reading to the first-order rate equation.

Polarimetric Kinetic Procedure. Polarimetric measurements were taken on a Perkin-Elmer Model 241 polarimeter. Kinetic data were collected by a TI 980 computer using programs written by McMullen[42] and Tomasik.[40] The data were analyzed on an IBM PC using the same nonlinear, doubly weighted least-squares program mentioned above but assuming that the observed rotations are directly proportional to concentrations.

The kinetics measurements were taken by using a 10-cm quartz cell fitted with a water circulation jacket and maintained at a temperature of 25 °C with water circulated from a constant-temperature bath.[37]

A typical procedure for doing a kinetic experiment is as follows. The desired amount of compound was weighted into a 1-mL volumetric flask. The flask was filled to the mark with the solvent of choice, and the compound was dissolved by vigorous shaking or by use of a small stirring bar. The reacting solution was placed into a previously cleaned cell (rinsed several times with chloroform and dried with dry argon) and stoppered. The cell was placed in the instrument, and the circulating hoses were attached. Data collection was initiated after waiting approximately 5 min for an equilibrium temperature to be reached.

Product Determination. Product studies by ^2H NMR spectroscopy were performed in the following manner. A 1.0-mL sample of the reaction mixture (approximately 0.1 M in deuterium) was prepared in a 1.0-mL volumetric flask with a molar excess of 2,6-lutadine. This was transferred to a NMR tube, sealed, and allowed to react for more than 10 half-lives. The ^2H spectra were recorded using a Nicolet 360 MHz spectrometer at 55.4 MHz. The fourier transform NMR spectra were taken using between 500 and 1000 scans. Product ratios were determined by comparison of the weighed cutouts of the peaks.

Chemical shifts for products, which vary slightly with solvent, are as follows in 97T: 4-(trimethylsilyl)-2-butanol-*2-d*, δ 3.84; 4-(trimethylsilyl)-2-butyltrifluoroethyl-2-*d* ether, δ 3.69; methylcyclopropane-*1-d*, δ 0.78.

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A Spectacular Example of the Importance of Rotational Barriers: The Ionization of Meldrum's Acid[1]

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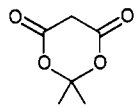
Abstract: The free energy of ionization of Meldrum's acid (I) is 11.68 kcal/mol more spontaneous than that of its acyclic analogue, dimethyl malonate. This energy difference must represent one of the *largest stereoelectronic effects in the literature of organic chemistry* and demands careful elucidation. This paper probes the problem by comparing the effects of various structural contributions to the carbon acidity of Meldrum's acid. The most dramatic effect results from increasing the size of the bislactone ring system. There is a rapid decrease in acidity between the 6-membered and 10-membered ring until the 13-membered ring has the same pK_a as dimethyl malonate. The obvious conclusion from the assembled results is that the difference between the acidities of Meldrum's acid and the larger ring bislactones or diesters lies in the barrier to rotation around the ester bonds. Over half of the 11.68-kcal/mol effect may be explained empirically through the 3–4-kcal/mol stabilization of the *Z* conformation of esters relative to the *E* conformation. Another 3 kcal/mol may be assigned to the cyclization effect seen also in the β-diketone series.

Meldrum[2] produced a product from the condensation of malonic acid and acetone which was so acidic that its structure was wrongly assigned as a carboxylic acid for 40 years until Davidson and Bernhard[3] showed it to be the bislactone I. The pK_a of I in water



Meldrum's acid (I)

is 4.83, putting it close to acetic acid and so far above all other α-carbonyl carbon acids that it could not be compared to them quantitatively using the classical aqueous pH scale.

Recently we[4] used Bordwell's DMSO/DMSYL system[5] to relate I to other well-known carbon acids such as the β-diesters represented by dimethyl malonate or the cyclic diketone, dimedone. The salient facts are summarized in Figure 1. Surprisingly, the effect of cyclizing the β-diester system from dimethyl malonate (pK_a = 15.87) to the bislactone I (pK_a = 7.32) reduced the standard free energy of ionization, $\Delta G°_i$, by 11.68 kcal/mol while the corresponding comparison for the acyclic β-diketone, acetylacetone (pK_a = 13.33) with dimedone (pK_a = 11.16) is only 3.07 kcal/mol. Thus, Meldrum's acid has a free energy of ionization that is over 5 kcal/mol more spontaneous than would be expected based on the cyclization of the diketone system. We related this remarkable result[4] empirically to the conformationally dependent dipole moments seen in a series of lactones by Huisgen and Ott[6] and theoretically to Deslongchamps orbital interpretation.[7]

Like other esters and lactones, I does not enolize in solution or in the crystalline state.[8,9] In contrast, its diketone analogue, dimedone, is totally enolized.

The question of the conformation of the ring has long been a matter for speculation and has now been settled, at least for the crystal, as being a boat.[9] Interestingly, a molecular mechanics

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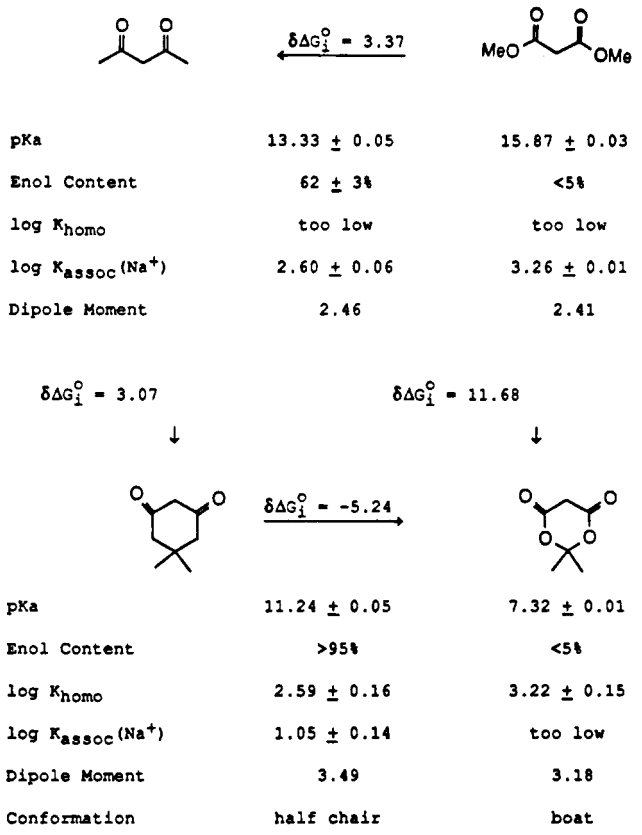

Figure 1. Comparison of various properties of cyclic and acyclic diketones and diesters with differences in standard free energies of ionization.

calculation[10] which we made long before the X-ray structure was published predicted its bond angles correctly within 2° and bond lengths within 0.001 Å.

In this article our previous interpretations of the behavior of I are tested through comparison against a series of related cyclic ketones, ethers, and lactones.

Experimental Section

Instruments and Analysis. Acidity constants were determined as described elsewhere[4,5] with one modification for monocarbonyl esters. These compounds deteriorated slowly under reaction conditions and the equilibrium absorbance of the indicator was determined by extrapolation of an absorbance vs. time plot to time zero. All keto/enol contents were determined by integration of ^{1}H NMR spectrum taken with an IBM NR-80 spectrometer using Me_2SO-d_6 (Merck).

Materials and Syntheses. All chemicals not mentioned in this section were prepared and/or purified as described previously.[1,4] Purity was checked by ^{1}H NMR, melting point, boiling point, GLC, and/or TLC where applicable. Cyclohexanone (Eastman), valerolactone (Aldrich), and methyl acetoacetate (Aldrich) were purified by distillation. Diacetamide (Aldrich) and 3,3-dimethylglutarimide (Aldrich) were purified by recrystallization from methanol and ethanol, respectively. Diethyl iminodicarboxylate[11] and 2,2-dimethyl-(4*H*)-pyran-6-one[12] (V) were prepared via literature procedures.

3,3-Dimethylcyclohexan-1-one (IV) was prepared by the procedure analogous to the one employed by Yamamoto et al.[13] for similar compounds. 3-Methyl-2-cyclohexen-1-one (Wiley Organics) was treated with dimethylcopperlithium and boron trifluoride etherate catalyst in THF solvent at -10 °C. The product was purified by flash chromatography on a silica column: ^{1}H NMR (80 MHz, $CDCl_3$) 2.2–2.4 (broad, 2 H, acidic $-CH_2-$), 1.25–1.8 (broad, 4 H, $-CH_2-$), 0.96 (s, 6 H, $-CH_3$); UV (ether) 275 nm; IR (neat, cm^{-1}) 2935, 2850, 1702, 1450, 1415, 1380, 1360, 1340, 1305, 1285, 1275, 1210, 1155, 1065, 960, 935, 880.

2,2-Dimethyl-(4*H*)-pyran-4,6-dione (II) was prepared by condensation of acetone with the dianion of methyl acetoacetate.[14] This dianion was formed by treating NaH (1 equiv), followed by *n*-butyllithium (1 equiv., 1.6 M in hexane), with methyl acetoacetate in THF. Cyclization was achieved by stirring the resulting acyclic product in 2 N NaOH(aq) at room temperature for 4 h. The solution was neutralized with 6 N HCl and the product was extracted with ether. The solvent was removed at reduced pressure and the resulting white crystals were recrystallized from ethanol/water: mp 126.0–126.5 °C; ^{1}H NMR (80 MHz, $CDCl_3$) 3.50 (s, 2 H, acidic $-CH_2-$), 2.70 (s, 2 H, $-CH_2$), 1.60 (s, 6 H, $-CH_3$). Anal. Calcd for $C_7H_{10}O_3$: C, 59.1; H, 7.1; O, 33.8. Found: C, 59.29; H, 7.32; O, 33.56.

2,2-Dimethyl-1,3-dioxane-4-one (VI) was prepared as follows. Dihydro-2,2-dimethyl-3(2*H*)-furanone was prepared by the method of Burke et al.[15] This compound was brought into reaction with a 2:1 complex of KF:*m*-chloroperbenzoic acid in dichloromethane solvent for 24 h at room temperature. The salts and remaining complex were removed by filtration. A clear viscous liquid was collected: ^{1}H NMR (80 MHz, $CDCl_3$) 4.05 (t, 2 H, $-CH_2O-$), 2.60 (t, 2 H, $-CH_2-$), 1.50 (s, 6 H, $-CH_3$); UV (ether) 280.2 nm; IR (neat, cm^{-1}) 2980, 2920, 1730, 1375, 1275, 1210, 1115, 975, 910, 800.

1,5-Dioxacycloheptadecane-2,4-dione was prepared by condensation of 1,12-dodecanediol (Aldrich) with malonyl dichloride (Aldrich) in benzene at 60 °C. This synthesis is similar to a crown ether synthesis reported by Bradshaw et al.[16] 1,12-Dodecanediol was insoluble in benzene but a suspension of 6.37 g (0.032 mol) in 200 mL of benzene was achieved with stirring. Malonyl dichloride (3.1 mL, 4.4 g, 0.032 mol) in 100 mL of benzene was added dropwise over 1 h. During the course of the reaction all of the solid disappeared as hydrochloric acid gas given off. The mixture was stirred at 60 °C for 30 min and at room temperature for additional 30 min. The volatiles were removed from the reaction mixture by rotary evaporation to yield a yellow semisolid material. This was dissolved in 30 mL of chloroform, and then 200 mL of hexane was added. At this point a yellow oil precipitated. The clear upper layer was decanted and the solvent was removed by rotary evaporation, yielding grainy white crystals. The product was recrystallized from acetone yielding 5.9 g (68%): mp 106–107 °C; ^{1}H NMR ($CDCl_3$) σ 4.20 (m, 4 H, $-CH_2O-$), 3.35 (s, 2 H, acidic $-CH_2-$), 1.8–1.1 (m, 20 H, $-CH_2-$). Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.6; H, 9.7; O, 23.7. Found: C, 66.80; H, 9.51; O, 23.81.

1,5-Dioxacyclotridecane-2,4-dione was prepared and purified in a manner analogous to that employed for 1,5-dioxacycloheptadecane-2,4-

Table I. Acidity Data for Cyclic and Acyclic β-Dicarbonyl Compounds in Dimethyl Sulfoxide at 25 °C

compound	pK_a
Esters and Lactones	
Meldrum's acid	7.32 ± 0.01
methyl Meldrum's acid	7.42 ± 0.01
ethyl Meldrum's acid	7.57 ± 0.01
1,5-dioxacycloheptadecane-2,4-dione	15.14 ± 0.06
1,5-dioxacyclotridecane-2,4-dione	15.22 ± 0.10
1,5-dioxecane-2,4-dione	12.99 ± 0.10
dimethyl malonate	15.87 ± 0.03
2,2-dimethyl-1,3-dioxan-4-one	23.25 ± 0.10
6,6-dimethylpyranone	24.45 ± 0.05
valerolactone	25.22 ± 0.07
ethyl acetate	27.45 ± 0.16
methyl 3-methoxybutyrate	26.53 ± 0.16
Ketones	
2,2-dimethylpyran-4,6-dione	10.50 ± 0.05
dimedone	11.24 ± 0.05
1,3-cyclohexanedione	10.30 ± 0.05
cyclohexanone	26.25 ± 0.03
3,3-dimethylcyclohexanone	25.84 ± 0.04
acetylacetone	13.32 ± 0.07
Nitrogen Acids	
diacetamide	17.89 ± 0.03
diethyl iminodicarboxylate	16.84 ± 0.05
3,3-dimethylglutarimide	17.28 ± 0.02

(10) The calculation employed Professor W. Clark Still's BACKMOD(MOD1) strain energy minimization program which uses the Allinger MM2 force field.
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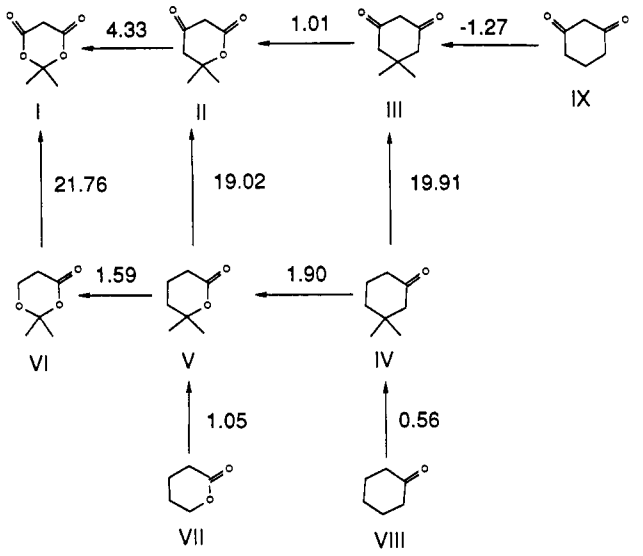

Figure 2. Effects of varying functionality on the acidities, in terms of kcal/mol of free energy, for six-membered cyclic ketones and esters.

dione, but 1,8-octanediol (Aldrich) was used instead of 1,12-dodecanediol. After purification 4.4 g (65%) was isolated: mp 85–86 °C; ^{1}H NMR ($CDCl_3$) σ 4.22 (m, 4 H, $-CH_2O-$), 3.40 (s, 2 H, acidic $-CH_2-$), 1.9–1.1 (m, 12 H, $-CH_2-$). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.7; H, 8.4; O, 29.9. Found: C, 61.57; H, 8.36; O, 30.08.

1,5-Dioxecane-2,4-dione was prepared in a manner analogous to that used for 1,5-dioxacycloheptadecane-2,4-dione, but 1,5-pentanediol (Aldrich, a liquid) was used instead of 1,12-dodecanediol. The product, 0.49 g (9%), was isolated after purification: mp 80–81 °C; ^{1}H NMR ($CDCl_3$) σ 4.2 (b, 4 H, $-CH_2O-$), 3.4 (s, 2 H, acidic $-CH_2-$), 1.9–1.5 (m, 6 H, $-CH_2-$).

Results

Table I combines acidity data relevant to the Meldrum's acid problem, most of which have not been published previously although a few are repeated from ref 4. Thermodynamic properties are referred to a standard state of infinite dilution in dimethyl sulfoxide following Bordwell's[5] convention for the process AH + DMSO = A– + $DMSOH^+$. Ion-pairing association constants and homohydrogen-bonding constants were all obtained using the Bordwell indicator titration methods, and the data were reduced using a program kindly supplied by Professor Bordwell.

Discussion

The anomalous acidity of Meldrum's acid, like any other structure–reactivity question, is a matter of comparison which in this case involves the effect of cyclization on ionization in the diester series as compared to the diketone series. Figure 1 poses the problem in terms of standard free energies of ionization which was discussed in ref 4 with respect to comparisons of mono- and dicarbonyl compounds. With the exception of Medrum's acid, ketones are generally somewhat more acidic than their ester analogues, and this is explained satisfactorily in terms of the resonance stabilization which normal acyclic esters enjoy that is not present in the initial state of ketones. This stabilization reduces the tendency of esters to enolize or to form enolate anions relative to analogous ketones.

Figure 1 summarizes some properties none of which appear to offer a promising explanation for the enormous difference in free energy of ionization between dimethyl malonate and Meldrum's acid. Clearly the effect is related to cyclization and we have probed our previous explanation in terms of the stereoelectronic difference between cis and trans esters by the systematic structural modifications presented in this paper.

Figure 2 investigates the stepwise introduction of ether functions, a second carbonyl group, and the *gem*-dimethyl functions as one passes from cyclohexanone (VIII) to Meldrum's acid (I). Comparison of VII with V, VIII with IV, or IX with III gives strong (but not conclusive) evidence that although introduction of *gem*-dimethyl groups or an ether oxygen may be weakly acidifying,

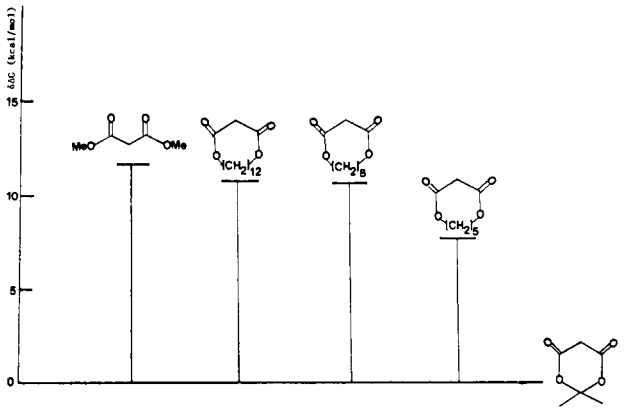

Figure 3. Effects of ring size on the acidities of cyclic β-Diesters.

neither would be adequate to explain the large difference on passing from dimedone (III) to I. Despite several attempts, we were unable to prepare 1,3-dioxane-4,6-dione (Meldrum's acid minus the *gem*-dimethyl group), but Figure 2 indicates that there is little reason to believe it would be more than 1 or 2 kcal/mol less acidic than Meldrum's acid. It might even be more acidic (see III and IX). This is an important point since Meldrum's acid is a boat and steric compression on the hydrogens at the 1 position could be a driving force for ionization, but since dimedone is a half-chair, the argument is not conclusive.

Clearly the addition of a second carbonyl group is very strengthening, but there is remarkably little difference between its effect on monoketone (IV) and lactone (V). Perhaps the most surprising difference in Figure 2 is the unusually large effect of introducing a second lactone oxygen in compound II which increases the acidity by 4.33 kcal/mol whereas introduction of the first lactone oxygen on going from IV to V was only worth 1.90 kcal/mol. Also interesting is the 1.59-kcal/mol increase on placing the remote oxygen on V to give VI.

In contrast to the oxygen compounds described, the nitrogen analogues of acetylacetone, dimethyl malonate, and dimedone (diacetamide, diethyl iminodicarboxylate, and 3,3-dimethylglutarimide) show virtually no effect either from cyclization or from the conversion of a methyl to an ether group. We interpret this simply in terms of the fact that the lone pair on nitrogen is already heavily involved in resonance with the flanking carbonyl groups and that this has relatively little effect on the process of removing a proton from the imino nitrogen.

Having disposed of any special effects from the presence of the *gem*-dimethyl group or of ether oxygens on the ring, the remaining question to be probed is the effect of cyclization itself on the ester function which we shall examine through the effect of ring size as Huisgen and Ott did in their classic study of the physical and chemical properties of the lactones.[6] Figure 3 shows the effect of size on acidity for Meldrum's acid and several of its homologues. Clearly ring size plays an important role in determining acidity. A large 13-membered ring system has a pK_a almost identical with that of dimethyl malonate while the 10-membered ring system shows an acidity almost halfway between Meldrum's acid and dimethyl malonate.

Unfortunately, we were unable to complete this interesting series. The synthetic difficulty of making intermediate-sized lactones is well-known, and despite many attempts by a variety of synthetic strategies we were unable to make the seven- and eight-membered rings.[7] Nonetheless, the results in Figures 2 and 3 make it clear that the unusual difference between the acyclic and cyclic esters compared to their cognate ketone compounds is primarily the result of restricted rotation in the ester function. This completely supports our previous analysis in which we treated Meldrum's acid as a bislactone in which the two (*Z*) trans-ester functions in the acyclic β-diesters or large ring lactones are eliminated by formation of a six-membered ring.

The Meldrum's acid problem requires a comparison of the difference between the ionization energies of β-diketones and analogous diesters in terms of the effects of bond angles on the

energies of the four initial states of the acyclic and cyclic diketone and diester carbon acids and their four enolate ion conjugate bases.

An estimate of a 3.8-kcal/mole energy difference between acyclic *Z* esters and lactones (or the *E*-ester conformation) was derived by Huisgen and Ott[6b] from the free energies of activation of 7- and 14-membered lactones based on the reasonable assignment of the rate difference to an initial state difference. We have determined an acidity difference between valerolactone (pK_a = 25.22 ± 0.07) and ethyl acetate (pK_a = 27.45 ± 0.16) which translates into a free energy difference of 3.03 kcal/mol. If this is attributed entirely to initial-state stabilization of the acyclic ester, it is reasonably close to Huisgen and Ott's estimate based on totally different criteria. However, we note at once that both the lactone and the ester are unstable in $DMSYL^-$/DMSO and that their pK_a's could only be obtained by back-extrapolation to zero time. Thus, either or both pK_a's may be in error. The small discrepancy between our value and Hüisgen and Ott's may also be due to a solvent effect since their rates were measured in 60:40 dioxane–water. Furthermore, as a referee has pointed out, there are differnces between the methyl group of the ester and the secondary hydrogens of the lactone in addition to entropy difference in the two systems.

The enolate anions of dimedone and Meldrum's acid should both be favored by a stabilizing factor owing to their enforced planarity, relative to their acyclic cognates. Aside from possible contributions due to differences in their initial-state conformations (dimedone a half-chair and Meldrum's acid a boat) we see no reason why cyclization should contribute more to stabilization of the bislactone enolate than that from the cyclic diketone and so assign 3 kcal/mol to both of them.

On the basis of these energy increments, the empirical analysis of 11.68-kcal/mole difference between dimethyl malonate and Meldrum's acid assigns 6–8 kcal/mol to an initial-state *E*/*Z* difference, based on our comparison of ethyl acetate and valerolactone (the estimate of Hüisgen and Ott) and a 3.07-kcal/mol cyclization factor based on the acetylacetone–dimedone difference. The total of 9–11 kcal/mol gives a fair empirical accounting and could probably be made more exact by choosing different model lactones, esters, and cyclic diketones as models.

In its simplest terms, the special acidity of compound I may be attributed to restricted rotation which removes the stereoelectronic factors that normally make esters less acidic than ketones and which adds, in addition, the electronegative acid-strengthening effect of the now unconjugated ether oxygen to the carbon next to that losing the proton.

The above interpretation may also be looked at in terms of a conformationally dependent inductive effect which is related to changes in dipole moments of the lactones observed by Hüisgen and Ott. The relationship between dipole moment and acidity should be viewed as a correlative rather than a causitive one where both properties reflect the changing interactions of the ether lone pairs with the carbonyl group, thereby producing a conformationally dependent influence both on acidity and on dipole moment.

The rotation barrier in carboxylic acids and esters has been assessed by various authors[7,17-25] to lie between 3.9 and 8.5 kcal/mol. Whatever may be its ultimate quantum mechanical origin, the present experiments show clearly that restricted rotation can have a large effect on the acidity of an adjacent enolizable methylene function. This is the source of the unusually high acidity of Meldrum's acid.

Conclusion

Data presented here give overwhelming evidence that the surprising acidity of Meldrum's acid relative to dimethyl malonate and dimedone is the result of restricted rotation of the ester linkage in the bislactone structure. It is reasonable that this unusual effect on acidity is related to empirical evidence from a variety of sources for the greater stability of the *Z* conformation of esters relative to the *E* conformation found in Meldrum's acid. The source of these large effects is a worthy target for theoretical elucidation.

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Registry No. I, 2033-24-1; II, 84465-82-7; III, 126-81-8; IV, 2979-19-3; V, 2610-95-9; VI, 106017-77-0; VII, 109-29-2; VIII, 108-94-1; IX, 504-02-9; EtOAc, 141-78-6; $CH_3CH(OMe)CH_2C(O)OMe$, 3136-17-2; $CH_3C(O)CH_2C(O)CH_3$, 123-54-6; methyl Meldrum's acid, 3709-18-0; ethyl Meldrum's acid, 17216-65-8; 1,5-dioxacycloheptadecane-2,4-dione, 106017-74-7; 1,5-dioxacyclotridecane-2,4-dione, 106017-75-8; 1,5-dioxecane-2,4-dione, 106017-76-9; dimethyl malonate, 108-59-8; diacetamide, 625-77-4; diethyl iminodicarboxylate, 19617-44-8; 3,3-dimethylglutarimide, 1123-40-6.

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