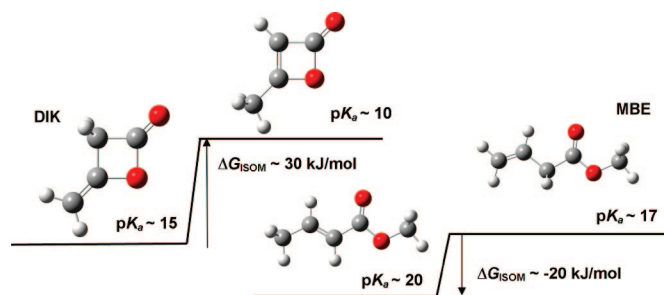# Computational Study of the Acid Dissociation of Esters and Lactones. A Case Study of Diketene

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A computational study of the aqueous pK_a of some saturated and unsaturated cyclic and linear esters and ketones was carried out at the DFT-B3LYP 6-31++G(2df,2pd), CBS-Q, and G2 levels, with the integral equation formalism polarizable continuum model for solvation, using a proton exchange mechanism. The influence of unsaturation, position of the double bond, and cyclization were studied. The computational results show that (a) in all cases studied except that of diketene (4-methylene-2-oxetanone), the α-β unsaturated isomer is 20−30 kJ mol^{-1} lower in energy that the β-γ unsaturated one; (b) α-β unsaturation lowers the pK_a of an ester ~6 units, whereas β-γ unsaturation lowers it by ~10 units, and cyclization lowers the pK_a by ~3 units. In order to check the predictive power of the methodology, the acid dissociation constant of diketene in water was measured via kinetic study of its base-catalyzed hydrolysis. The pK_a value obtained (15.2 ± 0.3) is in keeping with the expected value for a β-γ unsaturated β-lactone. This low value also suggests that deprotonated diketene does not interconvert to a more stable, less acidic α-β unsaturated isomer, which is also consistent with computational results.

Introduction

As a plausible alternative to experiment in the cases of intermediates and very weak or very strong acids, accurate computational calculation of pK_a values has attracted a great deal of attention,[1−8] and several approaches have been designed and applied to different compounds such as carboxylic acid derivatives,[9] alcohols,[10] carbenes,[11] amines,[12] phosphoranes,[13] and substituted phenols,[14] in aqueous as well as organic media.

Since esters are weak acids that rapidly hydrolyze in basic aqueous media, the experimental determination of their acid dissociation constants is challenging, and generally pK_a values are accurately known only for esters with acidifying substituents.[15−18]

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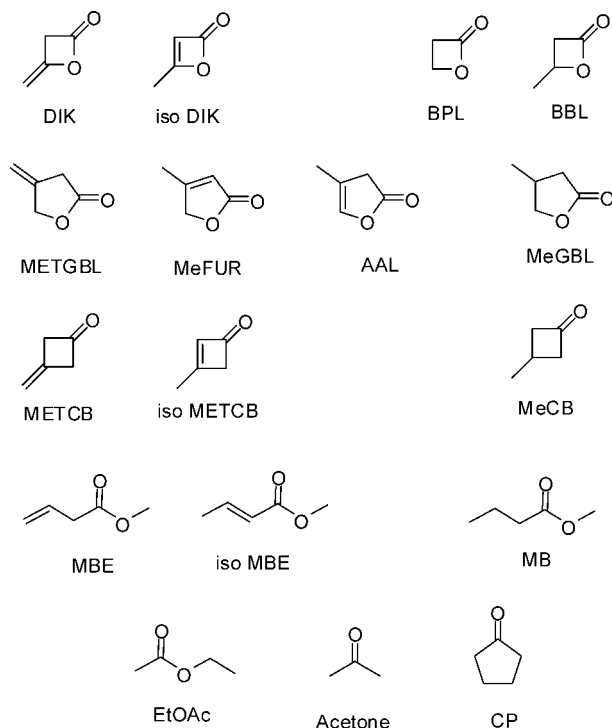
FIGURE 1. Chemical structures of the molecules studied.

Given the scarceness of experimental values and to test contemporary methodologies for theoretical pK_a calculation, a first-principle study of the acidity of some alkylic esters and ketones (Figure 1) has been carried out, and the influence of some structural parameters (presence and position of a double bond and cyclization) on the acid dissociation constant has been studied.

To check the quality of the results and the predictive power of the methodology, we have estimated the pK_a of diketene, 4-methyleneoxetan-2-one, by studying its base hydrolysis and compared it with the computational prediction.

Diketene is a reactive β-lactone obtained from the dimerization of ketene.[19] For many years its structure was an unknown challenge, some isomers being considered. The discussion was finally settled with the structure (DIK) shown in Figure 1 once the X-ray structure and NMR spectra of diketene had been obtained.[20–22] Diketene has the double bond as an exocyclic methylene group instead of the, presumably more stable, α-β unsaturation.

The reactivity of diketene is of interest because of its wide applications in organic synthesis,[23–33] where its common use

as an acetoacetylating agent has somewhat been superseded,[19,34] and the fact that it is not active as a carcinogen,[35–43] even though analogue β-lactones such as β-propiolactone and β-butyrolactone are powerful carcinogens.[44,45]

While the structure of diketene was still being discussed, the acidity of its α-hydrogen was considered. An extremely low value of $pK_a \approx 7$ was proposed but rapidly discarded.[46] The value obtained here is $pK_a \approx 15.2$ (see below), which is very low in comparison to saturated nonfunctionalized open-chain esters, with pK_a values around 25.[47]

Given its low pK_a and its distinctive structure, with a β-γ unsaturation, diketene constitutes a good probe for the capacities of the methodology.

Choice of Structures. The molecules chosen for the study are shown in Figure 1. In order to check how the pK_a value of an ester is affected by α-β and β-γ unsaturation, cyclization, and substitution of the ester group by a keto group, we chose the following molecules:

• diketene, its α-β unsaturated isomer (iso DIK), β-propiolactone (BPL), and β-butyrolactone (BBL); the saturated analogue of diketene

• a five-membered lactone with a methylene group on the β-carbon (METGBL), its other β-γ unsaturated isomer α-angelicalactone (AAL), its α-β unsaturated isomer (MeFUR), and the analogue lacking unsaturation (MeGBL)

• the ketone analogue of diketene (METCB), its α-β unsaturated isomer (iso METCB), and their saturated counterpart (MeCB)

• the simplest open-chain ester with a β-γ unsaturation, methyl but-3-enoate (MBE), its α-β unsaturated isomer methyl but-2-enoate (iso MBE), and their saturated analogue methyl butyrate (MB)

• ethyl acetate, chosen as a reference for the relative pK_a calculations, and acetone and cyclopentanone (CP), molecules chosen to check the accuracy of the method since both their gas-phase acidities and acid dissociation constants are well-known.

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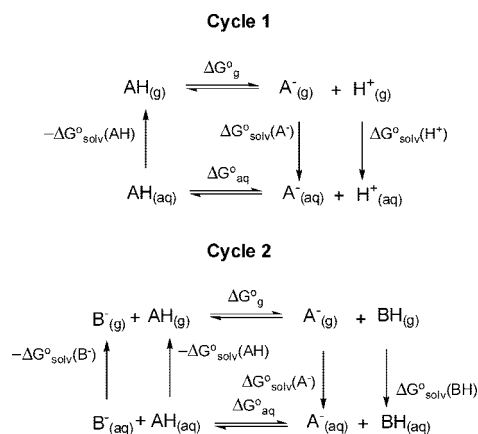(23) Tanaka, T.; Hayashi, M. *Synthesis* **2008**, 3361.

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SCHEME 1. Thermodynamic Cycles To Calculate Aqueous-Phase Acidities

Cycle 1

Cycle 2

Methodology and Computational Details

Computational Calculation of Acid Dissociation Constants. The computational calculation of pK_a values is very demanding. It may be seen from eq 1 that an error of 5.7 kJ mol^{-1} in ΔG°_{aq} results in a deviation of 1 pK_a unit.

$$pK_a = -\log K_a = \frac{\Delta G^\circ_{aq}}{2.303RT} \quad (1)$$

Different thermodynamic cycles have been proposed for this calculation, most commonly with the forms shown in Scheme 1. Generally the gas-phase proton affinities are computed accurately within 1−2 kcal mol^{-1} of the experimental value, whose uncertainty is also close to that figure, and the biggest source of error lies in the solvation energies.[48−53]

In Cycle 1,[54−56] the gas-phase free energy of reaction is calculated using high-level theoretical methods, and then a polarizable continuum method is used to calculate solvation energies. The values so obtained are often said to be *absolute* pK_a's, since no experimental references are used. This method has a drawback: the free energy of solvation of the hydronium ion cannot be calculated easily, and PCM methods underestimate it,[57] so experimental values are often used. There is a broad range of proposed values (from −254 to −261 kcal mol^{-1}),[58] which differ sufficiently to make the final results change appreciably. Also, the short-range solvent−solute interactions (hydrogen bonding, ion-dipole, etc.), which are very important in the case of ionic solutes are not rigorously modeled so the method is likely to introduce systematic errors. Finally a thermodynamic correction of $-RT \ln V$ has to be considered because the gas-phase calculations are referred to a standard state of 1 atm and the solvation calculations are referred to a

standard state of 1 mol dm^{-3}. ΔG°_{aq} is calculated in this cycle with eq 2:

$$\Delta G^\circ_{aq} = \Delta G^\circ_g - \Delta G^\circ_{solv}(AH) + \Delta G^\circ_{solv}(A^-) + \Delta G^\circ_{solv}(H^+) \quad (2)$$

In Cycle 2,[5,8,59−62] a proton exchange reaction with a species (BH), similar to AH, whose pK_a is well-known experimentally is used, so the solvation energy of H$^+$ is unnecessary. This method affords *relative* pK_a's, since an empirical reference value is needed. The use of a homodesmic reaction allows (partial) compensation of the effects that could be due to the method, systematically evaluating differently gas-phase energies and solvation energies for ions or neutral molecules, since there is both an ion and a neutral molecule on each side of the chemical equation. The effect of solvent hydrogen bonding, which is not taken into account in SCRF models, is also diminished, because the species on both sides of the chemical equation should show very similar degrees of hydrogen bonding with the solvent. This method has been shown to yield pK_a values within ±1 unit of experimental value for moderately strong acids.[9,10] The quality of the results depends strongly on the similarity between AH and BH. The second cycle also eliminates the need for thermodynamic correction.

For these reasons we chose this thermodynamic cycle, in which the pK_a is calculated via eqs 3 and 4, using ethyl acetate as a reference ($pK_a = 25.6$).[63]

$$pK_a = -\log K_a = pK_a(BH) + \frac{\Delta G^\circ_{aq}}{2.303RT} \quad (3)$$

$$\Delta G^\circ_{aq} = \Delta G^\circ_g - \Delta G^\circ_{solv}(AH) - \Delta G^\circ_{solv}(B^-) + \Delta G^\circ_{solv}(A^-) + \Delta G^\circ_{solv}(BH) \quad (4)$$

The inclusion of some explicit solvent molecules, often as few as one, also improves the results.[8,64]

Computational Details. All calculations were performed using Gaussian 03.[65] Gas-phase structures were optimized at the DFT-B3LYP[66,67] 6-31++G(2df,2pd), CBS-Q, and G2 levels, and all structures were checked to be true minima (zero imaginary frequencies).

The complete basis sets methods (CBS) are a model chemistry that uses a complete basis set extrapolation of the correlation

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TABLE 1.   Gas-Phase and Aqueous-Phase Free-Energy Differences between Isomers

| | ΔG_{isom} (kJ mol^{-1}) | | | | | |
| | DFT-B3LYP | | CBS-Q | | G2 | |
	gas	aq	gas	aq	gas	aq
DIK	−26.1	−30.4	−30.5	−35.1	−27.0	−31.2
METGBL	36.5	39.7	35.0	37.9	33.2	36.4
AAL	18.9	28.4	17.4	27.1	16.7	26.5
METCB	19.9	22.2	18.0	19.8	13.2	15.3
MBE	22.5	20.9	23.3	21.1	16.6	14.6

energy, performed at the MP2 level of theory and then corrected to the CCSD(T) level via additivity corrections.[68]

The G2 method developed by Pople and co-workers[69] uses an extrapolation scheme similar to CBS. An initial geometry is calculated at the HF/6-31G(d) level, and then harmonic frequencies are calculated and scaled by 0.8929 to give the zero point energy. Then the geometry is refined at the MP2(full)/6-31G(d) level, and this geometry is used for a series of single point calculations, which together with empirical corrections are used to arrive at a final G2 energy.

Solvation free energies were computed as single point calculations via the SCFVAC keyword on the gas-phase geometries using the Gaussian 03 default Integral Equation Formalism IEF-PCM[70−72] at the HF/6-31+G(d) level of theory. The UAHF radii were used, as suggested by the software recommendations. Other levels of theory were also tested, with inferior results (see Supporting Information): HF/6-31++G(2df,2pd) DFT B3LYP/6-31+G(d) and DFT-B3LYP/6-31++G(2df,2pd) DFT.

Results and Discussion

Acid Dissociation Constant of Open Chain and Cyclic Esters. Stability of the Isomers. First, the influence of the position of the double bond on the free energy of each isomer was studied. The differences in free energy among the different isomers of the unsaturated species, choosing the α-β unsaturated one as reference (ΔG_{isom}), are shown in Table 1.

Gas Phase. It can be seen that all three methods give very similar results for the differences. Nevertheless, the absolute values of the gas-phase free energies (see Supporting Information, G_{gas}) differ significantly depending on the computational method used; CBS-Q and G2, both high-level methods that use empirical corrections, give similar absolute values differing by less than 0.02 hartree, whereas DFT-B3LYP 6-31G++(2df,2pd) values are almost 0.5 hartree lower in free energy. The use of relative free energies, either between isomers or protonated and deprotonated especies, cancels this effect.

In all cases but one (diketene), the most stable isomer is the α-β unsaturated one; AAL, METCB, and MBE are about 20 kJ mol^{-1} less stable than their α-β unsaturated counterparts, and the difference rises to 35 kJ mol^{-1} in the case of METGBL, the exocyclic double bond being more unstable than the endo isomer.

TABLE 2.   Gas Phase Acidities and Effect of Unsaturation, $AH_g \rightarrow A_g^- + H_g^+$

| | ΔG_g° (kJ mol^{-1}) | | | | $\Delta\Delta G_{g\ unsad}^\circ$ (kJ mol^{-1}) |
ester	DFT-B3LYP	CBS-Q	G2	mean^a	mean^a
DIK	1435.8	1436.4	1446.5	1439.6 ± 6.0	−71.8 ± 2.3
iso DIK	1409.7	1405.8	1419.5	1411.7 ± 7.1	−99.6 ± 4.4
BPL	1509.4	1511.5	1513.7	1511.5 ± 2.2	
BBL	1507.5	1510.5	1516.0	1511.3 ± 4.3	
METGBL	1416.6	1426.5	1426.5	1423.2 ± 5.7	−84.2 ± 2.0
MeFUR	1453.2	1454.4	1458.2	1455.3 ± 2.6	−52.1 ± 2.4
AAL	1434.6	1437.0	1436.5	1436.0 ± 1.3	−71.3 ± 2.7
MeGBL	1503.0	1508.9	1510.2	1507.4 ± 3.8	
METCB	1419.4	1426.4	1428.0	1424.6 ± 4.6	−72.1 ± 3.7
iso METCB	1439.3	1444.5	1441.4	1441.7 ± 2.6	−55.0 ± 3.7
MeCB	1495.5	1495.2	1499.3	1496.7 ± 2.3	
MBE	1444.2	1455.7	1463.7	1454.5 ± 9.8	−78.5 ± 10.9
iso MBE	1466.7	1479.0	1480.2	1475.3 ± 7.5	−55.6 ± 11.5
MB	1530.4	1526.5		1528.5 ± 2.8	
EtOAc	1524.4	1533.1	1535.4	1531.0 ± 5.8	
acetone	1517.2	1515.8	1520.8	1517.9 ± 2.6	
CP	1498.8	1505.7	1510.8	1505.1 ± 6.0	

^{a} Standard deviations were calculated considering the ΔG_g° and $\Delta\Delta G_{g\ unsad}^\circ$ values obtained with each method as independent results.

TABLE 3.   Experimental Gas-Phase Acidities[74] and pK_a Values

	ΔG_g° (kJ mol^{-1}) $AH_g \rightarrow A_g^- + H_g^+$	pK_a $AH_{aq} \rightarrow A_{aq}^- + H_{aq}^+$
EtOAc	1527 ± 17	25.6
acetone	1516 ± 8	19.6
CP	1507 ± 17	16.5

Aqueous Phase. The effect of solvation on the energy differences among isomers is small (less than 5 kJ mol^{-1}) except in the case of AAL, which in water is about 10 kJ mol^{-1} more stabilized than in the gas phase with respect to MeFUR.

The average for the three methods, for the isomerization reaction of METGBL → AAL is $\Delta G_{isom} = -10.6$ kJ mol^{-1}, which is in agreement with the reported value of -8.9 ± 0.2 kJ mol^{-1} at 25 °C in cyclohexane.[73]

The most significant case is that of diketene. The β-γ unsaturated isomer is ~30 kJ mol^{-1} more stable, even though isomerization to the α-β unsaturated compound is favored in both METCB, with a very similar structure, and METGBL, with a very similar functionalization.

Acid Dissociation Constants. Gas-Phase Acidities. Table 2 shows the values obtained for the gas-phase acidities of the proposed molecules. The values are consistent among the different methods, with standard deviations equal to or below 6 kJ mol^{-1}, except in the cases of iso DIK, MBE and iso MBE, which are below 10 kJ mol^{-1}.

Results for MB at the G2 level could not be obtained because the molecule has too many orbitals for the system to be calculated at this level of theory with the software.

Comparison of the experimental results (Table 3) for the compounds ethyl acetate, acetone, and CP shows the accuracy of the three methods, since the experimental values of their gas-phase acidities are in excellent agreement with the theoretical values.

The saturated lactones are about 15−20 kJ mol^{-1} more acidic than the open-chain esters: BPL, BBL, and MeGBL as compared to EtOAc and MB; DIK, METGBL, and AAL as compared to MBE; and MeFUR as compared to iso MBE.

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TABLE 4. pK_a Values and Effect of Unsaturation

| ester | pK_a | | | | ΔpK_a unsatd |
	DFT-B3LYP	CBS-Q	G2	mean[a]	mean[a]
DIK	13.8	11.7	13.7	13.1 ± 1.2	−10.6 ± 0.4
iso DIK	8.4	5.5	8.3	7.4 ± 1.6	−16.3 ± 0.8
BPL	24.2	21.7	23.3	23.1 ± 1.3	
BBL	23.9	22.5	24.6	23.7 ± 1.1	
METGBL	13.6	13.3	13.7	13.5 ± 0.2	−8.8 ± 0.5
MeFUR	16.7	14.9	16.0	15.9 ± 0.9	−6.5 ± 0.6
AAL	11.8	10.1	10.5	10.8 ± 0.9	−11.6 ± 0.9
MeGBL	22.4	21.6	23.0	22.3 ± 0.7	
METCB	12.2	10.7	12.0	11.6 ± 0.8	−6.9 ± 0.4
iso METCB	16.0	14.2	14.7	15.0 ± 0.9	−3.5 ± 0.3
MeCB	19.5	17.5	18.6	18.5 ± 1.0	
MBE	16.2	16.1	17.9	16.7 ± 1.0	−9.5 ± 1.3
iso MBE	19.8	19.8	20.5	20.0 ± 0.4	−5.8 ± 1.3
MB	26.5	24.7		25.6 ± 1.3	
acetone	21.9	20.2	20.7	20.9 ± 0.9	
CP	19.7	19.4	19.9	19.7 ± 0.3	

[a] Standard deviations were calculated considering the pK_a and ΔpK_a unsatd values obtained with each method as independent results.

SCHEME 2. Alkaline Hydrolysis of Diketene
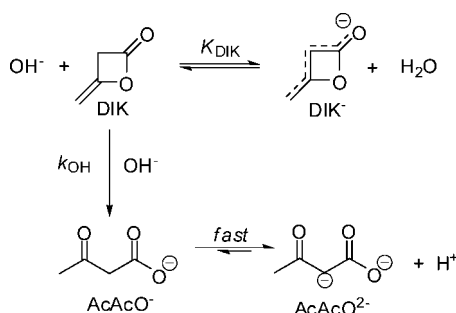
This effect is similar in the case of MeCB and CP, cyclic ketones in which the cyclization lowers the acidity by ~15 kJ mol^{-1} with respect to acetone. Also, MeCB is about 15 kJ mol^{-1} more acidic than BBL, the analogous lactone.

Table 2 also shows the average effect of the unsaturation on gas-phase acidity (the values obtained with each method are contained in Supporting Information), that is, the difference in the gas-phase acidities between the saturated and unsaturated analogues ($\Delta\Delta G_{g}^{\circ}{}_{unsatd} = \Delta G_{g}^{\circ}{}_{unsatd} - \Delta G_{g}^{\circ}{}_{satd}$). It can be seen that, with the exception of iso DIK, the α-β unsaturation lowers the value of the acidity by about 50 kJ mol^{-1}, whereas the β-γ unsaturation lowers it by about 70 kJ mol^{-1}. This difference increases to almost 85 kJ mol^{-1} in the case of METGBL. The acidity of diketene therefore lies in the range of the values obtained for β-γ unsaturated lactones.

When only the most stable isomer of each unsaturated species is compared (MeFUR, DIK, iso METCB, and iso MBE), diketene is observed to be exceptionally acidic, although its acidity is similar to that of other cyclic β-γ unsaturated esters.

Aqueous Phase. Table 4 shows the pK_a values obtained with the DFT-B3LYP, CBS-Q, and G2 gas-phase geometries, solvated with the IEF-PCM HF 6-31+G(d) SCRF method.

Comparison of the experimental results for acetone and CP reveals the accuracy of the three methods (Table 3), suggesting that the largest source of error lies in the solvation energies, given the accuracy of the gas-phase acidities, and that this approach is not useful to predict exact pK_a values, although the relative differences are valid for discussion.

The value predicted for MB, which lacks any acidifying substituents, is very close to the experimental one for EtOAc.

The value obtained for diketene is very close to the one obtained experimentally by us (~15.2, see below), confirming that the

methodology here used can help in the understanding of the anomalous case of the acid dissociation constant of diketene.

The trends observed in the gas-phase acidities also hold for solution, since the solvation free energies are very similar for all neutral species and all anions (see Supporting Information), which is not unexpected, given that all anions are very similar. The studied anions are well delocalized, especially the unsaturated ones, which means that their interaction with the solvent is not as strong as it would be for more localized anions. These would show higher solvation energies, and explicit solvent interactions would be more important.

A comparison shows that the lactones are about 3 pK_a units more acidic than the open-chain esters: BPL, BBL, and MeGBL as compared to EtOAc and MB; DIK, METGBL, and AAL as compared to MBE; and MeFUR as compared to iso MBE.

This effect is smaller in the case of MeCB and CP, in which the cyclization lowers the acidity less than 2 pK_a units with respect to acetone. Also, MeCB is about 5 pK_a units more acidic than BBL, the analogous lactone.

The average effect of the unsaturation on the pK_a is also shown in Table 4 (the values obtained with each method are contained in Supporting Information). ΔpK_a unsatd stands for the difference between the pK_a of an unsaturated species and its saturated counterpart (ΔpK_a unsatd = pK_a unsatd − pK_a satd). The average effect on pK_a of α-β unsaturation, excluding iso DIK, is a decrease of approximately 6 units for the esters (MeFUR and iso MBE) and 4 units for the ketone. β-γ unsaturation lowers the pK_a by about 10 units in the cases of esters (METGBL, AAL, DIK, and MBE) and 7 units in the case of the ketone. The case of iso DIK is special, because the decrease in pK_a is very high at ~16. This can be understood in terms of the instability of iso DIK.

Factors Influencing the pK_a of Diketene. If the effects of cyclization and β-γ unsaturation are additive, diketene would be ~13 pK_a units more acidic than its open-chain saturated counterpart (pK_a ≈ 25.5), this is in very good agreement with the calculated value of 13.1 ± 1.2. While the experimental value is higher (see below), the pK_a of diketene is approximately what would be expected for a β-γ unsaturated lactone.

What makes the case of diketene anomalous is that its α-β unsaturated isomer is unstabilized; unlike all of the other isomers, iso DIK is ~30 kJ mol^{-1} higher in energy than DIK. Also, the ΔpK_a unsatd for diketene is in agreement with that of similar molecules, and the ΔpK_a unsatd for iso DIK is exceptionally high. This suggests that iso DIK is exceptionally unstabilized rather than diketene being stabilized.

Thus, while other β-γ unsaturated lactones are as acidic as diketene, once deprotonated they would rapidly interconvert to the more stabilized, less acidic α-β unsaturated isomers.

Kinetic Estimation of the pK_a of Diketene. The base hydrolysis reaction of diketene is shown in Scheme 2.

K_{DIK} is defined as

$$K_{DIK} = \frac{[DIK^-]}{[DIK][OH^-]} \quad (5)$$

If $[DIK]_{Tot}$ stands for the total amount of unreacted diketene, be it protonated or not, then

$$[DIK^-] = \frac{[OH^-]}{1 + K_{DIK}[OH^-]}[DIK]_{Tot} \quad (6)$$

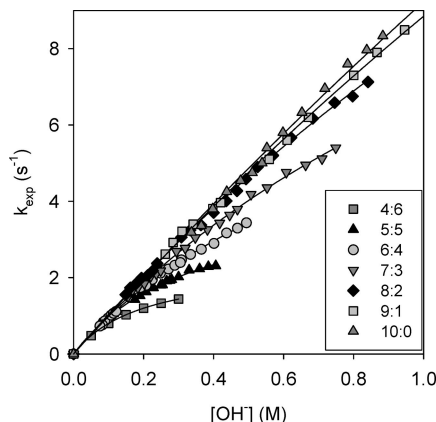The product of the hydrolysis reaction, acetoacetate,[19,43,46] rapidly

FIGURE 2. Dependence of k_{exp} on [OH$^-$] in different water–dioxane mixtures (v:v).

TABLE 5. Experimental Values for K_{DIK} in Different Water–Dioxane Media

water:dioxane (v:v)	K_{DIK} (M^{-1})^a
10:0	0.07
9:1	0.13
8:2	0.36
7:3	0.64
6:4	1.1
5:5	2.6
4:6	5.0

^{a} Values are reproducible within 15%.

deprotonates in the reaction conditions to its dianion. The rate equation for the formation of the acetoacetate dianion can be expressed as in eq 7, k_{OH} being the second-order rate constant.

$$r = \frac{d[AcAcO^{2-}]}{dt} = -\frac{d[DIK]_{Tot}}{dt} = k_{OH}[DIK^-] = $$

$$k_{OH}\frac{[OH^-]}{1 + K_{DIK}[OH^-]}[DIK]_{Tot} \quad (7)$$

The integrated counterpart of eq 7 is

$$[AcAcO^{2-}] = [DIK]_0(1 - e^{-k_{exp}t}) \quad (8)$$

With k_{exp} being

$$k_{exp} = k_{OH}\frac{[OH^-]}{1 + K_{DIK}[OH^-]} \quad (9)$$

Figure 2 shows the dependence of the experimental rate constant (k_{exp}) on [OH$^-$] at different water–dioxane ratios, and the fit to eq 9.

The values obtained for K_{DIK} (Table 5) suggest that the acidity of diketene increases with the dioxane ratio. This can be interpreted in terms of the structure of the deprotonated form, which has the negative charge delocalized in the π-system of diketene (Scheme 2). As the water ratio decreases, the solvation of the hydroxide ion decreases more intensely than that of the deprotonated diketene, and the negative charge becomes more stabilized in the π-system of the molecule.

The acid dissociation constant $K_{a\ DIK}$ can be calculated as $pK_{a\ DIK} = pK_{DIK} + pK_w$. The effect of the dioxane ratio on K_w is strong, and several diverging values have been proposed for

K_w in the different media used in this work (with differences up to 2 pK_a units).[75–77] Accordingly, only the value for pure water was used, and hence $pK_{a\ DIK} = 15.2$, in keeping with the predicted value (see above).

Conclusions

The theoretical calculations of the stability and acid dissociation constants of esters in aqueous solution allow us to extract the following conclusions:

(i) In general, α-β unsaturated esters are 20–30 kJ mol^{-1} more stable than their β-γ unsaturated counterparts.

(ii) β and γ lactones and square cyclic ketones are 2–3 units more acidic than the corresponding open chain molecules.

(iii) The pK_a of an ester is lowered ∼10 units by β-γ unsaturation and ∼6 units by α-β unsaturation.

(iv) The experimental pK_a of diketene measured by us (∼15.2) is in keeping with the calculated values for other β-γ unsaturated lactones.

(v) The anomaly in the case of diketene consists of the fact that the α-β unsaturated isomer is ∼30 kJ mol^{-1} less stable than the β-γ unsaturated one, contrary to the theoretical and experimental results for other unsaturated cyclic and open-chain esters.

(vi) The methodology and levels of theory used here are valid for a semiquantitative discussion but are not sufficiently exact for accurate predictions.

Experimental Section

Kinetics. The kinetics of the base hydrolysis of diketene (1.0–2.5 mM) was studied in excess NaOH (0.01–1.0 M) at constant ionic strength in aqueous and aquo-organic media, ranging from 9:1 to 4:6 water/dioxane (v:v).

A modular 3-syringe Bio-Logic sequential mixing stopped-flow spectrometer SFM300 was used to monitor the reaction.

Formation of the acetoacetate dianion (AcAcO^{2-}) was monitored at $\lambda = 400$ nm, where it shows maximum absorption. The reactants and the reaction mixture were maintained at constant temperature (±0.05 °C) using a Lauda Ecoline RE120 thermostat. All runs were performed in quintuplicate.

Chemicals. Diketene (98%) was from Aldrich.

Note Added after ASAP Publication. In point 4 under **Choice of Structures**, methyl but-3-enoate was corrected in the version published ASAP May 28, 2009.

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