

## Theoretical Studies on the Structure and Acidity of Meldrum's Acid and Related Compounds

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The structures and gas-phase ionization energies ( $\Delta G^\circ$ ) of Meldrum's acid (**I**) and related cyclic (**II-VI**) and acyclic compounds (**VII-IX**) are investigated theoretically at the MP2/6-31+G\*. B3LYP/6-31+G\*. B3LYP/6-311+G\*\*, B3LYP/6-311++G(3df,2p) and G3(+)(MP2) levels. Conformations of three neutral cyclic series vary gradually from boat (Meldrum's acid, **I**), to twisted chair (**II**) and to chair (**III**) as the methylene group is substituted for the ether oxygen successively. The preferred boat form of **I** can be ascribed to the two strong  $n_{\text{O}} \rightarrow \sigma_{\text{C-C}}^*$  antiperiplanar vicinal charge transfer interactions and electrostatic attraction between negatively charged  $\text{C}^1$  and positively charged  $\text{C}^4$  at the opposite end of the boat. All the deprotonated anionic forms have half-chair forms due to the two strong  $n_{\text{O}} \rightarrow \pi_{\text{C=O}}^*$  vicinal charge transfer interactions. The dipole-dipole interaction theory cannot account for the higher acidity of Meldrum's acid (**I**) than dimedone (**III**). The origin of the anomalously high acidity of **I** is the strong increase in the vicinal charge transfer ( $n_{\text{O}} \rightarrow \pi_{\text{C=O}}^*$ ) and 1,4-attractive electrostatic interactions ( $\text{C}^1 \leftrightarrow \text{C}^4$ ) in the ionization ( $\text{I} \rightarrow \text{I}^- + \text{H}^+$ ). In the acyclic series (**VII-IX**) the positively charged end atom,  $\text{C}^4$ , is absent and the attractive electrostatic stabilization ( $\text{C}^1 \leftrightarrow \text{C}^4$ ) is missing in the anionic form so that the acidities are much less than the corresponding cyclic series.

**Key Words** : Meldrum's acid. MO theoretical study. Charge transfer. G3(+)(MP2). Acidity

### Introduction

The acidity of Meldrum's acid,<sup>1</sup> **I**, in aqueous solution ( $\text{p}K_{\text{a}} = 4.83\text{--}4.93$ )<sup>2</sup> is comparable to that of acetic acid ( $\text{p}K_{\text{a}} = 4.75$ ), and hence its structure has been wrongly assigned earlier as the  $\beta$ -lactone of  $\beta$ -hydroxyisopropylmalonic acid.<sup>1</sup> However, Davidson and Bernhard<sup>3</sup> have reported that the structure of **I** is the bislactone of 2,2-dimethyl-1,3-dioxane-4,6-dione, and Pfluger and Boyle<sup>4</sup> have also shown its conformation to be a boat at least for the crystal. The relatively high acidity of **I** has been, therefore, attributed to acidic hydrogens bonded to a carbon existing between the two carbonyl groups. The acidity of **I** is anomalously higher than those of all other  $\alpha$ -carbonyl carbon acids. For example, the  $\text{p}K_{\text{a}}$  of **I** in DMSO is 7.32<sup>5</sup> but those of dimedone, **III**, and dimethyl malonate, **VII**, corresponding to the cyclic and acyclic diketone analogues are 15.87 and 11.16, respectively.<sup>5</sup> Therefore the Meldrum's acid has attracted considerable attention due to its unusually high acidity.

Recently, Arnett and Harrelson<sup>6</sup> have proposed that the high acidity of **I** relative to **III** or **VII** is resulted from the restricted rotation around ester bonds in the six-membered ring of **I** with a bislactone structure, since the acidities are rapidly decreased on going from 6-membered to 10-membered ring until 13-membered ring has the same  $\text{p}K_{\text{a}}$  as **VII**. On the other hand, Wang and Houk<sup>7</sup> have suggested theoretically that the high acidity of **I** is originated from the differences in steric and electrostatic (dipole-dipole) repul-

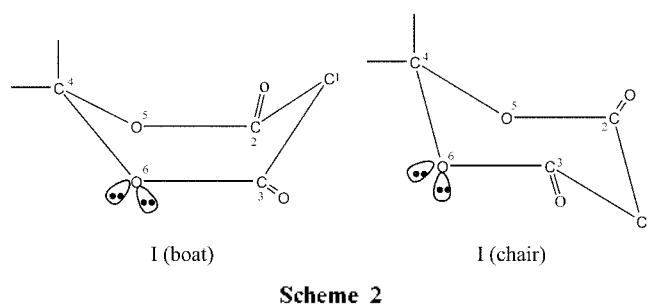
sions between *E*- and *Z*- ester conformers of neutral and deprotonated anionic molecules using the model compound, methyl acetate. Similarly, Wiberg and Laidig<sup>8</sup> have shown theoretically that the unusual acidity of **I** having a bis(*E*)-ester conformation can be accounted for by the difference in acidity between *Z*- and *E*- rotamers of methyl acetate. Recently, however, Gao and coworkers<sup>9</sup> pointed out that an additive effect due to the two *E* esters in the dilactone system is not responsible for the high acidity of Meldrum's acid. They have also shown that solvent effects are rather small, and the preferential stabilization of the enolate anion due to anomeric effects is an important factor contributing to the high acidity.

Nevertheless, several questions as to the origin of the unusually high acidity of **I** still remain: (i) it is not clear why **I** prefers to have a boat molecular conformation, (ii) it is doubtful that the boat conformation itself and 1,4-steric interaction in the boat conformation of **I** are not really relevant to the high acidity, although the possibility of a steric compression effect on the acidity was dismissed in earlier works,<sup>6</sup> and (iii) it is questionable that cyclization has no other significant effects than the unfavorable bis(*E*)-ester conformation in **I** as compared to **III** and acyclic cognates.

In this work we performed systematic investigations on the gas-phase ionization processes of various cyclic, eq. (1), and acyclic diketone analogues, eq. (2), theoretically using the density functional theory (DFT) and *ab initio* methods in order to elucidate more thoroughly the origin of the unusually high acidity of the Meldrum's acid.

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measurements.<sup>15</sup> NMR studies<sup>16</sup> and X-ray structural determination.<sup>4</sup> Our attempts to obtain optimized structure of **I** with chair conformation failed at all theoretical levels employed.

Why does **I** prefer to have a boat conformation? According to our analysis there are at least two factors which are in favor of the boat form: (i)  $n_{\text{O}} \rightarrow \sigma_{\text{C}-\text{C}}^*$  interactions. In the boat form the lone pairs on ether oxygens (e.g.  $\text{O}^6$ ) are oriented antiperiplanar to the C - C ( $\text{C}^1 - \text{C}^3$ ) bonds while in the chair form they are synperiplanar (Scheme 2). It is well known that antiperiplanar  $n \rightarrow \sigma^*$  ( $n_{\text{O}^5} \rightarrow \sigma_{\text{C}^1-\text{C}^2}^*$  and  $n_{\text{O}^5} \rightarrow \sigma_{\text{C}^1-\text{C}^3}^*$ ) vicinal charge transfer interactions are much stronger (and hence much more stabilizing) than the corresponding synperiplanar interactions.<sup>13,17</sup> Our natural bond orbital (NBO) analyses<sup>13</sup> show that **I** is stabilized by the two  $n_{\text{O}} \rightarrow \sigma_{\text{C}-\text{C}}^*$  interactions by 13.8 kcal mol<sup>-1</sup>.

In contrast, in the anionic form of **I**, i.e., in **I<sup>-</sup>**, the value is 9.2 kcal mol<sup>-1</sup>. Since in **I<sup>-</sup>** the lone pair ( $n_{\text{O}}$ ) is oriented gauche to the  $\sigma_{\text{C}-\text{C}}^*$  orbital, this means that in the synperiplanar  $n_{\text{O}} \rightarrow \sigma_{\text{C}-\text{C}}^*$  interactions the stabilization energy will be smaller than this (9.2 kcal mol<sup>-1</sup>). Thus the vicinal antiperiplanar arrangements of  $n_{\text{O}}$  and  $\sigma_{\text{C}-\text{C}}^*$  are conducive to boat conformation for **I**. It is to be noted that this  $n \rightarrow \sigma^*$  vicinal charge transfer stabilization is absent

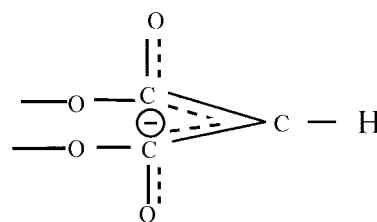
**Table 1.** The relevant natural population analysis (NPA) charges (in electronic unit) and electrostatic interaction energies ( $\Delta E_{\text{es}}$  in kcal mol<sup>-1</sup>) for **I-VI** and **I<sup>-</sup>-VI<sup>-</sup>**

	NPA charges				$\Delta E_{\text{es}}$	
	$\text{C}^1$	$\text{C}^1 + \text{H}_2$ (or H)	$\text{C}^4$	$\text{C}^4 + (\text{CH}_3)_2$	(a)	(b)
<b>I</b>	-0.610	-0.080	0.579	0.694	-42	-7
<b>I<sup>-</sup></b>	-0.628	-0.414	0.575	0.592	-44	-30
<b>II</b>	-0.600	-0.071	0.278	0.644	-19	-3
<b>II<sup>-</sup></b>	-0.571	-0.364	0.265	0.284	-17	-12
<b>III</b>	-0.570	-0.073	-0.073	0.020	5	0
<b>III<sup>-</sup></b>	-0.514	-0.314	-0.094	-0.072	5	3
<b>IV</b>	-0.612	-0.083	0.267	0.630	-21	-7
<b>IV<sup>-</sup></b>	-0.631	-0.418	0.280	0.564	-23	-30
<b>V</b>	-0.595	-0.077	-0.038	0.347	3	-3
<b>V<sup>-</sup></b>	-0.573	-0.368	-0.023	0.292	2	-13
<b>VI</b>	-0.571	-0.075	-0.381	0.099	24	0
<b>VI<sup>-</sup></b>	-0.514	-0.317	-0.384	0.006	23	1

(a) Between atoms  $\text{C}^1$  and  $\text{C}^4$ . (b) Between  $(\text{C}^1 - \text{H}_2)$  and  $\text{C}^4 - (\text{CH}_3)_2$  groups.

entirely in **III** which has a chair form, while there is only one such interaction in **II** (8.0 kcal mol<sup>-1</sup>) which has a twisted chair form. (ii) Electrostatic interactions. The relevant atomic and group charges by the natural population analysis (NPA)<sup>13,e,f</sup> are collected in Table 1. We note that the two out-of-plane carbons ( $\text{C}^1$  and  $\text{C}^4$ ), which are at two opposite ends (Scheme 3), are strongly charged in the boat form of **I** with negative ( $q(\text{C}^1) = -0.610$ ) and positive ( $q(\text{C}^4) = +0.579$ ) charges, respectively. In the twisted chair (**II**) the positive charge at  $\text{C}^4$  ( $q(\text{C}^4) = +0.278$ ) decreases while the chair form of **III** has negative charge at  $\text{C}^4$  ( $q(\text{C}^4) = -0.073$ ). The electrostatic interaction energies ( $\Delta E_{\text{es}}$ ) between the two atoms,  $\text{C}^1$  and  $\text{C}^4$ , decreases from -42 (**I**) to -19 (**II**) and to +5 kcal mol<sup>-1</sup> (**III**), and similarly between the two groups at  $\text{C}^1$  ( $\text{C}^1 + \text{H}_2$ ) and  $\text{C}^4$  ( $\text{C}^4 + (\text{CH}_3)_2$ ) decreases from **I** (-7 kcal mol<sup>-1</sup>) down to **III** (~0). This means that the boat form (**I**) is electrostatically stabilized whereas there is practically no such stabilization in the chair form of **III**. In fact there is repulsive interaction between  $\text{C}^1$  and  $\text{C}^4$  in **III** so that the two atoms are located as far as possible forming a chair structure. This is in quite contrast to the strong attractive interaction between the  $\text{C}^1$  and  $\text{C}^4$  atoms in the boat form of **I** in which the two atoms are located at a nearest distance. The twisted chair of **II** is in between the two extreme forms of **I** and **III**.

All the anionic forms, **I<sup>-</sup>-III<sup>-</sup>**, have half chair structure since the anionic charge at  $\text{C}^1$  is strongly delocalized over



the two carbonyl groups ( $\text{C}^2 = \text{O}$  and  $\text{C}^3 = \text{O}$ ) by strong  $n_{\text{C}} \rightarrow \pi_{\text{C}=\text{O}}^*$  vicinal charge transfer interactions and form a coplanar moiety.

Unfortunately, Gao and coworkers have not included these strong  $n_{\text{C}} \rightarrow \pi_{\text{C}=\text{O}}^*$  interaction energies in their NBO analysis of the Meldrum's acid.<sup>9</sup> These  $n_{\text{C}} \rightarrow \pi_{\text{C}=\text{O}}^*$  vicinal charge transfer energies are especially large since the lone pair on  $\text{C}^1$  is a p type (and hence is at a higher level than other  $\text{sp}^2$  or  $\text{sp}^3$  type lone pairs) and the  $\pi^*$  orbital is lower than  $\sigma^*$  orbitals leading to a narrower energy gap,  $\Delta\epsilon$ , in the second-order perturbation energy,<sup>13,17</sup>  $\Delta E_{\text{n} \rightarrow \pi^*}^{(2)}$  in eq. (3). The stabilization of anionic forms,

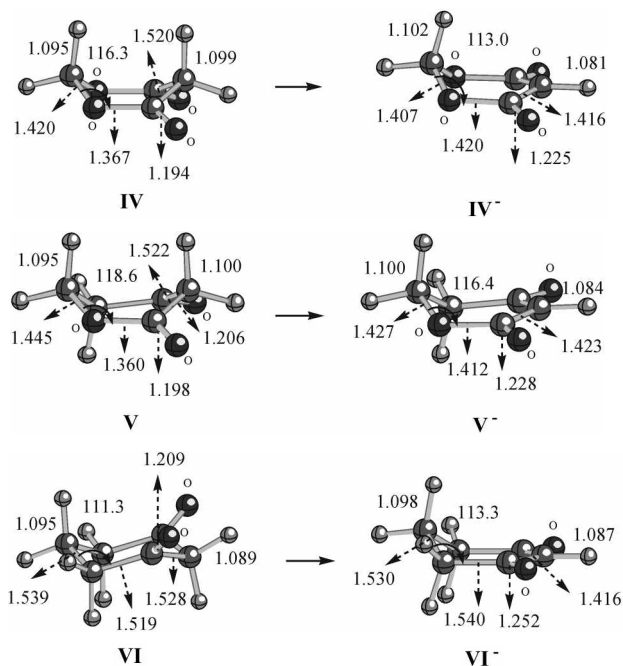
$$\Delta E_{\text{n} \rightarrow \pi^*}^{(2)} = -2(F_{\text{n}\pi^*})^2 / (\epsilon_{\pi^*} - \epsilon_{\text{n}}) = -2(F_{\text{n}\pi^*})^2 / \Delta\epsilon \quad (3)$$

**I<sup>-</sup>-III<sup>-</sup>**, due to these vicinal  $n \rightarrow \pi_{\text{C}=\text{O}}^*$  interactions is, however, the lowest in **I<sup>-</sup>** (Table 2).

This is due to elevation of the  $\pi_{\text{C}=\text{O}}^*$  level by the vicinal lone pairs on ether oxygen ( $\text{O}^5$  and  $\text{O}^6$ ). Thus the  $\pi_{\text{C}=\text{O}}^*$  level is the highest in **I<sup>-</sup>** ( $\epsilon_{\pi^* \text{C}=\text{O}} = 0.3802$  vs 0.3733 and 0.3587 a.u. for the corresponding orbitals in **II<sup>-</sup>** and **III<sup>-</sup>** respectively), and hence the  $n \rightarrow \pi_{\text{C}=\text{O}}^*$  charge transfer energy ( $\Delta E_{\text{n} \rightarrow \pi^*}^{(2)}$  in eq. (3)) is the smallest due to the widest

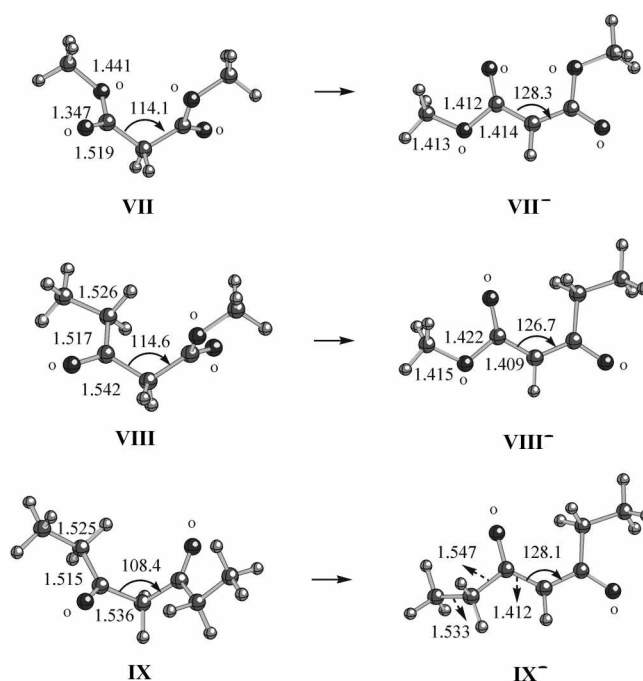
**Table 2.** The vicinal  $n_C \rightarrow \pi_{C=O}$  charge transfer energies ( $-\Delta E_{n \rightarrow \pi}^{(2)}$ ) in anionic forms,  $I^- \rightarrow VI^-$ , in kcal mol $^{-1}$ 

	$I^-$	$II^-$	$III^-$
$C^1 - C^2 = O$	124.9	127.3	150.6
$C^1 - C^3 = O$	124.9	156.1	150.6
	$IV^-$	$V^-$	$VI^-$
$C^1 - C^2 = O$	123.2	124.5	150.6
$C^1 - C^3 = O$	123.5	155.6	150.6

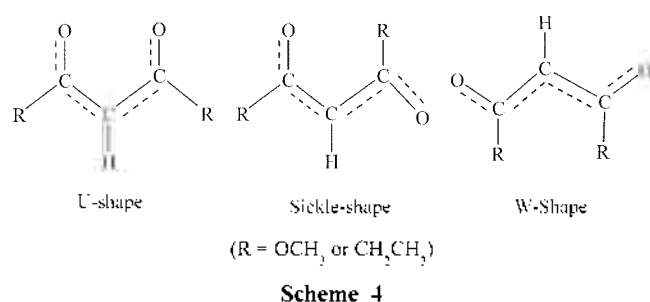
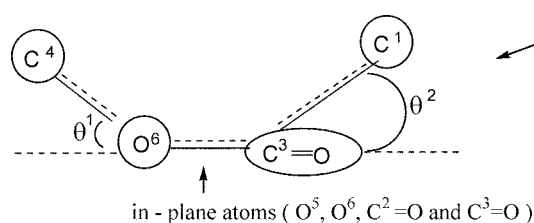
**Figure 2.** The optimized structures of cyclic species with  $R = H$ ,  $IV-IV^-$ , at B3LYP/6-311+G\*\* level.

energy gap,  $\Delta\epsilon$ . Based solely on the charge transfer stabilization, the stability of anionic forms should decrease in the order,  $III^- > II^- > I^-$ . However, this is misleading since there are stronger electrostatic stabilizations in  $I^-$  than in  $II^-$  and  $III^-$  as can be seen in Table 1.

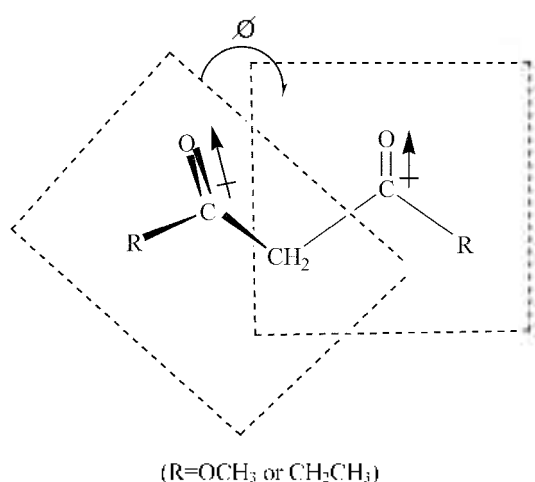
The optimized structures of cyclic neutral ( $IV-VI$ ) and anionic forms with  $R = H$  ( $IV^-VI^-$ ) at the B3LYP/6-311+G\*\* level are presented in Figure 2. The structures of  $IV-VI$  are similar to those of their dimethyl analogues,  $I-III$ , except that **V** has a boat form instead of a twisted chair which was found with **II**. This indicates simply that either there is some 1-4 steric repulsion in **II** due to the two bulky

**Figure 3.** The optimized structures of acyclic species,  $VII-IX$ , at B3LYP/6-311+G\*\* level.

$CH_3$  groups on  $C^4$ , or there is stronger 1,4-attraction in **V** than in **II**. In fact, the 1,4-steric attraction (*vide infra*) enforces shorter interatomic distance between  $C^1$  and  $C^4$  in **IV** by 0.17 Å than that in **I** and as a result torsional angles ( $\theta^1$  in Scheme 3) of the two ends,  $C^1$  and  $C^4$ , from the molecular base ( $O^5 - C^2 - C^3 - O^6$ ) plane in **IV** are larger by  $4.5^\circ$  compared to those in **I**. This suggests that Meldrum's acid, **I**, is a cyclic compound with no significant 1,4-steric repulsion so that its relaxation on going from neutral to anionic species does not contribute significantly to the high acidity of **I**.

**Scheme 4****Scheme 3**out-of-plane atoms at two ends ( $C^1$  and  $C^4$ )

	$\theta^1$	$\theta^2$
<b>I</b> :	59.2	64.2
<b>IV</b> :	63.7	66.0



Scheme 5

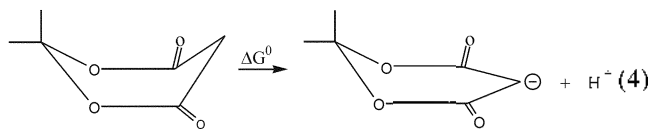
Optimized structures of the three acyclic species, **VII-IX**, at the B3LYP/6-311-G\*\* level are shown in Figure 3. Unlike in cyclic analogues, **I-VI**, the two carbonyl groups have to be W-shaped<sup>18</sup> (Scheme 4) within molecular plane.

Due to electrostatic or dipole-dipole repulsion the two carbonyl groups are twisted away each other as shown in Scheme 5. The twist angle ( $\phi$ ) increases in the order **VII** (35.3°) < **VIII** (49.6°) < **IX** (86.2°). However in the anionic forms, **VII-IX**<sup>-</sup>, two carbonyl groups and the anionic center are nearly coplanar due to  $n_{\text{O}} \rightarrow \pi_{\text{C}=\text{O}}$  vicinal charge transfer interactions with Sickle-shaped conformation in contrast to the W-shaped neutral species. For the charge delocalized anions, three conformations are possible as shown in Scheme 4, and relative preference depends on R which is OCH<sub>3</sub> or CH<sub>2</sub>CH<sub>3</sub>. In the absence of steric repulsion, the U-shaped anion has the strongest electrostatic repulsion and the W-shaped anion will be the most stabilized. However the Sickle-shaped anions are favored by *ca.* 1-5 kcal mol<sup>-1</sup> than the W-shaped ones in all cases indicating that steric interaction between the two R groups is significant. The stable conformations shown in Figure 3 are determined mainly by the favorable electrostatic interactions

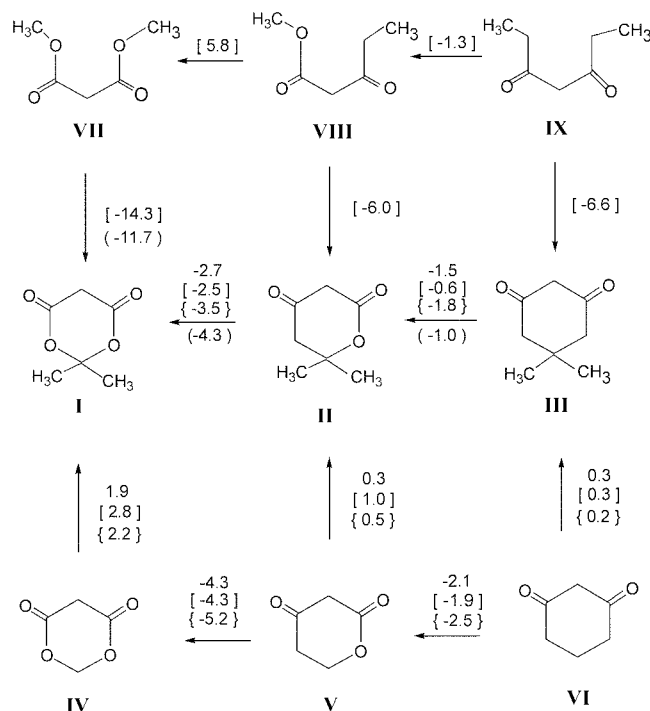
**Table 3.** The Gibbs free energy changes ( $\Delta G^\circ$  in kcal mol<sup>-1</sup>) for the ionizations of cyclic and acyclic species, **I-IX**, obtained at various levels of theory

	MP2/ 6-31-G*	B3LYP/ 6-31-G*	B3LYP/6- 311+G**	B3LYP/6- 311+-G(3df,2p)	G3(+) (MP2)
<b>I</b>	319.5	321.1	321.5	322.7	324.3
<b>II</b>	323.0	323.9	324.5	325.2	327.0
<b>III</b>	324.8	324.8	325.5	325.8	328.5
<b>IV</b>	317.3	318.0	318.5	319.9	322.4
<b>V</b>	322.5	322.8	323.4	324.2	326.7
<b>VI</b>	325.0	325.1	325.7	326.1	328.8
<b>VII</b>	338.4	336.6	337.0	337.0	
<b>VIII</b>	332.6	331.6	330.9	331.2	
<b>IX</b>	331.3	331.5	332.1	332.5	

within the molecules since the  $n_{\text{O}} \rightarrow \pi_{\text{C}=\text{O}}$  vicinal charge transfer stabilization will not differ significantly between many possible conformations.



**Acidity.** The gas-phase ionization energies,  $\Delta G^\circ$  at 298 K in eq (4) (for **I**  $\rightarrow$  **I**<sup>-</sup> + H<sup>+</sup>), calculated at various levels of theory are summarized in Table 3. The relative values at the G3(+)(MP2) and B3LYP/6-311+G(3df,2p) levels are presented in Figure 4 together with the experimentally (in DMSO at 25 °C) available values.<sup>6</sup> The  $\Delta G^\circ$  value of Meldrum's acid (**I**) is lower by 14.3 and 3.1 kcal mol<sup>-1</sup> than that of dimethyl malonate (**VII**) and dimedone (**III**) at the B3LYP/6-311+G(3df,2p) level, respectively. The former is larger ( $\delta\Delta G^\circ_{\text{DFT}} - \delta\Delta G^\circ_{\text{exp}} - 2.6$  kcal mol<sup>-1</sup> where  $\delta\Delta G^\circ = \Delta G^\circ(\text{VII}) - \Delta G^\circ(\text{I})$ ) but the latter is smaller ( $\delta\Delta G^\circ_{\text{DFT}} - \delta\Delta G^\circ_{\text{exp}} - 2.2$  kcal mol<sup>-1</sup> where  $\delta\Delta G^\circ = \Delta G^\circ(\text{III}) - \Delta G^\circ(\text{I})$ ) by *ca.* 2 kcal mol<sup>-1</sup> than the respective experimental values in DMSO. The G3(+)(MP2) result ( $\delta\Delta G^\circ - \Delta G^\circ(\text{III}) - \Delta G^\circ(\text{I}) - 4.2$  kcal mol<sup>-1</sup>) is in better agreement with the experimental value of  $\delta\Delta G^\circ - 5.2$  kcal mol<sup>-1</sup> than the DFT value ( $\delta\Delta G^\circ - 3.1$  kcal mol<sup>-1</sup>). However, the trends of changes in the  $\Delta G^\circ$  values ( $\delta\Delta G^\circ$ ) are all in good accord: (i) The acidity increases ( $\Delta G^\circ$  is reduced) greatly by cyclization (**VII**  $\rightarrow$  **I**, **VIII**  $\rightarrow$  **II** and **IX**  $\rightarrow$  **III**) and (ii) the introduction

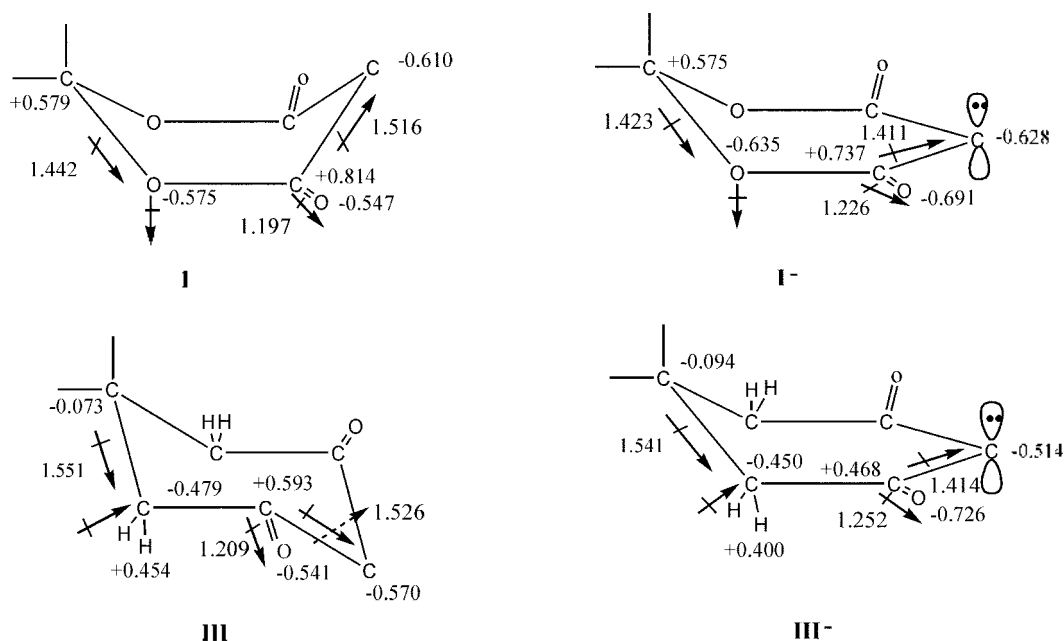


**Figure 4.** Differences in free energies of ionization ( $\Delta G^\circ$  at 298 K) calculated at the G3(-)(MP2), B3LYP/6-311+G(3df,2p) [in bracket] and MP2/6-31-G\* {in round bracket} levels. Values in parenthesis are experimental results in DMSO at 25 °C.

of second ether oxygen ( $\text{II} \rightarrow \text{I}$ ) leads to a greater decrease in  $\Delta G^\circ$  than the first ether oxygen ( $\text{III} \rightarrow \text{II}$ ). The disagreements of the theoretical gas-phase  $\Delta G^\circ$  values with the experimental results in DMSO may arise from solvent effects. It is conceivable that the highly polarized structure of  $\text{I}^-$  relative to  $\text{III}^-$  (Table 1) may lead to enhanced stabilization by solvation, which will give a stronger acidity for Meldrum's acid ( $\text{I}$ ) than for dimedone ( $\text{III}$ ) in DMSO. However, this possibility is low since a good correlation of the  $\text{p}K_a$  values in DMSO with gas phase values were found.<sup>7,11a,19</sup> Alternatively, improper accounting of interorbital correlation energy between localized lone pairs on the two neighboring oxygen atoms may be the cause for these discrepancies. The DFT method is known to overestimate electron correlation energy for delocalized systems,<sup>20</sup> but underestimate interorbital pair correlation energy between localized lone pairs on the two neighboring atoms.<sup>21</sup> In the deprotonation of  $\text{I}$  (into  $\text{I}^- + \text{H}^+$ ), electron population of lone pairs on the two ether oxygens increases (charge increases on the ether oxygen from  $-0.575$  to  $-0.635$ ). Underestimation of interorbital pair correlation energies between the lone pairs on the two in-plane ether oxygens (Scheme 3) should lead to an unduly high energy for  $\text{I}^-$  so that the  $\Delta G^\circ$  value will become higher than that would have been obtained if proper accounting had been made. Since there are no ether oxygens in  $\text{III}$ , no such inadequate accounting of pair correlation energy occurs in the  $\Delta G^\circ$  value for the deprotonation of  $\text{III}$ . Thus, approximately  $2 \text{ kcal mol}^{-1}$  difference in the acidity ( $\delta\Delta G^\circ_{\text{DFT}} - \delta\Delta G^\circ_{\text{exp}} = 3.1 - 5.3 = -2.2 \text{ kcal mol}^{-1}$ ) may have come from this underestimation in the deprotonation of  $\text{I}$ . On the other hand, the two ether oxygens are twisted away in  $\text{VII}$  (Scheme 5) but an ether and a carbonyl oxygen approach to a near distance within the

two coplanar ester groups in  $\text{VII}^-$  (Figure 3). This means that the underestimation of interorbital pair correlation energy will be large in the deprotonation of  $\text{VII}$  due to a large increase in the interorbital pair interaction from  $\text{VII}$  to  $\text{VII}^-$ . Consequently, the undue increase in  $\Delta G^\circ$  will be large for the deprotonation of  $\text{VII}$ . The relative acidity decrease due to the underestimated interorbital pair correlation energy by the DFT method may be ca.  $4.8 \text{ kcal mol}^{-1}$ , leading to enhanced acidity difference of  $2.6 \text{ kcal mol}^{-1}$  between  $\text{VII}$  and  $\text{I}$  since  $\delta\Delta G^\circ_{\text{DFT}} - \delta\Delta G^\circ_{\text{exp}} = 4.8 \text{ kcal mol}^{-1}$  results from  $(2.6 + 2.2) \text{ kcal mol}^{-1}$  where  $2.2 \text{ kcal mol}^{-1}$  is the decrease in the acidity of  $\text{I}$  due to the underestimated electron correlation. Interestingly, the dimethyl series,  $\text{I-III}$ , are all less acidic, *i.e.*,  $\Delta G^\circ$  values are higher, than the corresponding unsubstituted counterparts,  $\text{IV-VI}$ , *e.g.*,  $\text{I}$  is less acidic by  $\delta\Delta G^\circ = 2.8 \text{ kcal mol}^{-1}$  than  $\text{IV}$ , (*vide infra*).

What is the origin of the unusually high acidity of Meldrum's acid,  $\text{I}$ ? We first examine the dipole-dipole interaction theory for explaining the origin of the abnormal acidity of Meldrum's acid.<sup>7,8,22</sup> Experimentally, Meldrum's acid ( $\text{I}$ ) was found to be  $5.24 \text{ kcal mol}^{-1}$  more acidic than dimedone ( $\text{III}$ ), *i.e.*, deprotonation of  $\text{III}$  is  $5.24 \text{ kcal mol}^{-1}$  more endothermic than deprotonation of  $\text{I}$  in DMSO at  $25^\circ\text{C}$  ( $\delta\Delta G^\circ = 5.24 \text{ kcal mol}^{-1}$ ). The corresponding values in the gas phase obtained in the present work are  $\delta\Delta G^\circ = 5.3, 3.1$  and  $4.2 \text{ kcal mol}^{-1}$  at the MP2/6-31+G\*, B3LYP/6-311+G(3df,2p) and G3(+)(MP2) level respectively. The MP2 value is in excellent agreement with the experimental result. However, this may be fortuitous since it is well known that the MP2 method overestimates electron correlation energy for the delocalized structure.<sup>20a,21b,23</sup> Since the deprotonated forms ( $\text{I}^-$ - $\text{III}^-$ ) are strongly delocalized, overestimation of electron correlation for these anionic forms will result in an



**Figure 5.** The natural population analysis (NPA) atomic charges (electronic unit) and bond lengths ( $\text{\AA}$ ) with qualitative dipoles component arrows in deprotonation of Meldrum's ( $\text{I} \rightarrow \text{I}^-$ ) and dimedone ( $\text{III} \rightarrow \text{III}^-$ ).

enhanced acidity. The overestimation of electron correlation will be greater, naturally, for the system with a larger exclusion repulsion involving lone pairs, *i.e.*, the effect will be greater in **I** (with extra lone pairs on the two ether oxygens) than in **III** (with no ether oxygen). The MP2 acidity difference of 5.3 kcal mol<sup>-1</sup> between **I** and **III** may therefore be attributed partly to the overestimation of electron correlation energies by the MP2 method. The enhanced acidity due to the overestimation of electron correlation increases thus in the order **III** < **II** < **I**. This trend is evident in Table 3, since the lowest  $\Delta G^\circ$  value, or the strongest acidity, is obtained by MP2 than by any other method. For example, the  $\Delta G^\circ$  value is 319.5 kcal mol<sup>-1</sup> for **I** by MP2 but this is lower by 1.6 and 4.8 kcal mol<sup>-1</sup> than those by B3LYP/6-31+G\* and G3(+)(MP2), respectively.

The G3(+)(MP2) and DFT values are all somewhat smaller ranging from 3.1 to 4.2 kcal mol<sup>-1</sup> as the basis sets are varied (Table 3). The DFT (B3LYP) values do not converge to a limiting value as the basis set is increased, 3.7 (6-31+G\*)  $\rightarrow$  4.0 (6-311+G\*\*)  $\rightarrow$  3.1 kcal mol<sup>-1</sup> (6-311++G(3df,2p)). The best value is that (4.2 kcal mol<sup>-1</sup>) obtained by the G3(+)(MP2) theory, which is an improved method over the G2(MP2) as well as the G2 theory.<sup>12</sup> Since the composite ab initio method, G3(+)(MP2), can often achieve an accuracy of 1-2 kcal mol<sup>-1</sup> in the various energy calculation,<sup>12</sup> the agreement of our gas-phase (G3(+)(MP2)) value (4.2 kcal mol<sup>-1</sup>) with the experimental result in DMSO (5.2 kcal mol<sup>-1</sup>) should be deemed good considering errors involved in the experimental measurements.<sup>5,6</sup>

The NPA charges are shown in Figure 5 for atoms involved in the deprotonation of Meldrum's acid (**I**  $\rightarrow$  **I**<sup>-</sup>) and dimedone (**III**  $\rightarrow$  **III**<sup>-</sup>) with dipole moment components depicted qualitatively by arrows. We note that the boat conformation of **I** is stabilized by interaction of two out-of-plane dipoles pointing in opposite direction (antiparallel dipoles of C<sup>3</sup>  $\rightarrow$  C<sup>1</sup> and O<sup>6</sup>  $\leftarrow$  C<sup>4</sup>). In contrast, the corresponding out-of-plane dipoles are pointing in the same direction in **III** (parallel dipoles of C<sup>3</sup>  $\rightarrow$  C<sup>1</sup> and C<sup>4</sup>  $\rightarrow$  C<sup>6</sup>) leading to destabilization of the chair conformation of **III**. These relative stabilities of **I** and **III** based on dipole interactions involving the two out-of-plane end atoms (C<sup>1</sup> and C<sup>4</sup>) are consistent with the preferred conformations of **I** (boat) and **III** (chair), since the attractive force pull together in **I** to a shorter distance (boat) while the repulsive force push apart the two ends in **III** to a farther distance (chair). There are, however, another in-plane pair of dipoles within the base plane composed of the two ester groups (-O<sup>5</sup>-C<sup>3</sup>(=O)- and -O<sup>5</sup>-C<sup>2</sup>(=O)-) in **I** and the corresponding groups (-C<sup>6</sup>H<sub>2</sub>-C<sup>3</sup>(=O)- and -C<sup>5</sup>H<sub>2</sub>-C<sup>2</sup>(=O)-) in **III**: two in-plane dipoles within the molecular base plane of **I**, O<sup>6</sup>  $\rightarrow$  n<sub>O</sub> and C<sup>3</sup>  $\rightarrow$  O where n<sub>O</sub> is the lone pairs on the ether oxygen atom, are parallel (destabilizing) whereas the corresponding pairs in **III**, C<sup>6</sup>  $\leftarrow$  H<sub>2</sub> and C<sup>3</sup>  $\rightarrow$  O, are antiparallel (stabilizing). In the deprotonation of **I** ( $\rightarrow$  **I**<sup>-</sup>) and **III** ( $\rightarrow$  **III**<sup>-</sup>), these two sets of in-plane dipoles are not reduced to a similar extent. On the contrary, inspection of Figure 5 reveals that the two in-plane dipoles in **I** are

strengthened in **I**<sup>-</sup>, since (i) polarity of the carbonyl group is increased with bond length stretch, and (ii) the negative charge on the ether oxygen is increased (and hence a greater occupation of the lone pair orbital, n<sub>O</sub>). In contrast, changes in dipole strength will be small in **III**  $\rightarrow$  **III**<sup>-</sup>, since polarity of CH<sub>2</sub> decreases while that of C=O increases. These results indicate that the deprotonation of **I** into **I**<sup>-</sup> is accompanied by destabilization due to the increased repulsion of the in-plane parallel dipoles, whereas the deprotonation of **III** into **III**<sup>-</sup> causes little change in the dipole interaction between the in-plane antiparallel dipoles. The consequences of this in-plane dipole interaction analysis is that the acidity of **III** should be greater than that of **I** since the change of **III**  $\rightarrow$  **III**<sup>-</sup> is less endothermic than that of **I**  $\rightarrow$  **I**<sup>-</sup>. This conclusion, based solely on the in-plane dipole interactions, is of course absurd and in direct contradiction to the experimental ( $\delta\Delta G^\circ = 5.2$  kcal mol<sup>-1</sup>) as well as our gas-phase theoretical (G3(+)(MP2)) result ( $\delta\Delta G^\circ = 4.2$  kcal mol<sup>-1</sup>) of the enhanced acidity of **I** relative to **III**. We therefore turn our attention to the analysis based on the natural bond orbital (NBO) theory.<sup>13</sup> In the following, we will show based on the NBO analysis that the origin of the greater acidity of **I** than **III** lies in the large increase in the electrostatic attraction between the p type lone pair developed on the anionic center (C<sup>1</sup>) and the cationic center (C<sup>4</sup>) on going from **I** to **I**<sup>-</sup> compared to that from **III** to **III**<sup>-</sup>.

The energies ( $\Delta E^0$ ) of ionization are decomposed into charge-transfer ( $\Delta E_{CT}$ ) and non-charge-transfer ( $\Delta E_{NCT}$ ) terms<sup>13</sup> in Table 4. First of all we note that the charge-transfer term is negative ( $\Delta E_{CT} < 0$ ) while the non-charge-transfer term is positive ( $\Delta E_{NCT} > 0$ ) and the overall ionization energies are positive ( $\Delta E^0 > 0$ ). This means that the anionic forms (*e.g.* **I**<sup>-</sup>) are more stabilized by charge transfer delocalization but are more destabilized by non-charge-transfer energies than the neutral forms (*e.g.* **I**), and the latter ( $\Delta E_{NCT}$ ) is numerically greater than the former ( $\Delta E_{CT}$ ). As we have discussed above in the structure section, the charge transfer stabilization in the anionic forms increases a great deal due to the two strong n<sub>C</sub>  $\rightarrow$   $\pi_{C=O}^*$  vicinal charge transfer interactions involving a relatively high energy p type lone pair on the anionic center, C<sup>1</sup>. However, this charge

**Table 4.** Decomposition of energies of ionization at the B3LYP/6-311++G(3df,2p) level) into charge-transfer ( $\Delta E_{CT}$ ) and non-charge-transfer ( $\Delta E_{NCT}$ ) terms (in kcal mol<sup>-1</sup>)

	$\Delta E^0$	$\Delta E_{CT}$	$\Delta E_{NCT}$
<b>I</b>	336.6	-235.4	572.0
<b>II</b>	338.3	-270.5	608.8
<b>III</b>	339.7	-293.6	633.3
<b>IV</b>	334.0	-269.3	603.3
<b>V</b>	338.0	-299.6	637.6
<b>VI</b>	340.0	-325.6	665.6
<b>VII</b>	351.6	-292.5	644.0
<b>VIII</b>	346.5	-305.3	651.8
<b>IX</b>	346.1	-238.2	625.7

transfer stabilization is the lowest with  $\Gamma^-$  since the  $\pi_{C=O}^*$  level is elevated by lone pairs in the two ether oxygens. The p type lone pair on the anionic center  $C^1$ , however, causes enormous exclusion repulsion within the anionic forms. This is why there is large increase in destabilization represented by  $\Delta E_{NCT}$ , which includes exclusion repulsion, electrostatic and steric interaction energies.<sup>13</sup> This  $\Delta E_{NCT}$  ( $> 0$ ) term, being numerically greater than  $\Delta E_{CT}$  ( $< 0$ ), determines the overall ionization energy,  $\Delta E^\circ$  ( $> 0$ ). We can now consider repulsive, destabilizing, part and stabilizing, attractive part, which are comprised in  $\Delta E_{NCT}$  term. The strongest repulsion should be those between negative charges on  $C^1$  and ether ( $O^5$  or  $O^6$ ) (or methylene carbon) and carbonyl oxygens. The NPA charges on  $C^1$ ,  $O^6$  or methylene carbons are compared for **I** and **III** in Figure 5. We note that the negative charges on  $C^1$ ,  $O^6$  and carbonyl oxygen increase as **I** is ionized to  $\Gamma^-$ , which is as expected since there is an anionic center, a p-type lone pair, formed in  $\Gamma^-$ . However, the situation is reversed with **III**, for which negative charges both on  $C^1$  and methylene carbons decrease as **III** is ionized to  $\text{III}^-$  albeit negative charges increase on carbonyl oxygens. The negative charge decrease on  $C^1$  in  $\text{III}^-$  is due to the two strong  $n_C \rightarrow \pi_{C=O}^*$  vicinal charge delocalizations in  $\text{III}^-$ , which is, as discussed above, much stronger than the corresponding interactions in  $\Gamma^-$ ,  $-\Delta E_{CT}(\text{III}^-) > -\Delta E_{CT}(\Gamma^-)$ . Comparison of ionizations of **I**  $\rightarrow \Gamma^-$  with **III**  $\rightarrow \text{III}^-$ , thus leads to a greater destabilization by repulsive interactions between greatly increased negative charges in  $\Gamma^-$  than in  $\text{III}^-$  where negative charge increase is smaller. If this destabilization were to prevail in the  $\Delta E_{NCT}$  term, the acidity of the Meldrum's acid, **I**, should have been lower than that of dimedone, **III**, i.e.,  $\Delta G^\circ(\text{I}) > \Delta G^\circ(\text{III})$ . This is not the case, however, as we know well the reverse holds,  $\Delta G^\circ(\text{I}) < \Delta G^\circ(\text{III})$ . We therefore should introduce and compare attractive, stabilizing interactions included within  $\Delta E_{NCT}$  term. The stabilizing electrostatic interaction between  $C^1$  ( $q_1 < 0$ ) and  $C^4$  ( $q_4 > 0$ ) or between the groups ( $C^1 + H_2$  or  $H$  and  $C^4 + (CH_3)_2$ ) increases substantially in the ionization of **I** ( $\rightarrow \Gamma^-$ ) as shown in Table 1. This attractive interaction is absent in the ionization of **III** ( $\rightarrow \text{III}^-$ ) so that the  $\Delta E_{NCT}$  term is much larger positive with **III** (633.3 kcal mol<sup>-1</sup>) than with **I** (572.0 kcal mol<sup>-1</sup>). This greater repulsive  $\Delta E_{NCT}$  term with **III** than **I** more than compensate for the larger charge transfer stabilization,  $\Delta E_{CT}$  ( $< 0$ ), with **III** (-293.6 kcal mol<sup>-1</sup>) than **I** (-235.4 kcal mol<sup>-1</sup>). In effect, *the stronger acidity of **I** than **III** ( $\delta\Delta E^\circ = 3.1$  kcal mol<sup>-1</sup>)<sup>24</sup> can be attributed to the larger increase in the electrostatic stabilization accompanied with the ionization of **I** than that of **III**.*

The same argument applies to the stronger acidity of **I** compared to its acyclic analogues, **VII** ( $\delta\Delta E^\circ = 14.9$  kcal mol<sup>-1</sup>). In **VII** the strong cationic center  $C^4$  is absent (and hence the strong  $C^1 \leftrightarrow C^4$  attractive interaction is absent) and the increase in the stabilizing electrostatic interaction in the ionization of **VII** is so low that despite the larger increase in the charge-transfer stabilization ( $\Delta E_{CT} = -292.5$  for **VII** vs  $-235.4$  kcal mol<sup>-1</sup> for **I**) the acidity is much weaker than **I**.

Among the three acyclic series, **VII-IX**, the increase in the

$n_C \rightarrow \pi_{C=O}^*$  vicinal charge transfer stabilization in the ionization,  $\Delta E_{CT}$ , is the greatest for **VIII** ( $= -305.3$  kcal mol<sup>-1</sup>) and there is also a concomitant increase in the  $\Delta E_{NCT}$  ( $= 651.8$  kcal mol<sup>-1</sup>) term, Table 4. This is again due to the lowest  $\delta^*_{C=O}$  level (0.3375 a.u.) among the three anionic forms compared (0.3483 and 0.3625 a.u. for **VII**<sup>-</sup> and **IX**<sup>-</sup>, respectively). The stronger delocalization due to the  $n_C \rightarrow \pi_{C=O}^*$  interaction will result in a lower atomic charge on  $C^1$ , which should lead to a lower attractive electrostatic interaction between  $C^1$  and other neighboring positive atomic centers within the Sickle type anion, **VIII**<sup>-</sup>. This causes to raise the  $\Delta E_{NCT}$  term. In the acyclic series there is no strong cationic center on  $C^4$  ( $R_2C^+(O^-)_2$  where  $R = H$  or  $CH_3$ ) so that the strong attractive electrostatic interaction between  $C^1$  and  $C^4$  is missing. Instead there are several weak attractive interactions between anionic centers, ( $C^1$ , ether oxygens and carbonyl oxygens) and neighboring hydrogens within the Sickle shaped anions, **VII**<sup>-</sup>, **VIII**<sup>-</sup> and **IX**<sup>-</sup>. There is a general trend that an increased  $n_C \rightarrow \pi_{C=O}^*$  vicinal charge transfer stabilizations ( $\delta\Delta E_{CT} < 0$ ) in the anionic form leads to a decrease in the major electrostatic stabilization involving anionic center at  $C^1$  ( $C^1 \leftrightarrow C^4$ ) due to a decrease in the negative charge on  $C^1$ . The decrease in the electrostatic stabilization invariably raises the  $\Delta E_{NCT}$  term, ( $\delta\Delta E_{NCT} > 0$ ). This is why there is an inverse relationship between  $\delta\Delta E_{CT}$  and  $\delta\Delta E_{NCT}$  in the comparison of any two compounds, Table 4. Since the overlaps between the p type lone pair on the anionic center  $C^1$  and the two carbonyl  $\pi^*$  orbitals are similar and hence the term does not vary much in all the compounds, the  $\pi_{C=O}^*$  level (and hence  $\Delta\epsilon = \epsilon_{\pi^*} - \epsilon_n$ ) determines the  $n_C \rightarrow \pi_{C=O}^*$  delocalization stabilization,  $\Delta E^{(2)}_{n \rightarrow \pi^*}$  in eq. 3. The amount of negative charge on the anionic center  $C^1$  has a major effect on the  $\Delta E_{NCT}$  term since it is involved in the predominant electrostatic repulsions ( $C^1 \leftrightarrow$  ether and carbonyl oxygens) and attraction ( $C^1 \leftrightarrow C^4$ ) in the neutral as well as in the anionic molecules (vide supra).

Surprisingly, the acidity of 1,3-dioxane-4,6-dione, **IV**, is stronger than that of Meldrum's acid, **I**, by 2.1 kcal mol<sup>-1</sup> ( $\delta\Delta G^\circ = -2.1$  kcal mol<sup>-1</sup>). The component analysis suggested that the lower ionization energy of **IV** than **I** ( $\delta\Delta E^\circ = -2.6$  kcal mol<sup>-1</sup>) is due to a smaller increase in  $\Delta E_{NCT}$  term ( $\delta\Delta E_{NCT} = +31.3$  kcal mol<sup>-1</sup>) than the greater charge transfer stabilization ( $\delta\Delta E_{CT} = -33.9$  kcal mol<sup>-1</sup>). This may result from a greater electrostatic stabilization due to the larger increase in positive charge on  $C^4$  in **IV**<sup>-</sup> (from +0.267 to +0.280) than the corresponding charge on  $C^4$  in  $\Gamma^-$  (from 0.579 to 0.574) with similar negative charge on the opposite end of  $C^1$  [-0.610 (**I**)  $\rightarrow$  -0.628 ( $\Gamma^-$ ) vs -0.612 (**IV**)  $\rightarrow$  -0.631 (**IV**<sup>-</sup>)]. The greater acidity of **IV** than **I** predicted in the present work, however, cannot be verified in the absence of any experimental  $pK_a$  measurement for **IV**.

## Summary

Our results of DFT studies at the B3LYP/6-311+G(3df,2p) level predict a boat conformation for Meldrum's acid (**I**)



and gradual changes to a twisted chair (II) and to a chair (III) as the methylene group is substituted successively for the ether oxygens. All the cyclic anionic forms (I<sup>-</sup> → VI<sup>-</sup>) have half-chair forms due to planar delocalized structure (—C(=O)C=O—) involving the anionic carbon center (C<sup>-</sup>) and the two carbonyl groups. The major factor controlling the conformations in the cyclic compounds is the 1,4-electrostatic interaction, which is attractive in the boat form (I) whereas it is repulsive in the chair form (III). The dipole-dipole interaction theory cannot be invoked for rationalization of the higher acidity of Meldrum's acid (I) than dimedone (III). The driving forces in the ionization of Meldrum's acid are the strong charge-transfer delocalization ( $\Delta E_{CT} < 0$ ) and 1,4-electrostatic attraction in the ionized form (I<sup>-</sup>), both of which involve a p-type lone pair on the anionic center, C<sup>-</sup>. The lower acidities of acyclic series (VII-IX) than the corresponding cyclic series (I-VI) are mainly due to absence of the strong cationic center, C<sup>+</sup>, in the latter.

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