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New Insight on the Origin of the Unusual Acidity of Meldrum's Acid from ab Initio and Combined QM/MM Simulation Study

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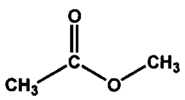
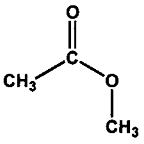
Abstract: Ab initio molecular orbital and combined QM/MM Monte Carlo simulations have been carried out to investigate the origin of the unusually high acidity of Meldrum's acid. Traditionally, the high acidity of Meldrum's acid relative to that of methyl malonate has been attributed to an additive effect due to the presence of two E esters in the dilactone system. However, the present study reveals that there is significant nonadditive effect that also makes major contributions. This results from preferential stabilization of the enolate anion over that of Meldrum's acid due to anomeric stereoelectronic interactions. To investigate solvent effects on the acidity in aqueous solution, the relative acidities of Z and E conformers of methyl acetate have been determined in combined ab initio QM/MM simulations. There is significant solvent effect on the conformational equilibria for both the neutral ester and its enolate anion in water, leading to stabilization of the E stereoisomer. However, the computed solvent effect of 4.4 kcal/mol in favor of the E isomer of methyl acetate is largely offset by the favorable solvation of 3.4 kcal/mol for the E conformer of the enolate anion. This leads to an enhanced acidity of 3.4 kcal/mol for the (*E*)-methyl acetate in water over the Z conformer. In Meldrum's acid, it is the preferential stabilization of the enolate anion due to anomeric effects coupled with the intrinsically higher acidity of the E conformation of ester that is responsible for its high acidity.

Introduction

The preference for the Z isomer over the E conformation is an intrinsic property of organic esters.[1−4] For example, the Z conformer of methyl formate is 4.8 kcal/mol more stable than the E counterpart, whereas a larger energy difference of 8.5 kcal/mol was found in methyl acetate because of the steric repulsion between two methyl groups.[1,5] There is also a rather large rotational barrier of 10−15 kcal/mol about the ester C−O bond due to resonance delocalization of the lone pair electrons of the ester oxygen.[1,2] A direct consequence of this conformational energy difference is that the E rotamer is significantly more acidic than the Z form because the energy difference between the corresponding enolate anions is much smaller. Thus, small lactones, which adopt the E ester conformation, are typically more acidic than linear esters and large lactones having the Z configuration.[6−8] The best known example perhaps is Meldrum's acid (pK_a 7.3), which is 11.7 kcal/mol more acidic than dimethyl malonate (pK_a 15.9).[9] The origin of the unusually high acidity of Meldrum's acid has been investigated through a series of gas-phase ab initio calculations and condensed-phase Monte Carlo simulations, primarily making use of simple esters as model systems. This phenomenon has been attributed to a roughly additive effect of the E ester conformation adopted in Meldrum's acid with small solvent effects.[2,4,5,9,10]



Z



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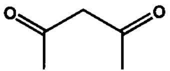
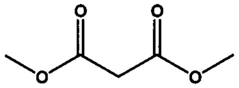


Meldrum's acid



dimethyl malonate

In this work, we revisit the Meldrum's acid system. The goal is to provide additional insight into the origin of the unusual acidity of Meldrum's acid in aqueous solution. To achieve this goal, we first investigate the solvent effects on the Z to E isomerization of methyl acetate and its anion in water, and validate our method by comparison with previous results. The origin of the intrinsically high acidity of Meldrum's acid is unraveled by using Weinhold's natural orbital analysis.[11] Here, we employ a multiple-level strategy that combines high-level ab initio density functional results for the gas-phase acidity and

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ab initio QM/MM results on aqueous solvation. We confirm the previous finding of minimal solvent effects on the relative acidity of E and Z conformers of organic ester; however, the origin of the high acidity of Meldrum's acid cannot be simply attributed to an additive effect of two E ester linkages as proposed before.[2,4,5,9,10,12] In fact, stereoelectronic anomeric effects in the cyclic dilactone system provide significant contributions.

Previous studies employed either continuum solvation models or simulations with empirical potential functions. Here, we employ a combined quantum mechanical and molecular mechanical (QM/MM) method at the ab initio level to estimate solvent effects.[13−19] Because the solute molecule is treated explicitly by quantum mechanics, solute electronic polarization effects are naturally included in combined QM/MM calculations.[15,20] Furthermore, an advantage of the combined QM/MM approach is that there is no need to adjust parameters or partial charges for the solute molecule as the solute conformation varies. In the following, we first describe the computational model, which is followed by results and discussion.

Computational Details

A. Ab Initio QM/MM Hamiltonian. The effective Hamiltonian used in the present combined QM/MM Monte Carlo simulations is:[16]

$$\hat{H}_{eff} = \hat{H}_{qm}^{0} + \hat{H}_{qm/mm} + \hat{H}_{mm/mm} \tag{1}$$

where $\hat{H}_{qm}^{0}$ is the Hamiltonian of an isolated solute molecule, whereas the last term is the MM energy for the solvent. The second term, $\hat{H}_{qm/mm}$, which also includes electronic degrees of freedom, accounts for solute−solvent interactions.

In this study, we separate QM/MM energies into a solvent-independent (gas phase) term and a solute−solvent interaction component. This separation of energy terms is particularly useful because it allows the use of a high-level (HL) method to determine the intrinsic energy of the solute molecule in the gas phase, while the time-consuming statistical simulations can be carried out with a lower-level (LL) quantum chemical model for the evaluation of the solvation energy. Thus, the total energy of the system is given as follows:[21−23]

$$E_{tot} = E_{qm}^{HL}(gas) + \Delta E_{Xs}^{LL} + E_{mm} \tag{2}$$

where $E_{qm}^{HL}(gas)$ is the gas-phase energy of the solute computed at a high level of theory, and ΔE_{Xs}^{LL} is the QM/MM interaction energy modeled with a lower-level method. Similar concepts have been described in other context:[21−23]

B. Umbrella Sampling. The potential of mean force (PMF), $\Delta G(\phi)$, for the torsional rotation about the ester bond is determined according to eq 3 as a function of the dihedral angle, ϕ, defined by the four atoms, O=C−O−C:

$$\Delta G(\phi) = -RT \ln P(\phi) + C \tag{3}$$

where R is gas constant, T is temperature, C is an arbitrary constant, and $P(\phi)$ is the probability density.[24,25] Although $\Delta G(\phi)$ can be obtained from a single and long simulation, in practice, it is more convenient to use several simulations (windows) to span the entire reaction coordinate, ϕ. This is achieved by using a simple harmonic potential to keep the system within a certain range in the conformational space. Thus, an additional term $U_w(\phi)$ is included as a harmonic restraining function, whose force constant is chosen to be 5 kcal/(mol·Å^2). Simulations are carried out for values of $\phi_0 = 0°$, 30°, 60°, 90°, 120°, 150°, and 180°.

C. Quantum Mechanical Calculations. The solute molecule, methyl acetate or its enolate anion, is treated at the HF/3-21G level in combined QM/MM simulations. This basis set is chosen because it has been calibrated at the HF level in combination with the TIP3P model for water to describe hydrogen bonding interactions.[15,16,26] The performance of the HF/3-21G:TIP3P potential as applied to a variety of organic compounds, representing amino acid side chains and nucleotide bases, was found to be in excellent agreement with full ab initio results, and has been used in condensed-phase simulations.[20,27,28] In addition, its modest computational cost allows extensive Monte Carlo sampling to be carried out by using explicit ab initio QM/MM potential on the fly during the simulation.

The computational accuracy necessary for predicting the acidity of organic acids is achieved by using a multiple-level approach.[21,23] To this end, Ab initio calculations along the torsional reaction coordinate ϕ have been carried out at the B3LYP/aug-cc-pVDZ//B3LYP/aug-cc-pVDZ level for methyl acetate and its enolate anion. Here, geometry optimizations are made for methyl acetate and its enolate anion at fixed dihedral angles from 0° to 180° with an interval of 15°. The B3LYP energies are used to approximate the $E_{qm}^{HL}(gas)$ term. Adopting a "triple slash" notation for dual-level dynamics calculations,[23] the present multiple level approach can be ascribed as B3LYP/aug-cc-pVDZ///HF/3-21G:TIP3P, with "///" separating HL calculations with LL simulations and the symbol ":" separating QM and MM models. All ab initio calculations in the gas phase are carried out with GAUSSIAN 94.[29]

Combined ab initio QM/MM simulations have been carried out for one methyl acetate (or the corresponding enolate anion) in a cubic box containing 360 water molecules. Potential of mean force for the dihedral rotation about the ester bond has been determined via umbrella sampling by using periodic boundary conditions along with the isothermal−isobaric ensemble at 25 °C and 1 atm.[30] During Monte Carlo simulations, the geometry of the solute is allowed to vary to within a range of ±0.005 Å for bond length, ±3° for bond angle, and ±10° for dihedral angle. To facilitate the self-consistent-field (SCF) convergence, the density matrix from the previous configuration is used as the initial guess in the subsequent SCF energy calculation. A full in-core computation has been carried out to eliminate any possible disk I−O, including intermediate density matrix and all electronic integrals, in the electronic structure calculation during the simulation.

Each simulation consists of an equilibration phase of at least one million configurations, followed by averaging over an additional two million configurations for methyl acetate, and three million configurations for the enolate anion. Spherical cutoffs are used to switch off intermolecular interactions between 8.5 and 9.0 Å. Although it would

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Table 1. Computed Gas-phase Thermodynamic Properties for Methyl Acetate and Its Enolate Anion[a]

	ΔE (kcal/mol)					
method	(Z)	(E)	TS[b]	ΔH^{298}	ΔS^{298}	ΔG^{298}
		$CH_3CO_2CH_3$				
HF/3-21G	0.0	9.6	12.2	9.5	−0.5	9.7
HF/6-31G(d)	0.0	9.4	13.4	9.3	−0.1	9.3
B3LYP/aug-cc-pVDZ	0.0	7.2	13.1	7.0	−2.0	7.6
		$[CH_2{=}CO_2CH_3]^-$				
HF/3-21G	0.0	5.7	7.8	5.7	−1.8	6.3
HF/6-31+G(d)	0.0	3.7	6.4	3.8	−1.5	4.2
B3LYP/aug-cc-pVDZ	0.0	2.1	4.9	2.1	−3.6	3.2

[a] ΔH and ΔG in kcal/mol and ΔS in cal/(mol·K). [b] Transition state. [c] HF/6-31+G(d) vibrational frequencies are used in DFT calculations.

Table 2. Predicted Solvation Free Energy Differences on the E and Z Conformer of Methyl Acetate and Its Anion in Solution (kcal/mol)

	QM/MM	OPLS[a]		SCRF[b]
	water	water	acetonitrile	acetonitrile
ester (E→Z)	4.4 ± 0.5	3.0	2.7	3.3
enolate (E→Z)	3.4 ± 0.5	2.3	1.5	

[a] Reference 10. [b] Reference 12.

be ideal to include explicit long-range electrostatic terms like the extended Ewald method as we have done in semiempirical QM/MM calculations,[31] it becomes computationally intractable at the ab initio level. Fortunately, previous studies have shown that the Born correction for ions or Onsager model for dipolar molecules are reasonable in computing the free energy of solvation.[31] The present study concerns the change in free energy, so the effect of a cutoff scheme should be smaller. The ranges for attempted translation and rotation of solvent and solute molecules are ±0.15 Å and ±15.0 Å, and ±0.05 Å and ±3.0 Å, respectively.[30] The probability in the preferential sampling was made proportional to $1/(r^2 + C)$, where $C = 150$ Å^2 and r is the distance between solute and solvent molecules. All simulations are performed with the MCQUB program,[32] in which the electronic structure calculations are performed with the GAMESS package.[33]

Results

Computed gas-phase thermodynamics quantities are given in Table 1 for the E and Z conformer of methyl acetate and its corresponding enolate anion. The energy difference between (*E*)- and (*Z*)-methyl acetate is 9.6, 9.4, and 7.2 kcal/mol at the HF/3-21G, HF/6-31G(d), and B3LYP/aug-cc-pVDZ levels, respectively. For the enolate anion, the Z isomer is preferred by 5.7 (HF/3-21G), 3.7 (HF/6-31+G(d)), and 2.1 kcal/mol (B3LYP/aug-cc-pVDZ). Clearly, both diffuse functions and electron correlation have significant effects on the computed energy difference in the ester and enolate, but the influence is more dramatic for the anions.

Computed solvent effects on the E and Z conformers of methyl acetate and its anion in water are listed in Table 2, while averaged molecular dipole moments and geometrical parameters are shown in Tables 3 and 4. The potentials of mean force for the dihedral rotation about the ester bond are depicted in Figures 1 and 2 for the neutral and anionic species. All results for aqueous solution are obtained from Monte Carlo simulations, and thus are ensemble averages.

Finally, to probe the origin of the abnormally high acidity of Meldrum's acid, we have carried out natural orbital analysis.

Table 3. Computed Dipole Moments (Debye) for Methyl Acetate in the Gas Phase and in Water

isomer	3-21G	6-31G(d)	DFT[a]	OPLS[b]	exp[c]	QM/MM	$\Delta\mu_{ind}$
(Z)	1.80	1.99	1.93	1.44	1.72	2.43 ± 0.05	0.63
(E)	5.18	4.85	4.62	4.18	4.12	6.54 ± 0.04	1.36

[a] B3LYP/aug-cc-pVDZ//B3LYP/aug-cc-pVDZ. [b] Reference 10. [c] References 42 and 43.

Table 4. Computed Geometrical Parameters for Methyl Acetate and Methyl Acetate Anion in the Gas Phase and in Water from QM/MM HF/3-21G:TIP3P Simulations[a]

	(Z) conformer		(E) conformer	
parameter	gas	water	gas	water
		$CH_3CO_2CH_3$		
$C_2{-}C_1$	1.501	1.500 ± 0.004	1.513	1.510 ± 0.005
$C_1{=}O_1$	1.203	1.210 ± 0.001	1.198	1.205 ± 0.001
$C_1{-}O_2$	1.354	1.349 ± 0.004	1.359	1.358 ± 0.003
$O_2{-}C_3$	1.453	1.449 ± 0.003	1.440	1.454 ± 0.003
$C_2{-}C_1{=}O_1$	127.2	125.9 ± 0.4	123.7	124.5 ± 0.6
$O_1{=}C_1{-}O_2$	122.4	122.6 ± 0.4	119.3	117.8 ± 0.4
$C_1{-}O_2{-}C_3$	117.9	120.4 ± 0.6	123.7	124.0 ± 0.6
		$[CH_2{=}CO_2CH_3]^-$		
$C_2{-}C_1$	1.359	1.368 ± 0.003	1.368	1.370 ± 0.003
$C_1{=}O_1$	1.251	1.265 ± 0.002	1.241	1.265 ± 0.002
$C_1{-}O_2$	1.449	1.405 ± 0.004	1.449	1.391 ± 0.004
$O_2{-}C_3$	1.424	1.440 ± 0.004	1.414	1.431 ± 0.003
$C_2{-}C_1{=}O_1$	133.5	128.4 ± 0.4	131.2	127.4 ± 0.5
$O_1{=}C_1{-}O_2$	115.1	118.1 ± 0.4	112.3	113.1 ± 0.3
$C_1{-}O_2{-}C_3$	116.7	120.7 ± 0.5	121.0	123.2 ± 0.6

[a] Bond lengths are given in angstroms and angles in degrees.

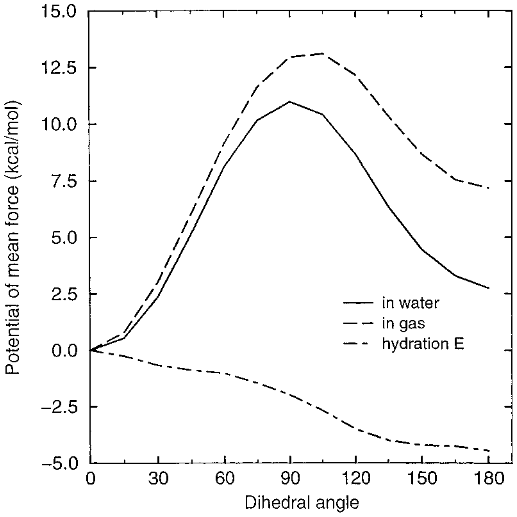

Figure 1. Potential of mean force for the dihedral rotation about the ester bond of methyl acetate in water from multiple-level calculations. Gas-phase free energy changes are obtained at the B3LYP/aug-cc-pVDZ level, whereas solvation free energies are from combined HF/3-21G:TIP3P simulations.

The localized natural orbitals that are involved in stabilization of Meldrum's acid through what is characterized as anomeric effects are illustrated in Figures 3 and 4. Gas-phase acidities are listed in Table 5 for a series of esters including Meldrum's acid determined at the B3LYP/aug-cc-pVDZ level. Computed strain energies for cyclic systems are given in Table 6.

Discussion

The primary goal of the present study is to unravel the origin of the exceptionally high acidity of Meldrum's acid in aqueous solution. To achieve this goal, two contributing factors must

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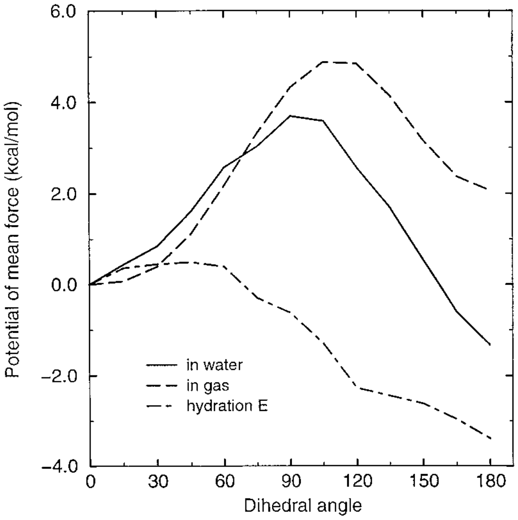

Figure 2. Potential of mean force for the dihedral rotation about the ester bond of the enolate anion of methyl acetate in water from multiple-level calculations. Gas-phase free energy changes are obtained at the B3LYP/aug-cc-pVDZ level, whereas solvation free energies are from combined HF/3-21G:TIP3P simulations.

be considered, including the intrinsic acidity of the compound in the gas phase, and solvent effects on the corresponding neutral and anionic species. Previous studies have focused on the characteristic feature of Meldrum's acid: the presence of two E ester bonds.[2,4,5,9,10] Consequently, both gas-phase and solution-phase studies made use of methyl acetate as a model compound to probe the relative acidity of the E and Z conformer in water. On the basis of the relative acidity of E and Z conformers of methyl acetate, these studies converge to a uniform conclusion that a roughly additive, destabilizing effect of two E esters in Meldrum's acid is responsible for its elevated acidity relative to dimethyl malonate.[2,4,5,10] However, as we show below, the two E esters in Meldrum's acid in fact enjoy remarkable stabilization effects in the cyclic system due to stereoelectronic anomeric interactions. The difference in anomeric stabilization between Meldrum's acid and its enolate anion introduces significant nonadditive contributions to the acidity.

For the sake of completeness, we first briefly summarize results from combined ab initio QM/MM Monte Carlo simulations of an aqueous solution of methyl acetate. Although we obtain the same main conclusion of small solvent effects on the relative acidity of methyl acetate as that by Evanseck et al., our computation also results in additional insights into solvent effects on electronic polarization and molecular geometry. We, then, focus on discussion of the intrinsic acidity of Meldrum's acid and its origin in the gas phase.

Ab Initio QM/MM-Monte Carlo Simulations.

A. Methyl Acetate. The potential of mean force for the torsional rotation about the ester C−O bond is depicted in Figure 1, which is obtained by a multiple-level simulation approach that combines high-level B3LYP/aug-cc-pVDZ results for the gas-phase free energy profile with combined HF/3-21G:TIP3P solvation free energies. The latter shows that the more polar (*E*)-methyl acetate is preferentially stabilized by −4.4 ± 0.5 kcal/mol over the Z conformer in water (Table 2). As a result, the free energy difference of 7.6 kcal/mol in the gas phase (Table 1) is reduced to 3.2 ± 0.5 kcal/mol in water at the B3LYP/aug-cc-pVDZ///HF/3-21G:TIP3P level. Wiberg and Wong predicted that the solvent stabilization of the E isomer is 3.3 kcal/mol in acetonitrile ($\epsilon = 35.9$) using the Onsager continuum reaction field model (Table 2).[12] Subsequently, Evanseck et al. found that the solvent effect is 2.7 kcal/mol in acetonitrile and 3.0 kcal/mol in water from Monte Carlo simulations (Table 2).[10] These results are in reasonable agreement with our combined ab initio QM/MM data.

The present ab initio QM/MM simulations provide additional insights on the solvation of methyl acetate, which are not available from previous investigations with empirical potential functions. The electronic polarization of the solute molecule is reflected by the average molecular dipole moments in water, which are averaged to be 2.43 ± 0.05 and 6.54 ± 0.04 D for the Z and E isomer of methyl acetate from HF/3-21G:TIP3P simulations (Table 3). This yields an induced dipole moment of ca. 0.6 D for the Z conformer and 1.5 D for the E configuration. Thus, not only does the E isomer have a larger dipole moment intrinsically, interactions with water lead to enhanced polarization and an even greater induced dipole in solution. This further emphasizes the importance of the solvent polarization effect on the solute electronic structure, giving rise to differential induced stabilization interactions as its conformation varies. Note that the OPLS potential employed charge distributions essentially reproduce gas-phase dipole moments (Table 3).[10]

The present calculation also gives an estimate of the location of the transition state and barrier height in aqueous solution (Figure 1). We found a solvent-induced shift of the transition state toward the Z configuration at 90° in water from a value of 105° in the gas phase. The free energy barrier is reduced by ca. 3 kcal/mol to 10.5 kcal/mol.

Furthermore, solvent effects are found to have modest influence on the molecular geometry of methyl acetate (Table 4). Noticeably, the carbonyl bond, C═O, is lengthened by about 0.007 Å on going from the gas phase into aqueous solution for both the Z and E conformation. This is consistent with the expectation that hydrogen bonding interactions polarize the charge distribution of the carbonyl group, which weakens the C═O covalent bonding character, leading to a longer bond distance. Variations in the IR carbonyl stretching mode have long been used as a probe to study solvent effects and hydrogen bonding interactions in solution. For example, the C═O stretching frequency of acetone is red-shifted from its gas-phase value of 1738 cm^{-1} to 1698 cm^{-1} in aqueous solution.[34−36] The computed geometrical change is clearly consistent with experimental IR shifts of carbonyl compounds in polar solvents.[36]

B. Enolate Anion. The pmf at the B3LYP/aug-cc-pVDZ///HF/3-21G:TIP3P level is shown in Figure 2, along with the computed solvation free energy profile. Again, solvation effects bring stabilization to the E conformer by 3.4 ± 0.5 kcal/mol over that of the Z conformer in water. Thus, the gas-phase free energy difference of 3.2 kcal/mol (Table 1) is attenuated by solvation to a value of −0.2 ± 0.5 kcal/mol in favor of the E isomer in aqueous solution (Table 2). In addition, the rotational barrier is reduced by 1.5 kcal/mol, and its location shifted to $\phi = 90°$. For comparison, Evanseck et al. also found a more favorable E-enolate anion in water with a predicted solvent stabilization of 2.3 kcal/mol.[10]

In contrast to the neutral form, the geometry of methyl acetate anion is significantly affected by aqueous solvation because hydrogen-bonding interactions are stronger for the anions (Table 4). The carbonyl C═O bond distance increases from 1.251 Å in the gas phase to 1.265 Å in water in the Z conformation,

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(34) Symons, M. C. R.; Eaton, G.; Shippey, T. A.; Harvey, J. M. *Chem. Phys. Lett.* **1980**, *69*, 344−7.

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Table 5. Computed Gas Phase Acidity (kcal/mol) from B3LYP/Aug-cc-pVDZ Calculations

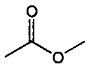
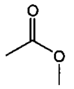
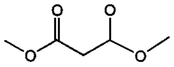
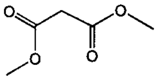
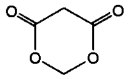
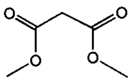
Compound	ΔG_{gas}	Compound	ΔG_{gas}
	369.4		365.0
	336.5		336.4
	325.1		336.1

Table 6. Computed Strain Energies for the Lactones (kcal/mol) at the B3LYP/aug-cc-pVDZ Level on the Basis of the Isodesmic Reaction: Ester + Cyclohexane → Lactone + *n*-Heptane

ester	lactone	strain energy
methyl pentanoate	2-oxacyclohexanone	9.8
methyl pentanoate anion	2-oxacyclohexanone anion	5.5
dimethyl malonate	Meldrum's acid	5.7
dimethyl malonate anion	Meldrum's acid anion	−7.9

while the change is the same (0.014 Å) from 1.241 to 1.265 Å in the E conformation. Concomitantly, the ester C(=O)−O bond length decreases by 0.04−0.05 Å, and the O−CH_3 bond distance lengthens by about 0.015 Å. The C=C bond distance shows an elongation of ca. 0.016 Å in both conformers. Bond angles also experience significant changes, particularly in the Z isomer. Competing for hydrogen-bonding interactions with the enolate oxygen by water favors an extension of the O=C−O and C−O−C angles, whereas the effect on the E isomer is not large because both oxygens are already exposed to the solvent.

C. Relative Acidity between the E and Z conformer of Methyl Acetate. The relative pK_a between E and Z-methyl acetate is related to the ionization free energy difference in the gas phase, and relative free energies of solvation for the neutral and ionic conformers:[10,37−39]

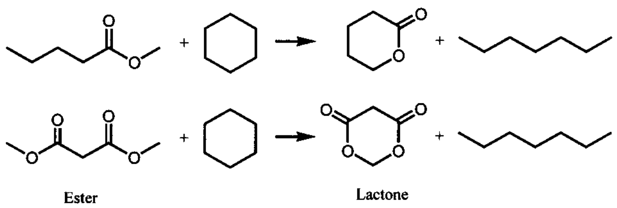
$$\Delta pK_a = pK_a(Z) - pK_a(E) = \frac{1}{2.303RT}[\Delta G_{ion}^{gas}(Z) - \Delta G_{ion}^{gas}(E) + \Delta\Delta G_{hyd}^{ester}(Z\rightarrow E) - \Delta\Delta G_{hyd}^{ion}(Z\rightarrow E)] \quad (4)$$

where $\Delta G_{gas}^{ion}(Z)$ and $\Delta G_{gas}^{ion}(E)$ are ionization free energies for (Z)- and (E)-methyl acetate in the gas phase, which can be determined by ab initio calculations, $\Delta\Delta G_{hyd}^{ester}(Z\rightarrow E)$ is the relative free energy of hydration between the ester conformers, and $\Delta\Delta G_{hyd}^{ion}(Z\rightarrow E)$ is the difference in free energy of hydration between the two ions.

Including solvation free energies (Table 2), the gas-phase acidity difference (Table 1) between (E)- and (Z)-methyl acetate is reduced to 3.4 kcal/mol in aqueous solution, resulting from compensating solvent effects of merely 1 kcal/mol. It is interesting to note that Arnett and Harrelson assigned a free energy contribution of 3−4 kcal/mol for each E ester linkage, which is in agreement with the present results.[9] The computed overall solvent effect on acidity of methyl acetate is also in excellent accord with a value of 0.7 kcal/mol from OPLS Monte Carlo calculations by Evanseck et al.[10]

Meldrum's Acid. A simple additive picture has often been evoked to explain the exceptionally high acidity of 11.7 kcal/mol in Meldrum's acid relative to dimethyl malonate.[9] Thus, it was suggested that the conversion of two Z esters to two E esters would contribute 10.6 kcal/mol using the estimate of 5.3 kcal/mol per ester bond by Evanseck et al.[10] This would have accounted for most of the acidity difference, plus about 1 kcal/mol nonadditive effect, between Meldrum's acid and dimethyl malonate.[10] However, previous analyses have all used either energy or enthalpy difference, rather than the free energy. Indeed, if free energy is used as is done in the present study, an E/Z acidity difference of 3.4 kcal/mol in water is obtained, which is substantially smaller than the previous estimate, and would only contribute 60% of the 11.6 kcal/mol. Consequently, the high acidity of Meldrum's acid relative to dimethyl malonate cannot be simply accounted for as a result of the conversion of two Z esters in dimethyl malonate to two E esters. Surprisingly, computation of the gas-phase acidity of Meldrum's acid has not been performed previously. Thus, its origin has never been directly probed.

To provide insight into the origin of the high acidity of Meldrum's acid, we have further analyzed this system by determining "strain energies" due to ring-closure in lactones, which in principle include both the effect of the Z to E ester conversion and ring-strain energy. Since both cyclohexane and all-trans *n*-heptane are considered to be strain free, they are used as the reference species in the following isodesmic reactions.



To begin, we have considered various conformations of the reference compound, dimethyl malonate, which were found to have virtually no effect (less the 0.4 kcal/mol) on its gas-phase acidity (Table 5). Thus, we used the expected, all-trans conformation of dimethyl malonate in the analysis. Table 6 lists the computed strain energies for the simple δ-lactone, 2-oxacyclohexanone (δ-valerolactone), Meldrum's acid, and their anions. For valerolactone, the total strain energy is estimated to be 9.8 kcal/mol by B3LYP/aug-cc-pVDZ calculations (Table 6), which is in good agreement with an estimate of 10.7 ± 0.7 kcal/mol derived from experimental enthalpies of hydrolysis and reduction reactions.[40] Considering an E/Z energy difference of 7.2 kcal/mol for methyl acetate (Table 1), we estimate that cyclization in lactone formation further brings about 2.6 kcal/mol destabilization relative to methyl pentanoate. The corresponding strain energy for δ-valerolactone anion is 5.5 kcal/mol (vs a value of 2.1 kcal/mol for the methyl acetate anion). Thus, there is an even larger ring-destabilization effect (3.4 kcal/mol) on the enolate anion. Combining these strain effects, it translates to a predicted increase in acidity of 4.3 [9.8 − 5.5] kcal/mol for δ-valerolactone over the straight-chain analogue methyl pentanoate. This is consistent with the energy difference for the ionization of (Z)- and (E)-methyl acetate in the gas phase

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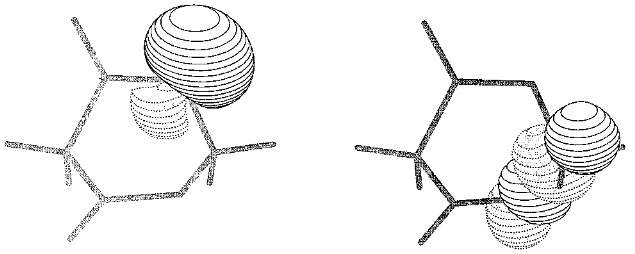

Figure 3. Schematic representation of the natural bond orbital for an ester oxygen lone pair (n_O) and the natural antibonding orbital of the C_4−O bond in Meldrum's acid, which are positioned for anomeric interactions. Electron contours are made at the level of 0.005 e/bohr^3.

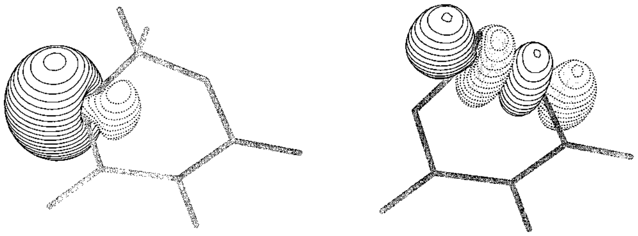

Figure 4. Schematic representation of the natural bond orbital for an ester oxygen lone pair (n_O) and the natural antibonding orbital of the C_4−O bond in the enolate anion of Meldrum's acid, which are positioned for anomeric interactions. Electron contours are made at the level of 0.005 e/bohr^3.

(Table 1) and experimental observations.[6,7,9,40] Thus, relative strain energies from isodesmic reactions can be used to assess the E ester effect to account for the higher acidity of small lactones.

If additivity was valid, the conversion of two Z esters into two E isomers in Meldrum's acid would introduce strain energies of at least 19.6 [2 × 9.8] kcal/mol. Surprisingly, what we actually find is a strain energy of only 5.7 kcal/mol for Meldrum's acid relative to that of dimethyl malonate (Table 6), which is even 4 kcal/mol smaller than that of δ-valerolactone. Clearly, there is a strong *stabilizing* effect in Meldrum's acid. Furthermore, the enolate anion of Meldrum's acid is predicted to be even "less strained" than the linear reference compound, dimethyl malonate anion, by 7.9 kcal/mol. Therefore, there is, in fact, no destabilizing effect due to the presence of two E ester bonds in Meldrum's acid.[4,5,9,10,12] The notion that the E ester effect, which is a destabilizing effect, is responsible for the exceptionally high acidity of Meldrum's acid is not supported by our computational results. Instead, the results in Table 6 indicate that there is significant stereoelectronic effect when two lactone units are cemented together, which can be attributed to anomeric interactions for the delocalization of electron density from the oxygen lone pair orbitals into the σ^* orbitals between the ester oxygens and the C_4 carbon. These interactions lead to *stabilization* of the dilactone Meldrum's acid and its anion, rather than destabilization, relative to the reference species, dimethyl malonate.

To quantify the difference in anomeric effect between Meldrum's acid and its enolate anion, we carried out natural orbital analysis and used Weinhold's natural orbital deletion scheme to determine the stabilization energy due to $n_O \rightarrow \sigma_{CO}^*$ charge delocalization.[11] In this scheme, the localized bonding and antibonding orbitals are first localized through natural orbital analysis of Weinhold.[11] Then, the bonding and antibonding orbital pairs corresponding to anomeric interactions are removed to evaluate the energy of a reference system, lacking anomeric charge delocalization. The energy difference between this reference state and the fully delocalized ground state gives a quantitative measure of the anomeric stabilization, ΔE_{AS}.[41] Illustrated in Figures 3 and 4 are two interacting orbital pairs, one for Meldrum's acid and another for its enolate anion. Note that in each species, there are two lone pair orbitals participating in anomeric interactions from each of the ester oxygens. Thus, a total of six orbitals (4 occupied, lone pair orbitals and 2 unoccupied, σ^* orbitals) are removed in the calculation. The computed ΔE_{AS} is −22.2 kcal/mol for Meldrum's acid and −25.5 kcal/mol for its enolate anion at the HF/aug-cc-pVDZ level, giving rise to a net effect of 3.3 kcal/mol in favor of the anion. The larger anomeric stabilization in the anionic species is due to its greater electron density on oxygen and high orbital energy, both of which favor stronger bonding−antibonding orbital interactions. Consequently, the high acidity of Meldrum's acid relative to methyl malonate results from a combination of the relative acidity difference between E and Z conformations of two ester bonds, which contribute 8.6 kcal/mol (from valerolactone) in the gas phase, and a preferential anomeric stabilization of the enolate anion by 3.3 kcal/mol. The sum of these factors, which is 11.9 kcal/mol, is consistent with the computed value of 11.4 kcal/mol (Table 5).

Conclusions

The present study provided new insight into the origin of the unusually high acidity of Meldrum's acid. We found that the stabilization of the enolate anion of Meldrum's acid due to anomeric charge delocalization in a cyclic system makes significant contributions to the enhanced acidity. The conversion of two Z esters to two E esters in Meldrum's acid in fact stabilizes the system, which is in contrast to previous proposals emphasizing destabilization effects. To ascertain that the acidity difference between Meldrum's acid and dimethyl malonate is an intrinsic (gas phase) property, solvent effects were determined on model compounds by combined ab initio QM/MM Monte Carlo simulations on the E and Z conformers of methyl acetate and the corresponding enolate anions. The computed free energy preference for the Z isomer over the E ester is 7.6 kcal/mol at the B3LYP/aug-cc-pVDZ level in the gas phase, and is reduced to 3.2 kcal/mol in aqueous solution. The free energy difference between the two conformers of the enolate anion is 3.2 kcal/mol in the gas phase and −0.2 kcal/mol kcal/mol in water, in favor of the E ester enolate anion. The predicted overall solvent effect of 1 kcal/mol is in good agreement with previous Monte Carlo simulations (0.7 kcal/mol).[10] Thus, the enhanced acidity of 4.4 kcal/mol for (*E*)-methyl acetate in the gas phase is reduced to 3.4 kcal/mol in water. The present simulations also yield the potential of mean force for the torsional rotations about the ester bond in both its neutral (methyl acetate) and ionic (enolate) forms. The activation barrier is reduced by 3 kcal/mol for methyl acetate to a value of ca. 10.5 kcal/mol in water, and by 2 kcal/mol for its enolate anion to 5 kcal/mol. Aqueous solvation also exerts significant effects on the solute geometry, particularly for the enolate ion. The present study also shows that combined ab initio QM/MM simulations can be explicitly carried out in condensed phase simulations for the study of solvent effects on the structure and reactivity in organic chemistry.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for partial support of this research.

Supporting Information Available: Results on bimolecular interactions determined by the combined ab initio QM/MM potential that is used in the present calculation (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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