}}(\Phi_j)$
0	10	−0.04 ± 0.05	0.0
10	20	−0.04 ± 0.04	−0.04
20	30	−0.17 ± 0.03	−0.08
30	40	−0.11 ± 0.03	−0.25
40	50	−0.06 ± 0.05	−0.36
50	60	−0.07 ± 0.04	−0.42
60	70	−0.10 ± 0.03	−0.49
70	80	−0.10 ± 0.04	−0.59
80	90	−0.12 ± 0.04	−0.69
90	100	−0.10 ± 0.05	−0.81
100	110	−0.06 ± 0.06	−0.91
110	120	−0.09 ± 0.06	−0.97
120	130	−0.10 ± 0.03	−1.06
130	140	−0.06 ± 0.04	−1.16
140	150	−0.17 ± 0.02	−1.22
150	160	−0.05 ± 0.03	−1.39
160	170	−0.04 ± 0.03	−1.44
170	180	0.03 ± 0.03	−1.48
			−1.45 ± 0.17

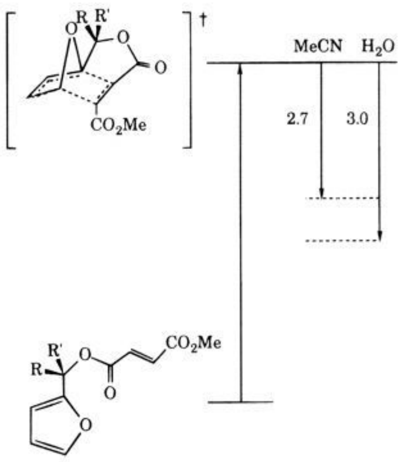
[a] Angle Φ is the Me−O−C=O dihedral angle in degrees. Free energies are reported in kilocalories per mole. The error bars (±1σ) were obtained from separate averages over blocks of 10^5 configurations during the Monte Carlo simulations.

ca. 5 kcal/mol enhancement of the *E* ester by *ca.* 1 kcal/mol.



Comparing these results with the experimental data on dimethyl malonate and Meldrum's acid, the conversion of two *Z* esters to two *E* esters is predicted to increase the acidity by 2 × 5.3 = 10.6 kcal/mol, as compared to the experimental increase of 11.7 kcal/mol. Thus, 1 kcal/mol is not accommodated by the simple ester comparisons.

Jung and Gervay found that the rates of the intramolecular Diels−Alder reactions of the furan−fumarate (see below) are linearly dependent on the dielectric constant of the solvent.[4] Since the reactants are *Z* esters and the transition structures must approach an *E* conformation, solvent is expected to lower the activation energy of the reaction in the fashion shown schematically below.



The liquid simulations predict a 2.7 kcal/mol greater solvation of the *E* ester than the *Z* conformer in acetonitrile and 3.0 kcal/mol larger free energy of solvation of the *E* ester than the *Z* conformer in aqueous solution. The observed rate enhancements of up to 3200 in polar solvents are consistent with the substantial computed effects.

Conclusion

This study has provided quantitative predictions of solvation effects on the relative free energies of the *E* and *Z* isomers of a simple ester and its corresponding anion in acetonitrile and water. New parameters for fluid simulations were also developed for the anions of esters. Significant solvent effects are

Table 10. Computed Relative Free Energies of Solvation in H_2O for the Interconversion of (*Z*)- to (*E*)-Methyl Acetate Anion Using the OPLS Force Field[a]

Φ_i	Φ_j	$i \rightarrow j$	$\Delta G_{\text{total}}(\Phi_i)$
0	10	0.15 ± 0.05	0.0
10	20	−0.04 ± 0.05	−0.15
20	30	0.17 ± 0.04	−0.19
30	40	−0.03 ± 0.04	−0.36
40	50	0.02 ± 0.06	−0.39
50	60	0.05 ± 0.06	−0.41
60	70	0.03 ± 0.07	−0.36
70	80	−0.03 ± 0.07	−0.39
80	90	0.16 ± 0.04	−0.42
90	100	−0.14 ± 0.05	−0.58
100	110	0.16 ± 0.05	−0.72
110	120	−0.09 ± 0.05	−0.88
120	130	0.08 ± 0.06	−0.97
130	140	−0.04 ± 0.05	−1.05
140	150	0.26 ± 0.05	−1.09
150	160	−0.28 ± 0.05	−1.35
160	170	0.31 ± 0.06	−1.63
170	180	−0.33 ± 0.05	−1.94
			−2.27 ± 0.23

[a] Angle Φ is the Me—O—C=O dihedral angle in degrees. Free energies are reported in kilocalories per mole. The error bars ($\pm 1\sigma$) were obtained from separate averages over blocks of 1.5×10^5 configurations during the Monte Carlo simulations.

found favoring the *E* form of both the ester and its enolate anion. The less polar solvent, acetonitrile, provide 2.7 ± 0.1 kcal/mol greater stabilization for (*E*)-methyl acetate. Aqueous simulations predict better solvation of the more polar *E* isomer by 3.0 ± 0.2 kcal/mol. The difference in free energy of solvation between the *E* and *Z* isomers of the enolate anion of methyl acetate was computed to be 2.3 ± 0.2 and 1.5 ± 0.2 kcal/mol in water and acetonitrile, respectively. The two factors largely negate each other such that the *ca.* 5 kcal/mol enhancement of the acidity of the *E* ester relative to the *Z* form in the gas phase is reduced by about 1 kcal/mol in the polar solvents.

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Supplementary Material Available: Ab initio energies, structures, and frequencies in Gaussian archive format for the *Z* and *E* esters and corresponding anions (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.