J. Am. Chem. Soc. **1984**, *106*, 6759-6767

angular $4n\pi$ conjugated polycycles, exemplified by phenanthrene dianion $\mathbf{3}^{2-}$, sustain larger antiaromatic contributions than are exhibited by the linear systems. This theoretical-based assumption is now clearly demonstrated experimentally by the anions derived from dibenzotetracene (**1**) and 9-(9′-phenanthryl)anthracene (**4**).

Experimental Section

Dibenzotetracene (1) was prepared by a bis-Wittig reaction between phenanthrenequinone and the bis(triphenylphosphine) dibromide salt derived from 2,3-dimethylnaphthalene. The reaction was conducted under phase-transfer catalysis conditions using LiOH as a base.[16]

9-(9′-Phenanthryl)anthracene (4) was prepared by a Grignard reaction between 9-phenanthrylmagnesium bromide and anthrone in a mixture of dry benzene and THF. The reaction was conducted at room temperature for 24 h while strict anhydrous conditions and nitrogen atmosphere were maintained.

The anionic species were prepared by reduction of the respective neutral compounds with sodium or lithium metals. A wire of the metal was introduced to the upper part of an extended 5-mm NMR tube containing 10^{-2} M of the hydrocarbon dissolved in THF-d_8 (Aldrich). The frozen solution was degassed, and then the tube was sealed under vacuum. The solution was brought into contact with the metal for controlled periods by turning the tube upside down.

The NMR spectra were obtained on Bruker WH-300 pulsed FT spectrometer operating at 300.133 and 75.46 MHz for ^{1}H and ^{13}C NMR, respectively, equipped with an Aspect-2000 computer.

Registry No. **1**, 216-00-2; $\mathbf{1}^{2-}$, 91586-08-2; $\mathbf{1}^{2-}\cdot 2Li^+$, 91586-12-8; $\mathbf{1}^{2-}\cdot 2Na^+$, 91586-14-0; **4**, 91586-10-6; $\mathbf{4}^{4-}$, 91586-09-3; $\mathbf{4}^{4-}\cdot 4Na^+$, 91606-04-1; Li, 7439-93-2; Na, 7440-23-5; 9,10-phenanthrenequinone, 84-11-7; 2,3-dimethylnaphthalene bis(triphenylphosphonium) dibromide, 39013-98-4; 9-phenanthrylmagnesium bromide, 71112-64-6; anthrone, 90-44-8; pentacene dianion, 34484-46-3; tetracene dianion, 53571-97-4; anthracene dianion, 56481-92-6; phenanthrene dianion, 67382-15-4; 9,10-benzophenanthrene dianion, 66973-59-9; 1,2-benzanthracene dianion, 78858-01-2.

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Ion Pairing and Reactivity of Enolate Anions. 5. Thermodynamics of Ionization of β-Di- and Tricarbonyl Compounds in Dimethyl Sulfoxide Solution and Ion Pairing of Their Alkali Salts[1]

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Received March 23, 1984. Revised Manuscript Received May 25, 1984

Abstract: A variety of β-di- and triketones and esters with different substituents and conformations were deprotonated by the potassium salt of Me_2SO in that solvent. Standard free energies, enthalpies, and entropies of ionization are derived from pK_a's and heats of deprotonation. The overall effects of structure variation for the ketones and esters reported here follow generally accepted patterns based on the merged results of many previous studies in various solvents: acyclic ketones are slightly more acidic than analogous esters, cyclic members of both series are more acidic than acyclic analogues, and alkyl substitution on the carbon bearing the acidic proton reduces acid strength while accumulation of carbonyl groups on the acidic carbon increases acidity. These trends are also followed in the gas phase and so are not the result of solvent effects. Although a good extrathermodynamic correlation is found for pK_a's of ketones vs. pK_a's of analogous esters and a fair correlation is found for $\Delta G_i°$ vs. $\Delta H_i°$, an attempted "isoequilibrium plot" of $\Delta H_i°$ vs. $\Delta S_i°$ is a virtual random scatter of points. In view of the many stereoelectronic and solvation factors which may be affecting the acidities of these compounds, we have avoided interpreting variations of less than 2 kcal/mol in making comparisons between individual compounds. However, the acidities of the Meldrum acids are so large compared either to acyclic diesters or to analogous dimedones that discussion seems to be justified in terms of Huisgen's analysis of dipole opposition in cis vs. trans ester conformations. Ion-pairing constants (K_{assoc}) for the alkali enolates were obtained for several cases both by conductance and the Bordwell titration method with good agreement in most of those cases studied by both methods. In terms of log K_{assoc}, there is a generally good correlation between the interaction of potassium and sodium ions with the enolate anions reported here, but the lithium ion and the proton (pK_a's) show no correlation with the larger cations. The complexities of this extensive analysis of relatively simple and well-defined enolates provide a warning against the interpretation of relatively small rate or product differences (e.g., <2 kcal/mol) of more complex enolates under less controlled conditions in terms of ad hoc structure–reactivity arguments.

Base-promoted reactions of carbonyl compounds are the largest single class of synthetic processes in organic chemistry.[2-5] One need only consider the many classical variants of aldol chemistry or of its most recent applications to stereochemical control[6-8] to appreciate the importance of enolates as reactive intermediates. However, there have been a disproportionately small number of systematic studies of enolate reactions from the viewpoint of physical organic chemistry. These have been summarized in several reviews.[9-12]

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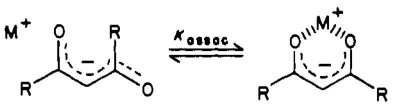
Some years ago we began to attack the problem through a study of the ionization, ion pairing, and alkylation of the relatively stable alkali salts of symmetrical β-diketones.



Dimethyl sulfoxide (Me_2SO) was chosen as solvent because of the expanding understanding of ionization processes to form anions in this medium.[13-15] Also, there was increasing evidence that ion-pairing equilibria could be studied conveniently in Me_2SO[16-18] so that the influence of this factor on the thermodynamics, kinetics, and regiochemistry of base-promoted reactions could be elucidated quantitatively.

Earlier work[1] demonstrated clearly (for at least the systems which we had studied) that a rapid equilibrium exists between free enolate anions and the chelate ion pairs and that the free enolate ions are by far the more reactive toward alkyl iodides, alkylation occurring almost exclusively on carbon.

However, when we attempted to extend the study to a wider range of diketones and diesters we were plagued with nonreproducible rates and heats of reaction. Eventually this problem was solved by improved purification of the Me_2SO solvent, and we are now ready to report the results of our continued study.

The present paper will be devoted to the thermodynamics of formation of the enolate anions by ionization of symmetrical β-di- and tricarbonyl precursors in Me_2SO at 25 °C. Ion-pairing constants for the lithium, sodium, and potassium salts are also reported and in many cases are compared by two methods: conductance and Bordwell's titration method.[19]

In a subsequent paper these thermodynamic results will be combined with rate data and activation parameters to analyze the effects of molecular and ionic structure on enolate reactivity.

Experimental Section

All compounds were either available commercially or prepared via simple literature procedures. Liquids were usually fractionally distilled through a Vigreux column under reduced pressure. Solids were usually purified by multiple recrystallizations and dried at ≈1-mm pressure in a vacuum oven overnight. Purity was checked by boiling point or melting point determinations (Thomas Hoover capillary apparatus), ^1H NMR spectroscopy (IBM NR-80), and GC (Varian aerograph 920) or HPLC (Varian 5000). Compounds were stored away from light either under argon or in a vacuum desiccator. All glassware was dried at 125 °C for 12 h and cooled under a flow of argon prior to use.

Acetylacetone (2,4-pentanedione, Aldrich) was fractionally distilled through a Vigreux column; bp 39–40 °C (25 mm).[20] Methylacetylacetone (3-methyl-2,4-pentanedione) and ethylacetylacetone (3-ethyl-2,4-pentanedione) were prepared by alkylation of excess acetylacetone[21] and purified by fractional distillation under reduced pressure: methylacetylacetone, bp 68–70 °C (26 mm);[22] ethylacetylacetone, bp 75–76 °C (20 mm).[23] Gas chromatography was used to check for dialkylation. The purification of dipivaloylmethane (2,2,6,6-tetramethyl-3,5-heptanedione) and dibenzoylmethane (1,3-diphenyl-1,3-propanedione) have been described elsewhere.[1c] Dimethyl malonate, dimethyl methylmalonate, and dimethyl ethylmalonate were prepared by transesterification of the corresponding diethyl malonates in refluxing methanol, to which acid catalyst had been added[24] until proton NMR showed complete conversion. The products were then purified by fractional distillation under reduced pressure: dimethyl malonate, bp 165–70 °C (745.4 mm); dimethyl methylmalonate, bp 78–78.5 °C (20 mm); dimethyl ethylmalonate, bp 87.5–88 °C (20 mm).[25] Diethyl malonate (Aldrich) was fractionally distilled: bp 70.5–71 °C (5 mm).[25] Dimedone (5,5-dimethyl-1,3-cyclohexanedione, Aldrich) was purified by recrystallization from acetone: mp 147–147.5 °C.[26] Methyldimedone (2,5,5-trimethyl-1,3-cyclohexanedione) was prepared by the method of Heathcock[27] and recrystallized from ethyl acetate: mp 159.5–160 °C.[28] Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione, Aldrich) was recrystallized from water: mp 94–95 °C.[29] Methyl Meldrum's acid (2,2,5-trimethyl-1,3-dioxane-4,6-dione) and ethyl Meldrum's acid (2,2-dimethyl-5-ethyl-1,3-dioxane-4,6-dione) were prepared by the acidic condensation of methyl- or ethylmalonic acid with acetone in the presence of acetic anhydride.[30] The product was purified by recrystallization from an acetone–water mixture: ethyl Meldrum's acid, mp 108–109 °C;[30] methyl Meldrum's acid, mp 114.5–115 °C.[31] 2-Methyl-1,3-cyclopentanedione (Aldrich) was recrystallized from water; mp 211.0–211.8 °C.[32] Triacetylmethane (3-acetyl-2,4-pentanedione, Aldrich) was fractionally distilled; bp 93–94 °C (19.5 mm).[22] Tricarbomethoxymethane was prepared by the reaction of sodium dimethylmalonate with methyl chloroformate[33] and purified by distillation under reduced pressure: bp 130–140 °C (20 mm).[33] This was followed by recrystallization from methanol and washing with petroleum ether: mp 43.5–44 °C.[33] Acetyldimedone (2-acetyl-5,5-dimethyl-1,3-cyclohexanedione) was prepared following the method of Smith[34] by refluxing dimedone with anhydrous sodium acetate in acetic anhydride for 5 h. The acetic anhydride was then removed and the product was extracted into aqueous sodium hydroxide, followed by neutralization and extraction with ether. After the solution was dried over sodium sulfate, the ether was removed and the product was fractionally distilled: bp 134–135 °C (21 mm);[35] mp 33.6–34 °C.[36]

Alkali iodide salts were obtained commercially and dried in excess of 100 °C at ≈1-mm pressure in a vacuum oven prior to use.

Indicators. Preparation of the Bordwell pK_a indicators has been described elsewhere.[13] 2-Bromo-9-phenylthiofluorene (mp 117–118 °C) was prepared in a manner analogous to 9-phenylthiofluorene starting with 2-bromofluorene (Aldrich). The indicators used are as follows with their pK_a's in Me_2SO:[13,37] 9-cyanofluorene (8.3), 9-phenylsulfonylfluorene (11.55), 2-bromo-9-phenylthiofluorene (13.2), 9-phenylthiofluorene (15.4), 9-phenylfluorene (17.9).

Dimethyl sulfoxide (Aldrich) was predried over 4-Å molecular sieves. It was then treated with enough *n*-butyllithium to turn a small amount of triphenylmethane (as an indicator) a deep red color. Next it was doubly distilled at a pressure of 0.02 mm at <30 °C, the middle 70% being retained in each distillation. The purified Me_2SO was stored under positive pressure of argon gas in a solvent bottle taped to exclude light and equipped with an automatic zeroing solvent buret. The water content was checked by Karl Fischer titration by using a Fisher automatic titrimeter system and consistently found to be below 100 ppm. An essential feature of the purification for reproducible heats and kinetics of reaction, to be discussed in a subsequent paper, was the extended pumping for 4–5 days at 0.02-mm pressure during the distillation through

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an 18-in. Vigreux column. This treatment was not important for most of the ionization procedures reported here but was followed for the preparation of all of the batches of Me_2SO since they were used as solvent for a variety of applications.

The alkali metal–Me_2SO anion (Me_2SYL^-) salt was prepared from Me_2SO and KH or NaH, following the procedures of Bordwell and co-workers.[19,38]

Preparation of Enolates. Enolates were prepared from the carbonyl compounds and the alkali metals as follows. Approximately 25 mL of methanol was distilled from sodium into a 50-mL round-bottom flask. A piece of the alkali metal which had been cleaned was then weighed under benzene and added to the methanol. An approximate 1% excess of the carbonyl compound was then added to the methanol solution along with the several milliliters of dry benzene, which was added to azeotrope any water, and the solvent was removed by rotary evaporation. The solid enolate precipitate which formed was then washed with several portions of benzene and dried under vacuum. The enolates were stored under vacuum away from light until needed. Solutions of known concentrations were made immediately before use by weighing the enolate in a tared 50-mL volumetric flask purged with argon. Next, Me_2SO was added with stirring and the flask and contents weighed again after solution was complete.

Calorimetry. Heats of solution in Me_2SO and heats of deprotonation with $K^+Me_2SYL^-$ in Me_2SO were measured by using a Tronac Model 1250 solution calorimeter. The reaction vessel was a 50-mL silvered Dewar flash which contained an ampule breaker–stirrer assembly, a thermistor for measuring temperature change, and an electrical heater for calibrating the system. Temperature changes were presented on a Sargent Model SRG strip chart recorder. All measurements were made in the isoperibolic mode at 25 °C.

The β-dicarbonyl compound was sealed in a glass ampule made of 3-mm Pyrex tubing and weighed carefully. Me_2SO or $K^+Me_2SYL^-$/Me_2SO solution (40 mL) was placed in the reaction vessel, and the apparatus was assembled. The system was brought to 25 °C and allowed to equilibrate in the thermostated constant temperature bath. A heating curve was then run to determine the heat capacity of the system. After reequilibration, the ampule was broken and the temperature change was recorded. This was followed by a second heating curve. The enthalpy of solution was calculated from the measured temperature change and the heat capacity determined from the heating curves.

pK_a and K_{assoc}. Ion-pairing association constants and pK_a's were measured by using the method developed by Bordwell and co-workers.[13,19] Measurements were made in a 1-cm glass cell topped with a three-way glass stopcock. Stock solutions were prepared and kept under a positive pressure of argon. Additions were made by using gas-tight syringes with stainless steel needles. Absorbance was measured on a Cary 15 UV/vis spectrophotometer at an appropriate wavelength. Weighing was done on a Mettler Model H524 balance. Indicators used are listed above along with their pK_a values.

Conductance. Association constants (K_{assoc}) of several alkali enolate salts were also measured in Me_2SO by using conductance. Conductance was measured with a Beckman Model RC-18A conductance bridge. This is an AC bridge operated at either 1000 or 3000 Hz and is rated as a 0.05% bridge over a range of 500–50 000 ohms. It is far superior to the 1% bridge used in our earlier work. The conductivity cell was a Beckman Model CEL-6J95 Jones-type cell. The electrodes were platinum disks that had been platinized by electrolyzing a solution of platinic chloride containing approximately 1% lead acetate.[39] The Jones cell was thermostated to ±0.05 °C with a Hotpack Model 63340 refrigerated bath-circulator oil bath. All samples were equilibrated at 25 °C for 45 min. Seven readings were taken over 30 min to assure that there were no temperature fluctuations. The Jones cell constant that was measured by using aqueous 0.01000 demal (D) KCl solution was found to be 0.5049 ± 0.0002 cm^{-1}. Association constants (K_{assoc}) were calculated by using the Grunwald–Marshall method as before.[1c]

Results

Experimental results from this study are presented in Table I which is organized to expedite comparisons of di- and triketones with the corresponding esters and to compare acyclic and cyclic members of both series. For the sake of comparing points in the following figures with the compounds in Table I, the abbreviations given there will frequently be used. Equilibrium constants for ionization of these carbon acids and their association constants with alkali cations were determined with frequent reference to the comparable studies by Professor F. G. Bordwell and his students.[19] In nearly every case where we repeated a pK_a determination using the Bordwell method, our results agreed with theirs within experimental error, based on their values for the indicator's pK_a.

Heats of deprotonation, ΔH_D, were determined in our laboratory by using the methods described previously.[40,41] Thermodynamic properties for ionization were placed on the same standard state used by Bordwell for free-energy calculations according to the following equations as discussed previously.[41]

$$AH + Me_2SO \rightarrow A^- + Me_2SOH^+ \qquad (1)$$

$$\Delta H_i = \Delta H_D + 48.0 \pm 0.8 \text{ kcal/mol} \qquad (2)$$

$$\Delta G_i^\circ = 2.303RT(pK_a + \log 14) \qquad (3)$$

$$\Delta S_i^\circ = (\Delta H_i^\circ - \Delta G_i^\circ)/T \qquad (4)$$

The last two columns of Table I provide a comparison between ion-pair association constants determined by the Bordwell indicator titration technique and independent measurements determined by conductance. Our results using the indicator method to measure the association constants of the three alkali cations show very close agreement, well within experimental error, between our values and those of the Bordwell group using the same method.

Although association constants determined by the indicator titration methods and conductance method agree quite well in many cases, several examples (e.g., lithium MAA, potassium DPM, and sodium MDMM) show discrepancies far beyond the pooled experimental errors. We are unable to account for these discrepancies but wish to emphasize that the conductance measurements were made by different workers with different samples of solvent and other materials over a period of 5 years. In view of other difficulties which we encountered in our earlier studies due to impurities in the solvent, we consider the overall agreement of the two methods to be reasonably good. However, if a choice must be made when using these values, we recommend those derived from the indicator titration method as a larger more self-consistent data base.

Two other factors could affect comparisons of ion-pairing data by the two methods. Lithium enolates have a tendency to form triple ions and higher aggregates which may complicate interpretation in the more concentrated solutions used for conductance studies.[10,42-44] Also, the dimedones have a marked tendency to form homoconjugated anions (A^-–HA) through hydrogen bonding from the enolic form of the diketone.[15b,19] This was corrected for in the indicator titrations, but correction was not necessary in the conductance work because no unionized carbonyl compound was present since these solutions were prepared from the purified solid alkali enolate.

Discussion

Introduction. We are now in a position to examine the effects of molecular and ionic structure on the thermodynamics of ionization and ion-pair association for an extensive series of related cyclic and acyclic di- and tricarbonyl compounds. Although many of the largest effects have been known qualitatively for many years, it is now possible to dissect their origins in far greater detail than was previously possible. In solution, the extensive pK_a studies by Bordwell and his students provide by far the broadest comparison of acidities under a single set of conditions (Me_2SO solvent at 25 °C) that is available in the literature. We have employed their techniques for determining pK_a's and ion-pair association constants

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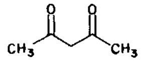
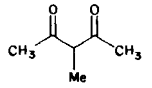
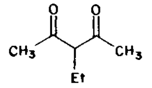
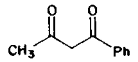
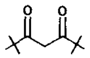
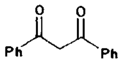
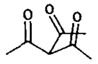
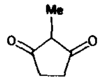
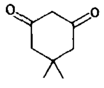
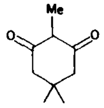
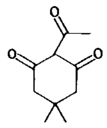
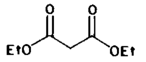
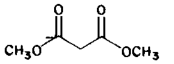
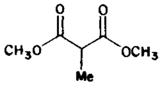
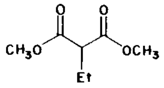
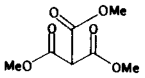
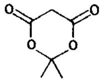
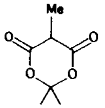
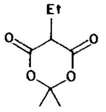
Table I. Thermodynamic Properties for Ionization and Ion Association of Di- and Triketones and Esters and Their Alkali Enolates in Dimethyl Sulfoxide at 25 °C

compounds	pK_a	ΔH_D, kcal/mol	ΔG_i°, kcal/mol	ΔH_I°, kcal/mol	ΔS_i°, cal/mol K^{-1}	log K_{assoc} indicator	log K_{assoc} conductance
 AA, acetylacetone	13.33 ± 0.05^{a} 13.41 ± 0.01	−31.73 ± 0.34^{b}	19.86 ± 0.02	16.3 ± 0.9 (0.34)	−12.1 ± 2.9 (1.2)	K$^+$ 1.39 ± 0.09^{a} 1.399 ± 0.009 Na$^+$ 2.60 ± 0.06^{a} 2.57 ± 0.05 Li$^+$ 4.77 ± 0.1^{a} 4.76 ± 0.04	
 MAA, methylacetylacetone	15.07 ± 0.06^{a} 15.068 ± 0.005	−31.7 ± 1.2	22.125 ± 0.007	16.3 ± 1.5 (1.2)	−19.5 ± 4.8	K$^+$ 0.79 ± 0.1^{a} 0.73 ± 0.04 Na$^+$ 1.52 ± 0.09^{a} 1.56 ± 0.02 Li$^+$ 3.38 ± 0.14^{8} 3.33 ± 0.06	0.89 ± 0.22 1.58 ± 0.19 2.76 ± 0.08
 EAA, ethylacetylacetone	15.346 ± 0.006	−32.7 ± 1.1	22.504 ± 0.008	15.3 ± 1.4 (1.1)	−24.2 ± 4.6 (3.7)	K$^+$ 0.85 ± 0.09 Na$^+$ 1.48 ± 0.04 Li$^+$ 3.36 ± 0.07	
 BA, benzoylacetone	12.684 ± 0.009^{a}	−32.9 ± 0.40	18.87 ± 0.01	15.1 ± 0.9 (0.4)	−12.8 ± 3.0 (1.4)		
 DPM, dipivaloylmethane	15.41 ± 0.03	−30.28 ± 0.37	22.59 ± 0.04	17.72 ± 0.88 (0.37)	−16.3 ± 3.0 (1.3)	K$^+$ 2.61 ± 0.09 Na$^+$ 3.63 ± 0.13 Li$^+$ too high	3.13 ± 0.04^{c} 3.47 ± 0.10^{c} conductance negligible
 OBM, dibenzoylmethane	13.36 ± 0.06^{a}	−33.2 ± 0.4^{b}	19.79 ± 0.08	14.80 ± 0.89 (0.40)	−16.8 ± 3.0 (1.4)	K$^+$ 2.76 ± 0.07^{a} Na$^+$ 3.97 ± 0.04^{a} Li$^+$ 5.86 ± 0.11^{a}	2.72 ± 0.04^{c} 3.79 ± 0.10^{c} conductance negligible
 TAM, triacetylmethane	8.60 ± 0.03	−46.68 ± 0.72	13.30 ± 0.04	1.3 ± 1.1 (0.72)	−40.2 ± 3.6 (2.4)	K$^+$ no IP observed Na$^+$ no IP observed Li$^+$ 1.33 ± 0.13	1.45 ± 0.27 1.42 ± 0.06 1.40 ± 0.20
 MCPD, methylcyclopentanedione	10.418 ± 0.006	−33.75 ± 0.36	15.78 ± 0.01	14.25 ± 0.87 (0.35)	−5.1 ± 2.9 (1.2)	K$^+$ negligible Na$^+$ Li$^+$	0.68 ± 0.04 1.23 ± 0.2 insoluble
 DD, dimedone	11.16 ± 0.02^{a}	−33.93 ± 0.40^{b}	16.79 ± 0.03	14.07 ± 0.89 (0.40)	−9.1 ± 3.0 (1.4)	K$^+$ <1^{a} Na$^+$ 1.05 ± 0.14^{a} Li$^+$ 1.58 ± 0.03^{a}	
 MDD, methyldimedone	11.33 ± 0.24^{a} 11.73 ± 0.02	−32.39 ± 0.54	17.57 ± 0.03	15.61 ± 0.96 (0.54)	−6.6 ± 3.2 (1.8)	K$^+$ negligible Na$^+$ Li$^+$	0.64 ± 0.06 1.03 ± 0.07 1.73 ± 0.14

 ADD, acetyldimedone	9.83 ± 0.05	−50.26 ± 0.86	14.98 ± 0.07	−2.26 ± 1.17 (0.86)	−57.8 ± 3.9 (2.9)	K^+ 2.10 ± 0.07 Na^+ 3.07 ± 0.09 Li^+ 4.32 ± 0.04	
				Diesters			
 DEM, diethyl malonate	16.37 ± 0.06[a]	−31.01 ± 0.36	23.90 ± 0.08	16.99 ± 0.88 (0.36)	−23.2 ± 3.0 (1.3)	K^+ 2.31 ± 0.02[a] Na^+ 3.30 ± 0.06[a] Li^+ 4.56 ± 0.07[a]	
 DMM, dimethyl malonate	15.88 ± 0.03	−30.60 ± 0.49	23.23 ± 0.04	17.34 ± 0.94 (0.49)	−19.8 ± 3.2 (1.7)	K^+ 2.23 ± 0.04 Na^+ 3.26 ± 0.01 Li^+ 4.50 ± 0.12	
 MDMM, dimethylmethylmalonate	18.04 ± 0.02	−27.95 ± 0.53	26.18 ± 0.03	20.05 ± 0.96 (0.53)	−20.6 ± 3.2 (1.8)	K^+ 2.05 ± 0.03 Na^+ 3.22 ± 0.09 Li^+ 4.72 ± 0.09	2.04 ± 0.15 2.74 ± 0.01 conductance negligible
 EDMM, dimethyl ethylmalonate	18.47 ± 0.02	−27.83 ± 0.26	26.77 ± 0.03	20.17 ± 0.84 (0.26)	−22.1 ± 2.8 (0.9)	K^+ 2.02 ± 0.06 Na^+ 3.22 ± 0.07 Li^+ 4.86 ± 0.06	
 TCM, tricarbomethoxymethane	10.81 ± 0.03	−37.53 ± 0.49	16.32 ± 0.04	10.47 ± 0.94 (0.49)	−19.6 ± 3.1 (1.6)	K^+ 1.62 ± 0.10 Na^+ 2.22 ± 0.07 Li^+ 2.96 ± 0.06	
 MA, meldrum's acid	7.32 ± 0.01	−38.47 ± 0.30	11.55 ± 0.02	9.53 ± 0.86 (0.30)	−6.8 ± 2.9 (1.0)	K^+ negligible Na^+ Li^+	
 MMA, methyl meldrum's acid	7.42 ± 0.01	−39.71 ± 0.88	11.69 ± 0.02	8.29 ± 1.2 (0.88)	−11.4 ± 4.0 (2.9)	K^+ negligible Na^+ Li^+	
 EMA, ethyl meldrum's acid	7.57 ± 0.01	−38.87 ± 0.75	11.89 ± 0.02	9.13 ± 1.10 (0.75)	−9.3 ± 3.7 (2.5)	K^+ negligible Na^+ Li^+	

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[a] From ref 19 or 64. [b] From ref 41. [c] From ref 1c. Errors in parentheses do not include contribution of ±0.8 kcal mol^{-1} from error in heat of autoprotolysis. Blank spaces indicate that no measurement was attempted.

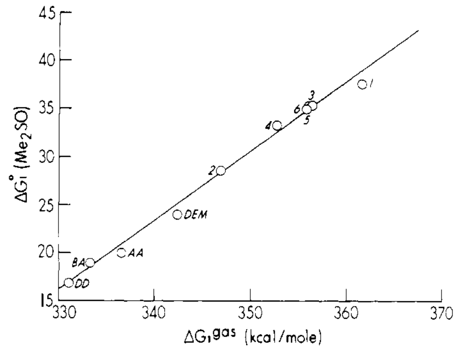


Figure 1. Correlation of standard free energies of ionization, $\Delta G_i°$, in dimethyl sulfoxide,[19,64] with free energies of ionization in the gas phase.[45] Letters refer to compounds in Table I; numbers refer to the following compounds: (1) acetone, (2) phenylacetone, (3) acetophenone, (4) *m*-chloroacetophenone, (5) *m*-methoxyacetophenone, (6) ethyl phenyl ketone.

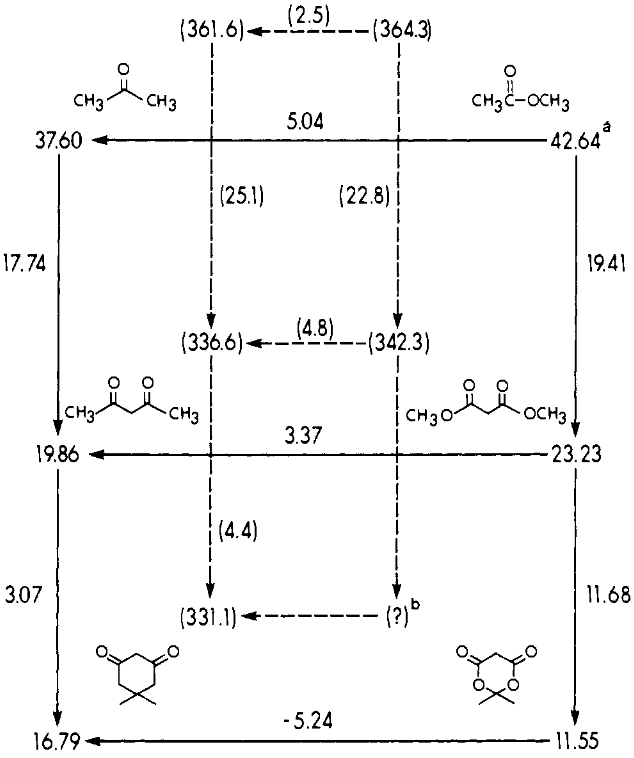
for the ketones and esters in Table I. Complementary thermochemical results from this laboratory allow dissection of the Gibbs free-energy terms derived from pK_a's into enthalpy and entropy terms. During the past decade gas-phase acidity measurements[45] have provided the necessary information to factor out the effects of solvation on the thermodynamics of ionization from inherent structural effects due to steric and electronic terms. A variety of techniques have provided reliable data on the degree of enolization of carbonyl-activated carbon acids. A growing appreciation of the importance of ion pairing[19] and homoconjugative stabilization[15b,19] of enolate anions in solution has led to the information needed to separate true pK_a's for the conversion of acids to dissociated ions at high dilution from the apparent values at higher concentrations where aggregation effects become involved. In the following discussion we will examine the role that molecular and ionic structure, enolization, ion-pairing, and solvation have on the thermodynamic properties for ionization in Me_2SO.

Cyclic and Acyclic Ketones and Esters. Scheme I summarizes the most interesting comparisons of ketones with esters and the influence of cyclization in both series. Gibbs free energies of ionization in Me_2SO ($\Delta G_i°$) were derived from pK_a measurements (Table I) and are referred to the same standard state as the calorimetric $\Delta H_i°$ measurements (see Results section). For comparison, gas-phase acidities (ΔG_i^{gas}) are presented from a common source.[45]

It is clear from the structural comparisons shown by arrows in Scheme I and the correlation of $\Delta G_i°$ vs. ΔG_i^{gas} (Figure 1) that the pK_a measurements in Me_2SO give a realistic representation of the inherent response of the ionization process to structural change. Within this series there is no evidence that large solvation energies are confusing the order of stability. (The classic study of Brauman and Blair[46] which demonstrated a complete reversal of alcohol acidities on passing from the gas phase to solution emphasizes the devastating effects of such a possibility.) Also the major trends shown in Scheme I for prototype compounds are supported by supplementary data for numerous related compounds (e.g., the data for MA are supported by those for MMA and EMA; for comparison with DD there is MDD).

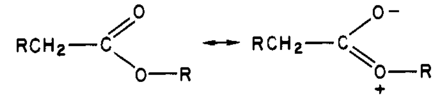
The overall pattern of $\Delta G_i°$'s is roughly what is accepted as "common knowledge" from such authoritative compilations as the monographs of Cram[47] and House.[2] However, although it is also "common knowledge" that dimedone and Meldrum's acid are more acidic than their acyclic analogues, we know of no previous publication which presents a direct comparison that does full justice to the magnitude of the effect in the cyclic diester.

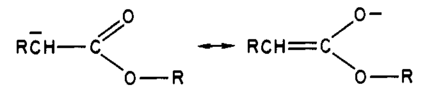
Scheme I. Comparison of Energies of Ionization of Acyclic and Cyclic Ketones and Esters[a]



[a] Numbers not in parentheses and solid lines connecting them refer to $\Delta G_i°$ in dimethyl sulfoxide. Numbers in parentheses and dotted lines refer to gas-phase free energies of ionization. (a) pK_a value is for *tert*-butyl acetate in Me_2SO. (b) An attempt by Professor R. W. Taft to measure the gas-phase acidity of Meldrum's acid was unsuccessful due to rapid decomposition of the isolated ion.

The principal questions raised by Scheme I are as follows: (1) Why are acyclic esters less acidic than corresponding ketones even though the alkoxy groups of the former should be electron attracting? (2) Why are cyclic carbon acids such as dimedone more acidic than acyclic analogues? (3) Why is Meldrum's acid so strong relative to the acyclic malonate esters and even to dimedone? The traditional answer to the first question[48,49] is that the ester functionality enjoys resonance stabilization which will make it more stable relative to its enolate anion than is the corresponding ketone relative to its enolate anion. Put another way, delocalization of negative charge from the α-methylene carbon to the ester carbonyl group (formula B) must partially disrupt the delocalization shown in formula A but would not do so for a corresponding ketone. The data in Scheme I are consistent with this argument,


$$RCH_2{-}C(=O){-}O{-}R \longleftrightarrow RCH_2{-}C(-O^-){=}\overset{+}{O}{-}R$$ (A)


$$R\bar{C}H{-}C(=O){-}O{-}R \longleftrightarrow RCH{=}C(-O^-){-}O{-}R$$ (B)

and the polarized structure in formula A is supported by the dipole moments and rotation barriers of esters.[48,50] Going from monoketones or monoesters to their dicarbonyl cognates results in a large, and nearly equivalent increase in acidity in both series, both in Me_2SO, and other solvents,[2] and in the gas phase.[45]

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(45) Bartmess, J. E.; McIver, R. T. In "Gas Phase Ion Chemistry"; Bowers, M. T.; Ed.; Academic Press: New York, 1979; Vol. 2, Chapter 11.

(46) Brauman, J. I.; Blair, L. K. *J. Am. Chem. Soc.* **1970**, *92*, 5986.

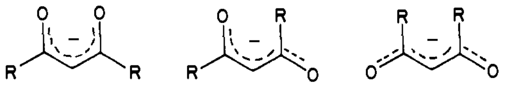
(47) Cram, D. J. "Fundamentals of Carbanion Chemistry"; Academic Press: New York, 1965.

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

(49) (a) Huisgen, R. *Angew Chem.* **1957**, *69*, 341–59. (b) Huisgen, R.; Ott, H. *Tetrahedron* **1959**, *6*, 253. (c) Deslongchamps, P. "Stereoelectronic Effects in Organic Chemistry"; Pergamon Press: Elmsford, NY, 1983; pp 52–53.

(50) Wyn Jones, E.; Pethrick, R. A. In "Topics in Stereochemistry"; Eliel, E. L., Allinger, N. L., Eds.; Wiley: New York, 1970; Vol. 5, p 245.

A further increase in acidity on passing to the cyclic dicarbonyl compounds has been explained in terms of the improved overlap of the carbanionic center with the flanking carbonyl groups in the more or less planar ring system. A number of NMR studies[41,51-53] have indicated that Coulombic repulsion in the U-shaped (*Z*,*Z*) conformation of dicarbonyl compounds and their free enolate anions makes the sickle-shaped (*E*,*Z*) or W-shaped (*E*,*E*) conformations preferred arrangements even though all three could enjoy good overlap in a planar π system.



Z,*Z* *Z*,*E* *E*,*E*

The remaining problem is the spectacular acidity of Meldrum's acid which in water is equivalent to acetic acid and is half a p*K* unit stronger than dimedone.[54] Clearly, if planarity were the only factor and the diketones were a model, $\Delta G_i°$ for Meldrum's acid should be about 20 kcal/mol. Alternatively, in terms of the 3.37 kcal/mol difference between DMM and AA, a similar estimate (16.79 + 3.37 kcal/mol) is reached.

In our opinion the most reasonable source of the large "extra acidity" of Meldrum's acid is related to Huisgen's[49b] observations of the relative stabilities of esters, which can assume the trans conformation (shown in formula A) in contrast to the enforced cis conformation of the cyclic lactone structure. The dipole moments, boiling points, and reactivities of the lactones indicate a considerable destabilization due to their cyclic cis arrangement with a maximum dipole moment and hydrolysis rate for seven- and six-membered rings. An initial-state increment of 3.8 kcal/mol for the cis-to-trans difference was estimated.[49b] Deslongchamps[49c] has presented a reasonable explanation of this effect in terms of extra stabilization of the trans ester form through overlap of unpaired electrons on the ether oxygen with the σ^* orbital of the carbonyl carbon. If now we regard Meldrum's acid as a bislactone for comparison with the bis-*trans*-diesters an important contribution to its acidity is recognized in addition to the benefit from the planar W arrangement, which it shares with dimedone. If the cis ester dipole contribution may be regarded as a conformationally dependent inductive effect whose destablization energy is accessible as a driving force for ionization two such contributions (7.6 kcal/mol) in Meldrum's acid when added to the cyclization factor (3.07 kcal/mol) come close (10.7 kcal/mol) to the difference (11.7 kcal/mol) between the acyclic diesters and Meldrum's acid. Although the successful result of this numerological exercise may be fortuitous it appears to fit the facts and we have found no alternative explanation or an appropriate means of extending Deslongchamps orbital arguments to the cis or trans enolate anions. This question and related experimental work are presently under further investigation in our laboratory.

Enolization. The keto-enol equilibrium of carbonyl compounds has been recognized as an important kinetic factor in their reactivity for at least 80 years[55] and has been the subject of several recent authoritative reviews.[2,56] It is widely recognized that in solution hydroxy acids, such as enols, are thermodynamically stronger acids by several pK units than are their carbon acid tautomers.[2,57] Me_2SO is an excellent hydrogen bond acceptor[13] and the β-dicarbonyl compounds studied here include several classical examples (e.g., AA) which form cyclic chelates with intramolecular hydrogen bonds.[58] However, the available data[2] indicate that diesters are much less enolized than are diketones—perhaps another manifestation of the cost of disrupting the resonance stabilization shown in formula A. The contrast is striking in the comparison of dimedone, which exists 95% as the enol in aqueous solution, and Meldrum's acid, which is over 99.99% keto.[54,59] Thus, any argument based on the superior acidities of enols would be countereffective in explaining the high acidity of Meldrum's acid. For the other comparisons of esters and ketones, the contribution of variable degrees of enolization to thermodynamic acidities (in contrast to kinetic acidities) should be so small (<1 kcal/mol) compared to the large effects we are attempting to elucidate that it should be lost in the background "noise" of other structural effects.

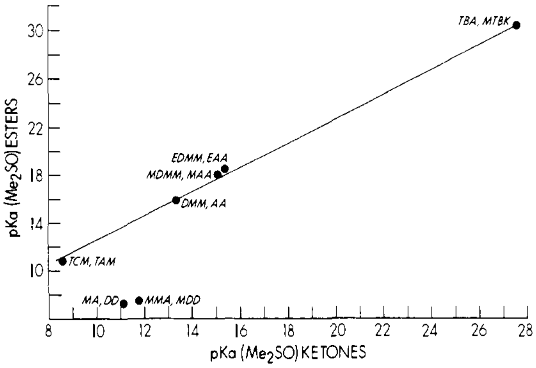


Figure 2. Correlation of pK_a's of mono-, di-, and tricarbonyl acids of comparable structures in ester and ketone series. TBA refers to *tert*-butyl acetate and MTBK refers to methyl *tert*-butyl ketone (64). All other points are listed in Table 1.

Substitution on the Acidic Carbon. Alkylation of the acidic methylene carbon causes a clear decrease in acidity in the acetylacetone and dimethyl malonate series but has much less effect on their cyclic cognates in the dimedones or Meldrum's acids. Tempting though it may be to interpret these results as clear evidence of conformational effects it is important to note that such small effects of alkyl groups on acidities in solution can be ascribed to a variety of factors. Aside from the small formal symmetry difference ($RT \log 2 = 0.41$ kcal/mol), which inherently would make all CH_2 acids twice as strong as their alkylated CRH homologues in the absence of other factors, the results of alkylation are not simple. Bordwell, Bartmess, and Hautala[60] analyzed the varying effects of substituting methyl for hydrogen on 28 carbon acids in terms of four classes. A flagrant example of complete reversal from the inherent acidity order as a result of solvation is the well-known case of the alcohols.[46] Against this background of complications, an ad hoc interpretation of the effects of alkylation on the pK_a's for the limited series shown in Table I in terms of conformational effects seems to be unwarranted.

The tricarbonyl compounds TAM, ADD, and TCM are considerably more acidic than the corresponding dicarbonyl compounds. Undoubtedly, added opportunities for charge delocalization play a major factor in these changes, but it is reasonable that they might be offset partly by the added steric problems for achieving the most favored conformation in the anion as a result of crowding around the central methine carbon. As will be seen below, the tricarbonyl acids have enormously larger entropies of ionization than do the dicarbonyl analogues, but there is no straightforward way to separate conformational from solvation effects.

Figure 2 demonstrates the close correspondence (slope ≈ 1.0) of the ketones and esters in their response to structural changes. Here each point is derived from the pK_a's of an ester and of the ketone closest to it in structure. The points for acyclic mono-, di-, and tricarbonyl compounds of each functionality all lie on a

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(51) (a) Noe, E. A.; Raban, M. *Chem. Commun.* **1976**, 165. (b) Raban, M.; Haritos, D. P. *J. Am. Chem. Soc.* **1979**, *101*, 5178.

(52) Cambillau, C.; Guibe, F. *Can. J. Chem.* **1982**, *60*, 634.

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(55) Lapworth, A. *J. Chem. Soc.* **1904**, 30.

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(59) Eigen, M.; Ilgenfritz, G.; Kruse, W. *Chem. Ber.* **1965**, *98*, 1623.

(60) Bordwell, F. G.; Bartmess, J. E.; Hautala, J. A. *J. Org. Chem.* **1978**, *43*, 3095.

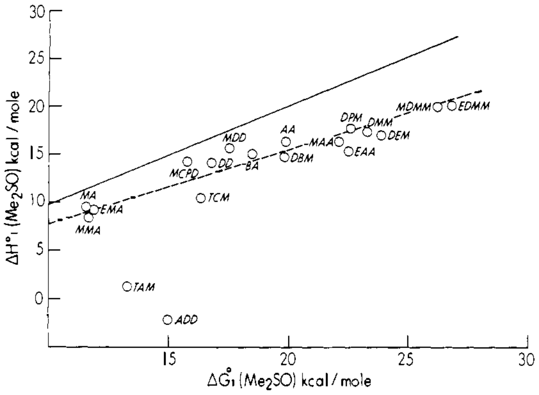

Figure 3. Correlation of standard enthalpies and free energies of ionization for compounds in Table I. Solid line is for reference to carbon acids such as hydrocarbons.[62] Dotted line refers to a variety of carbonyl acids[41] including some of those included in this study.

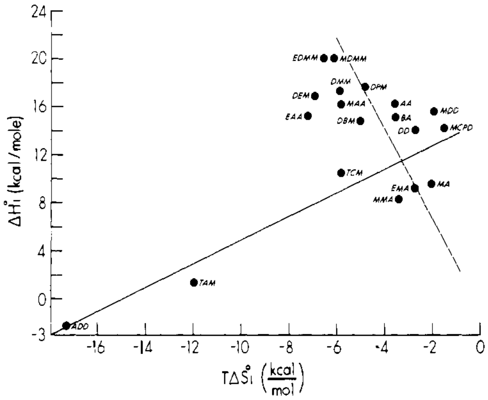

Figure 4. Plot of enthalpy vs. entropy of ionization in dimethyl sulfoxide for compounds in Table I. Solid line represents an "isoequilibrium line" of unit slope. Dashed line separates points above and below dotted correlation line in Figure 3.

single correlation line. Far below the line for acyclic compounds are the points for the cyclic ester MA and cyclic diketone DD and their methylated analogues. The anomalous position of these two points reflects primarily the very high acidity of the Meldrum's acids. In terms of displacement below the correlation line, they are 6–7 kcal/mol more acidic than would be expected relative to the rest of the compounds. We have already presented other estimates which make the discrepancy even larger.

Phenyl substitution can have a modest acid-strengthening effect for carbon acids.[61] For example, the pK_a's of acetone and acetophenone in Me_2SO are, respectively, 26.5 and 24.7. However, from Table I it is clear that in the case of diketones (AA, BA, DBM, and DPM) the effects of phenyl groups on the thermodynamic properties for ionization are not much different from methyl groups.

Figure 3 displays the relationship between the free energies of ionization and the corresponding enthalpies of ionization. In several previous articles[40,41] we have examined such extrathermodynamic relationships for different types of carbon acids in Me_2SO. The solid line shown above the data points was that determined previously for ionization of hydrocarbons, nitriles, and dimethyl sulfone—compounds for which a minimum of complicating contributions from conformational changes or specific solvent–solute interactions might be expected.[62] With the reasonable exception of the tricarbonyl compounds (TCM, TAM, ADD) all of the points for the diesters and diketones, both cyclic and acyclic, fall in a band which is distributed along the dashed line determined previously for 14 ketones and 4 nitroalkanes.[41] We can perceive no systematic departure from this general pattern which is related to either the nature of the functionality or the cyclic or acyclic compound determination. Figure 3 implies a general proportionality between enthalpy changes for the ionization process (eq 1) and the corresponding free-energy changes with dispersion of points around the common line for these compounds being a reflection of different entropy contributions to the free-energy change.

Entropy–Enthalpy Comparison. Examination of entropy factors may be approached more explicitly through Figure 4 where structural effects on entropies and enthalpies of ionization are compared. If all the points fell on the solid line, the familiar "isoequilibrium" compensation of enthalpy and entropy changes would be implied. Obviously, no such simple extrathermodynamic relationship holds here. However, a few trends are apparent if one considers groupings of points. The rough relationship between Figure 3 and Figure 4 is suggested by reference to the dashed lines on the two figures. Thus, all of the points which lie above the dashed line on Figure 3 lie to the right of that on Figure 4. Of these, the points for MDD, MCPD, MA, DD, EMA, and MMA all refer to cyclic compounds for which there should be the least conformational reorganization as a result of ionization. In terms of eq 1, these are the compounds which show the least entropy change as a result of ionization, while correspondingly, the tricarbonyl compounds TCM, TAM, and ADD show the largest. Again, it is the cyclic diketones and esters and the triketones which fall closest to the solid "isoequilibrium" line with the triketone ADD showing both the most exothermic heat of ionization and the largest entropy change for the process. By comparison, methyldimedone (MDD), the closest structural cognate to ADD, is less exothermic by nearly 18 kcal/mol and has a reorganization entropy that is nearly 50 *G*/mol greater.

The acyclic diketones and diesters, although clustered together above the solid line of Figure 4, show the following pattern which seems to relate reorganization entropy to conformational changes. The diketones AA, DBM, MAA, and EAA are differentiated more strongly by entropy than by enthalpy. Thus, substitution with a methyl or an ethyl group at the 3-position of acetylacetone results in only about a 1 kcal/mol decrease in enthalpy of ionization but a 3–4 kcal/mol change in $T\Delta S_i$, the largest loss in entropy coming from the most substituted diketone, EAA. A small symmetry correction ($RT \ln 2 = 0.41$ kcal/mol) should be applied for the substituent on the acidic carbon. However, this formal correction is much too small to account for most of the differences shown in Table I.

Unlike the diketones, the diesters MDMM, EDMM, DMM, and DEM are differentiated more by enthalpy than by entropy, although EDMM shows a slightly greater entropy loss than MDMM, corresponding perhaps to a similar difference between EAA and MAA. However, the observed structural effects on enthalpies and entropies of ionization can obviously be assigned to such a variety of conformational and solvation factors that detailed interpretations have little credibility. This lends particular importance to Figure 1 to prove that the observed structural effects on free energies of ionization truly reflect inherent acidity changes.

Association of Enolate Ions with Alkali Cations and Protons. All of the thermodynamic properties discussed above refer to a state of high dilution where complete dissociation of the enolate anions from their counter ions may be assumed. At higher concentrations the enolate anions begin to compete successfully with Me_2SO for the alkali cations. Since Me_2SO solvates cations well,[63] ion association occurs only at much higher concentrations than in less polar media. Figure 5 compares the association constants of the enolates in Table I with potassium, sodium, and lithium ions and the proton (through the pK_a's). Potassium is taken as the standard for association as shown by the scale on the ordinate of Figure 5. A unit slope would be generated if the other ions associated to the same extent with all anions as did K^+. The solid points refer to Na^+, and the solid line represents a fair correlation ($r = 0.977$) of association constants with Na^+ compared to K^+. The order of points along the line suggests important factors which may contribute to chelation. First, sodium and

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(61) Bordwell, F. G.; Drucker, G. E. *J. Org. Chem.* **1980**, *45*, 3325.

(62) Reference 41; Figure 2.

(63) Arhland, S. *Pure Appl. Chem.* **1982**, *54*, 1451.

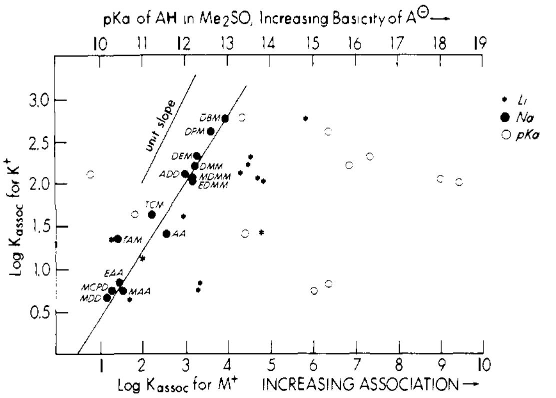

Figure 5. Comparison of logarithm of association constants, K_{assoc}, for Na^+ (●), Li^+ (*), and protons (○) with K^+ for enolate anions of compounds in Table I. Line is drawn through points for acyclic diesters and diketones.

potassium chelation are related closely to each other for the acyclic di- and triketones and esters. The sodium ion shows a higher degree of association for the acyclic diketones and diesters and a slightly smaller sensitivity to structural change than the potassium ion (slope = 1.20). Surprisingly, the data for cyclic diketones, DD, MDD, and MCPD, show association constants with the potassium ion comparable to those for the acyclic diketone even though the cyclics are constrained to the nonchelating W conformation, while the acyclic β-diketones and diesters are easily disposed to the U conformation.

Our previous spectroscopic studies[1] and many other published accounts[44,51-53] indicate a preferred U-shaped chelate ring for the alkali ion pairs of acyclic β-diketones and diesters. However, the present results show that the free-energy advantage for this structure is surprisingly small compared to that of the W-shaped cyclic system where the alkali metal cation cannot associate directly with more than one oxygen at a time.

Our experimental results for triacetylmethane are inconsistent, the value from conductance being the same for sodium, potassium, and lithium, while the indicator association method shows only complexing with lithium (see, however, Experimental Section). Comparison of di- and tricarbonyl enolates shows that tricarbomethoxymethane has roughly equivalent complexing ability with sodium, potassium, or lithium in contrast to dimethyl malonate. Acetyldimedone gives roughly the same response to variation of alkali cations as does dibenzoylmethane.

On Figure 5 points for lithium or the proton lie directly to the right of the corresponding solid points since they too are being compared with log K_{assoc} for the K^+ ion. The points for Li^+ are represented by stars and show an increasingly strong association compared to Na^+ or K^+ for almost all compounds but a much poorer correlation with K^+ association constants than do sodium ions.

Open points on Figure 5 correspond to association of the proton with the anions shown as determined through their pK_a's. Not surprisingly, the proton is generally bound more strongly than are any of the cations, and also, not surprisingly, the correlation is very poor. In addition to the drastic differences between the types of solvation of the proton and of the alkali cations it is noted that pK_a's were derived by proton removal from either the enolic oxygen or the α carbon whereas the alkali cations probably interact primarily with the enolate oxygens.

Conclusions

This study presents the most complete and systematic investigation to date of the thermodynamics of ionization of carbonyl compounds and ion-pair dissociation of their anions by a variety of experimental techniques under conditions where the structures of the precursor carbon acids, the ions, and ion pairs may be firmly established. The gross comparisons of esters with ketones confirm previous studies in Me_2SO and other solvents, and a good correlation with gas-phase acidities (Figure 1) confirms that the major effects of structure on solution acidities are not dominated, or complicated, by solvation factors.

In general ketones are more acidic than esters, cyclic carbonyl acids are more acidic than their acyclic analogues, and alkylation of the active methylene carbon reduces the acidity while accumulation of carbonyl groups strongly increases acidity from mono- to di- to tricarbonyl methane acids. Figure 1 emphasizes the overall tendency of ketone and ester acids to respond in the same way to structural changes, the glaring exception being Meldrum's acid which is 8–10 kcal/mol more acidic in terms of $\Delta G_i°$ than would be expected by comparison with trends for the other compounds. This may be understood by considering Meldrum's acid as a six-membered bislactone which (as Huisgen and Ott have proposed) would be destablized considerably relative to acyclic esters that can assume the favored trans arrangement (formula A).

Ion-pair association constants (K_{assoc}) are reported for *many enolates* with K^+, Na^+ and Li^+ using both conductance and the Bordwell titration method. In most cases there is good agreement. Although there is a fairly good correlation between log K_{assoc}'s for Na^+ with K^+ (taken as the standard ion), the correlation deteriorates for Li^+ and is reduced to a virtual random scatter when comparison is made to the proton (pK_a).

Enthalpies and entropies of ionization are also reported for the carbonyl acids, and extrathermodynamic plots of $\Delta G_i°$, $\Delta H_i°$, and $\Delta S_i°$ are presented. Detailed structure–energy interpretations for these compounds are not justifiable, and we have avoided interpreting small differences for this reason. The results raise a warning against the frequently facile interpretations of reactivity patterns for complex enolate reactions in arbitrary stereoelectronic terms. We shall approach the thermodynamics and kinetics of enolate alkylation in a future paper.

Acknowledgment. This work was supported entirely by NSF Grant No. CHE-80-06202. We are glad to acknowledge many helpful conversations with Professor Frederick Bordwell, Dr. David Hughes, and Dr. G. W. Schriver.

Registry No. AA, 123-54-6; MAA, 815-57-6; EAA, 1540-34-7; BA, 93-91-4; DPM, 1118-71-4; DBM, 120-46-7; TAM, 815-68-9; MCPD, 765-69-5; DD, 126-81-8; MDD, 1125-11-7; ADD, 1755-15-3; DEM, 105-53-3; DMM, 108-59-8; MDMM, 609-02-9; EDMM, 26717-67-9; TCM, 1186-73-8; MA, 2033-24-1; MMA, 3709-18-0; EMA, 17216-65-8.

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(64) Bordwell, F. G., private communication.