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Acidities and Homolytic Bond Dissociation Enthalpies (BDEs) of the Acidic H−A Bonds in Acyclic and Cyclic Alkoxycarbonyl Compounds (Esters and Carbamates)

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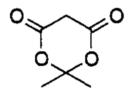
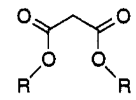
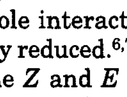
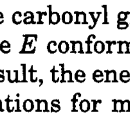
The equilibrium C−H bond acidities of three cyclic carboxylic esters wherein the alkoxycarbonyl group is locked into an *E* conformation have been shown to be about 4 pK_{HA} units greater than those of their acyclic analogues. Also, replacement of an α-methylene group in 2-indanone by an oxygen atom to form a cyclic ester of this type has been shown to cause an acidity increase of a comparable magnitude. These acidity increases are roughly one-half that observed for Meldrum's acid, a similarly constituted cyclic diester, relative to that of an acyclic analogue, dimethyl malonate. A similar increase in the N−H acidity of an acyclic carbamate was found to occur when its alkoxycarbonyl moiety was locked into a five-membered (2-oxazolidone) ring. These structural changes were found to cause little or no change in the BDEs of the acidic C−H or N−H bonds in these esters or carbamates. On the other hand, introduction of a C=C bond into 2-oxazolidone caused a 15 kcal/mol decrease in BDE.

In an earlier paper we reported that ring closures for ketones, carboxamides, or thiocarboxamides usually caused little change in their equilibrium acidities in DMSO. For example, cyclohexanone is only 0.7 pK_{HA} unit more acidic than 3-pentanone, 2-piperidone has essentially the same pK_{HA} as *N*-ethylpropionamide, and 2-thiopyrrolidone is only 0.4 pK_{HA} unit more acidic than thioacetamide.[1] On the other hand, Arnett and his co-workers found that Meldrum's acid (**1**)[2] was 8.6 pK_{HA} units more acidic in DMSO than its acyclic analogue, dimethyl malonate (**2**).[5] Arnett also showed that, whereas esters are known usually to be weaker acids than the corresponding ketones, Meldrum's acid is a stronger acid than the corresponding 1,3-cyclohexadiones by 3−4 pK_{HA} units.[5] The unexpectedly high acidity of **1**, relative to **2**, was recognized as being a consequence of the locked *E* conformation of the alkoxycarbonyl moiety present in **1**.[5] Calculations carried out by Wang and Houk,[6] and by Wiberg and Laidig,[7] supported this interpretation by showing that the *E* conformer of methyl acetate is 8−9 kcal/mol less stable than the *Z* conformer due to strong steric and dipole−dipole interactions present in the *E* conformer. These calculations agreed with the 8.5 kcal/mol higher energy of the *E* than *Z* conformer found for methyl acetate in the gas phase.[8] (Henceforth kcal/mol will be abbreviated as kcal.)


1


2


Z(syn)


E(anti)

The energy difference between the *Z* and *E* conformations for methyl acetate anion is calculated to be only about 3.8 kcal, however, because the negative charge is appreciably delocalized into the carbonyl group, and the dipole−dipole interaction in the *E* conformation will be significantly reduced.[6,7] As a result, the energy difference between the *Z* and *E* conformations for methyl acetate anion is about 5 kcal smaller than that between the corresponding neutral ester conformations. In other words, the equilibrium acidity of the *E* conformer of the ester is about 5 kcal (~4 pK_{HA} units) greater than that of the corresponding *Z* conformer.[6,7] This explains why the acidity of Meldrum's acid is about 8 pK_{HA} units (~10 kcal) greater than that of the dimethyl malonate since the *two* alkoxycarbonyl groups in Meldrum's acid are fixed in the *E* conformation.

In this paper we present additional examples of enhanced acidities of cyclic esters wherein the alkoxycarbonyl moiety is locked in an *E* conformation, relative to the acidities of their acyclic ester analogues. We have

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® Abstract published in *Advance ACS Abstracts*, September 15, 1994.

(1) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218−4225.

(2) In 1908, Meldrum isolated a colorless crystalline solid, $C_6H_8O_4$, from a condensation of malonic acid with acetone in acetic anhydride, which was believed to be a carboxylic acid because it had a pK_{HA} value almost identical with that of acetic acid in aqueous solution.[3] It was not until 40 years later that the correct carbon acid structure **2** was assigned to Meldrum's acid.[4]

(3) Meldrum, A. N. *J. Chem. Soc.* **1908**, *93*, 598−601.

(4) Davidson, D.; Bernhard, S. A. *J. Am. Chem. Soc.* **1948**, *70*, 3426−3428.

(5) (a) Arnett, E. M.; Maroldo, S. G.; Schilling, S. L.; Harrelson, J. A. *J. Am. Chem. Soc.* **1984**, *106*, 6759−6767. (b) Arnett, E. M.; Harrelson, J. A. *Gazz. Chim. Ital.* **1987**, *117*, 237−243. (c) Arnett, E. M.; Harrelson, J. A. *J. Am. Chem. Soc.* **1987**, *109*, 809−812.

(6) Wang, X.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 1870−1872.

(7) Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1988**, *110*, 1872−1874.

(8) Blum, C. E.; Gunthard, H. H. *Chem. Phys. Lett.* **1981**, *84*, 267.

(9) The conjugate anions of alkyl acetates are unstable in DMSO, but extrapolations and one-point titrations indicate that the pK_{HA} value of ethyl acetate is about 30.[10]

(10) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 4327−4331.

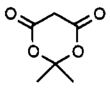
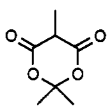
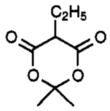
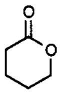
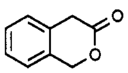
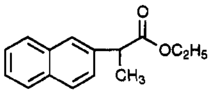
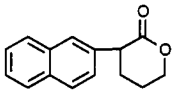
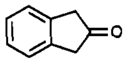
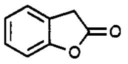
(11) Bordwell, F. G.; Zhang, X.-M.; Alnajjar, M. S. *J. Am. Chem. Soc.* **1992**, *114*, 7623−7629.

(12) Wheland, G. W. *Resonance in Organic Chemistry*; Wiley: New York, 1955.

(13) Bordwell, F. G.; Cheng, J.-P.; Ji, G.-Z.; Satish, A. V.; Zhang, X.-M. *J. Am. Chem. Soc.* **1991**, *113*, 9790−9795.

0022-3263/94/1959-6456$04.50/0

Table 1. Equilibrium Acidities and Homolytic Bond Dissociation Enthalpies (BDEs) of the Acidic C—H Bonds in Acyclic and Cyclic Esters

no.	acid	pK_{HA}[a]	ΔpK_{HA}	$E_{ox}(A^-)$[h]	BDE_{HA}[i]	ΔBDE
1	$CH_2(CO_2CH_3)_2$	15.9^{b}	(0.0)	0.010	95.3	(0.0)
2		7.32^{b}	8.58	0.400	92.6	2.7
3	$CH_3CH(CO_2CH_3)_2$	18.0^{b}	(0.0)	−0.324	90.5	(0.0)
4		7.42^{b}	10.58	0.185	87.5	3.0
5	$C_2H_5CH(CO_2CH_3)_2$	18.5^{b}	(0.0)			
6		7.57^{b}	10.9			
7	$CH_3CO_2C_2H_5$	$\sim30^{c}$	(0.0)			
8		25.2^{b}	4.8			
9	$PhCH_2CO_2C_2H_5$	22.6^{d}	(0.0)	−0.879	84.0	(0.0)
10		18.8	3.8	−0.678	83.4	0.6
11		$\sim24^{e}$	(0.0)			
12		20.1^{f}	4.1	−0.826	81.8	
13		16.9^{g}	(0.0)	−0.750	79.1	(0.0)
14		13.5^{1}	3.4	−0.504	80.1	−1.0

[a] In p*K* units; equilibrium acidities measured in DMSO soution against two indicators or standard acids with three-point titration by the overlapping indicator titration method as described previously[13] unless otherwise indicated. (See the Experimental Section). [b] Reference 5. [c] Estimated.[9] [d] Reference 10. Estimated from the pK_{HA} of ethyl phenylacetate and the usual 1 pK_{HA} unit increase in acidity of replacing a phenyl group by a naphthyl group and the usual 2.2 pK_{HA} unit decrease in acidity for the α-methyl substitution. [f] Measured by A. V. Satish in this laboratory. [g] Reference 15. [h] In volts; oxidation potentials of the conjugate anions measured by cyclic voltammetry under the conditions previously described.[13] [i] In kcal/mol; estimated using eq 1.[13]

$$\mathrm{BDE(kcal)} = 1.37\ pK_{HA} + 23.1E_{ox}(A^-) + 73.3\ \mathrm{kcal} \quad (1)$$

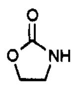
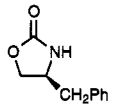
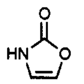
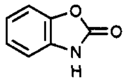
also found that cyclic carbamates having alkoxycarbonyl moieties locked into an *E* conformation have similarly enhanced acidities, relative to their acyclic analogues. Comparisons of the BDEs of the acidic C—H or N—H bonds in a number of these weak acids have also been made.

Results and Discussion

Effects of Ring Closure on the Acidities of Weak Acids Containing Alkoxycarbonyl Groups. The acidities of the acyclic and cyclic weak acids bearing alkoxycarbonyl groups are compared in Table 1.

The first six entries in Table 1 compare data for Meldrum's acid and its methyl and ethyl derivatives with those of the corresponding α-methyl and α-ethyl dimethyl malonates. The Meldrum's acids are seen to have acidities that are greater than those of their acyclic analogues by an average of 10 pK_{HA} units (13.7 kcal). Similarly, valerolactone (entry 8 in Table 1), a cyclic analogue of ethyl acetate in which the alkoxycarbonyl group is locked in a relatively unstable *E* conformation, has an enhanced acidity. The same is true of the lactones in entries 10 and 12, relative to their acyclic analogues. The acidities of these three lactones are greater by an average of about 3.9 pK_{HA} units (5.3 kcal) than those of their acyclic analogues. These acidity increases are about one-half those observed for Meldrum's acid, relative to its acyclic analogue, as expected.

Table 2. Equilibrium Acidities and Homolytic Bond Dissociation Enthalpies of the Acidic N—H Bonds in Acyclic and Cyclic Carbamates

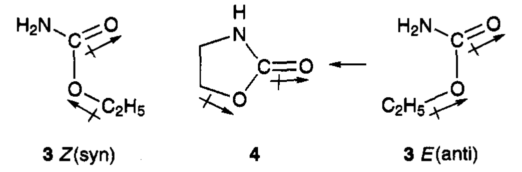
no.	acid	pK_{HA}[a]	ΔpK_{HA}	$E_{ox}(A^-)$[b]	BDE_{HA}[c]	ΔBDE
1	$C_2H_5OCONH_2$ (**3**)	24.6	(0.0)	−0.075	105.3	(0.0)
2	 (**4**)	20.87	3.73	0.169	105.8	−0.5
3		20.6	4.0	0.180	105.7	−0.4
4	 (**5**)	15.0	9.6	−0.129	91.0	14.3
5	 (**6**)	12.1	12.5	0.213	94.8	10.5

[a] In p*K* units; equilibrium acidities measured in DMSO solution against two indicators or standard acids with three-point titration by the overlapping indicator titration method as described previously[13] unless otherwise indicated. (See the Experimental Section). [b] In volts; oxidation potentials of the conjugate anions measured by cyclic voltammetry under the conditions previously described.[13] [c] In kcal/mol; estimated using eq 1.[13]

$$\mathrm{BDE(kcal)} = 1.37\ pK_{HA} + 23.1E_{ox}(A^-) + 73.3\ \mathrm{kcal} \quad (1)$$

The final entries in Table 1 (13 and 14) provide an example of a lactone wherein the alkoxycarbonyl group is locked in a relatively unstable *E* conformation and is thereby made more acidic than a closely related cyclic ketone, 2-indanone.

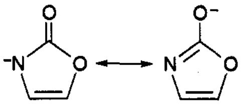
In Table 2 we have examined the effect of cyclization on the N—H acidity of *O*-ethyl carbamate (**3**). Here the acidic site has been changed from that of a methyl group in an ester to an amino group in a carbamate (**3**). Here too it seems likely that the cyclic analogue **4** (2-oxazolidone) of *O*-ethyl carbamate (**3**) has its alkoxycarbonyl moiety locked in a relatively unstable *E* conformation.



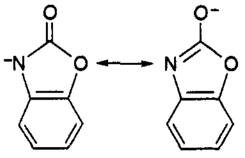
3 *Z*(syn) **4** **3** *E*(anti)

This causes an acidity enhancement, relative to an acyclic analogue, that is comparable to that observed for the lactones, relative to their acyclic esters (Table 1). This acidity enhancement has been observed thus far for two examples (entries 2 and 3 in Table 2). Additional examples are being sought. For example, it would be of interest to make acidity measurements on the nitrogen analogue of Meldrum's acid, where the acidic methylene group has been replaced by NH.

Entries 4 and 5 in Table 2 also have their alkoxycarbonyl moieties locked in a relatively unstable *E* conformation, but here the large enhancement in acidities must be associated primarily with the presence of the C=C bond for **5** [2(3*H*)-oxazolone] and the fused benzo ring for **6**. The anions **5**⁻ and **6**⁻ are stabilized by the presence of heteroaromatic (oxazole) ring systems, which offers at least a partial explanation for the 5.9 pK_{HA} unit (8 kcal) and 8.8 pK_{HA} unit (12 kcal) increase in the acidities of **5** and **6**, respectively, relative to that of **4**.



5⁻

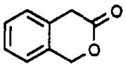
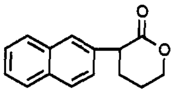
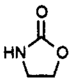
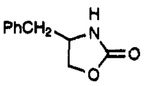
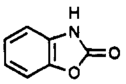


6⁻

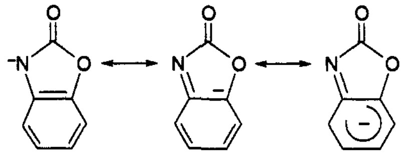
Homolytic Bond Dissociation Enthalpies. Examination of Table 1 shows that substitution of one of the acidic hydrogen atoms in dimethyl malonate by a methyl group causes about a 5 kcal/mol decrease in the BDE of the remaining acidic carbon−hydrogen bond, and that a similar effect is observed for substituting a methyl group for one of the acidic hydrogen atoms in Meldrum's acid. These effects on BDEs are comparable to those observed for introduction of a methyl group into methane,[14] acetophenone,[15] or nitromethane.[16] On the other hand, the structural change from dimethyl malonate to Meldrum's acid, which causes a 13.7 kcal increase in acidity, causes only about a 3 kcal decrease in the BDE of the acidic carbon−hydrogen bond. Also, the structural change from ethyl phenylacetate (entry 9) to 3-isochromanone (entry 10) in Table 1, which causes a 3.8 pK_{HA} unit (5.2 kcal) increase in acidity, causes only a 0.6 kcal decrease in the BDE of the acidic carbon−hydrogen bond. Also, the structural change from 2-indanone (entry 13) to benzo[*b*]furan-2(3*H*)-one (entry 14) causes a 4.6 kcal increase in acidity and only a 1 kcal increase in the BDE of the acidic C−H bond.

Turning to the enthalpy effects recorded in Table 2, we find that, as with esters, a change from the acyclic *O*-ethyl carbamate (**3**) to the cyclic analogue **4**, which causes about a 5 kcal increase in acidity, has essentially no effect on the BDE of the N−H bond. We conclude that for carbamates, as well as for esters, the structural change from an acyclic to a cyclic structure probably has little or no effect on the ground state energy. On the other hand, the introduction of a C=C bond in going from **4** to **5** causes not only an 8 kcal increase in acidity but a 15 kcal weakening of the N−H bond enthalpy. We have often observed that such large decreases in pK_{HA} values and large decreases in BDEs go hand in hand[17] and have suggested that such changes may sometimes be associated with an *increase* in ground state energy.[17] We suggest, therefore, that this is a possible explanation for the striking effects on acidity and BDE for the structural change from **4** to **5**. Ordinarily one would expect, however, that inclusion of the C=C bond in an aromatic ring, as occurs in the structural change from **5** to **6**, would cause a further increased in acidity and decrease in BDE since the negative charge in the anion or the odd electron in the radical can be delocalized into the benzene ring (e.g., **6a**⁻ ↔ **6c**⁻). This effect is realized for the acidity, but the BDE of the N−H bond has been *strengthened* by about 5 kcal.

Table 3. Equilibrium Acidities of Carbon Acids and Nitrogen Acids Determined by the Overlapping Indicator Method[a]

acid	pK_{HA}	indicator	pK_{In}[g]	SDV[h]	runs	selected pK_{HA}
	18.9	CNAH[b]	18.9	0.003	2	18.8
	18.74	PFH[c]	17.9	0.018	1	
	20.10	CNAH	18.9	0.03	1	20.1
	20.16	2NPANH[d]	20.6	0.02	1	
	20.87	CNAH	18.9	0.03	2	20.8
	20.75	2NPANH	20.6	0.02	2	
	20.58	CNAH	18.9	0.02	2	20.5
	20.45	2NPANH	20.6	0.02	1	
	12.13	HZFO2[e]	12.95	0.014	2	12.10
	12.09	HZFO2P[f]	11.98	0.011	1	

[a] See Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456 and references cited therein. [b] 4-Chloro-2-nitroaniline. [c] 9-Phenylfluorene. [d] 2-Naphthylacetonitrile. [e] 9-Fluorenone, 2-chlorophenylhydrazone. [f] 9-Fluorenone, 2,4-dichlorophenylhydrazone. [g] pK_{HA} value of the indicators used. [h] Standard deviation.



6a⁻ **6b**⁻ **6c**⁻

Experimental Section

Materials. 4-Benzyloxazolidone was a gift from David Evans, Harvard University. The other compounds used were commercial samples (Aldrich), which were checked for purity by ^1H NMR and mp for solids.

Equilibrium acidities and cyclic voltammograms were carried out as previously described.[13] The detailed acidity measurement data are summarized in Table 3.

Acknowledgment. This research was supported by the Donors of the Petroleum Research Fund administered by the American Chemical Society. We are grateful to David Evans for sending us a sample of 4-benzyl-2-oxazolidone with the suggestion that it might exhibit enhanced acidity, relative to an open-chain analogue.

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[14] McMillen, D. F.; Golden, D. M. *Annu. Rev. Phys. Chem.* **1992**, *33*, 493−532.

[15] Bordwell, F. G.; Harrelson, J. A. *Can. J. Chem.* **1990**, *68*, 1714−1718.

[16] Bordwell, F. G.; Satish, A. V. *J. Am. Chem. Soc.* **1994**, submitted.

[17] Bordwell, F. G.; Satish, A. V.; Zhang, S.; Zhang, X.−M. *J. Org. Chem.* **1994**, submitted.