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ION PAIRING AND REACTIVITY OF β-KETOENOLATES

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Abstract - Relationships between structure and reactivity for alkali salts of the following symmetrical β-diketones in dimethyl sulfoxide solution are considered: dibenzoylmethane; dipivaloylmethane; 3-methylpentane-2,4-dione; 2-methyldimedone; dimethyl methylmalonate and isopropylidene methylmalonate (methyl Meldrum's Acid). Lithium, sodium, potassium, cesium and tetrabutylammonium salts were compared in several cases. The stabilities and structures of the ion-pairs were studied by conductance, nmr, far infrared and by the rates and heats of reaction with methyl iodide. The results, for the most part, are consistent with a simple two-state equilibrium and imply that the cyclic enolate anions are more stable than their acylic analogues both in terms of dissociation from the ion pair and also in terms of their reactivities to proton transfer and alkylation.

INTRODUCTION

Structure-reactivity relationships of enolate anions are a perennial topic of interest because of their role as intermediates in the largest single family of synthetically important processes - base-catalysed carbonyl reactions. The bold proposal by Lapworth (1) that enolate anions were the reactive intermediates in base catalyzed halogenations of ketones is often cited as the first example of a "modern" mechanism study. Again, from the perspective of this conference, Acree's studies (2) of the reactivity of alkoxide salts provided the basis for kinetic analysis of systems which we would now call "ion-paired". In 1912 the Arrhenius Theory of electrolyte dissociation was still seeking acceptance and little of our present factual framework (or vocabulary) for describing ion-ion, ion-dipole or dipole-dipole interactions in terms of electrostatic continuum models or "specific" factors such as coordination or hydrogen bonding had been invented. The crucial discovery of the role of the electron in chemistry had not yet been made by most organic chemists, although Acree's paper shows clear evidence that he was beginning to think in these terms. Thus, the question of ion pairing and reactivity of enolates has a long history.

Fortunately, the enormous literature on the alkylation and acylation of enolate systems has been the subject of a number of excellent reviews(3-6). Most of these have focussed primarily on the response of the synthetically significant factors - rate, yield and the ratio of products formed from C *versus* O attack (enolate anions are ambident nucleophiles). Of these reviews the most recent is that of Reutov and Kurts (3) -- as of this writing it has not yet been translated.

The picture that emerges from these many product studies is that C *versus* O alkylation is affected sharply by most of the obvious variables which could be used to influence the reaction - the structure of the initial carbonyl compound, the solvent, the alkylating agent, the metal counter ion and the strength of the ionizing base. More recently, the influence of polybasic ligands such as crown ethers which could tie up the counter ion in a complex has become useful. It is found that (in general) oxygen alkylation is favored by aprotic solvents of high dielectric constant, counter cations of large radius, and often by the addition of polybasic ligands. C-alkylation is favored by hydrogen-bonding solvents, small counter cations (e.g. Li^+), non-polar media and the addition of alkali metal salts.

The obvious (but somewhat oversimplified) generalization is that O-alkylation occurs most facilely on the "free" enolate anion and that encumbrance of the anion oxygens by hydrogen-bonding or the formation of ion-pairs, or higher aggregates not only reduces overall reactivity but favors attack on the enolate carbon. These simple rules of thumb are elaborated further by the useful facts that "hard" reagents (8) such as $(CH_3)_3O^+ BF_4^-$ or CH_3OTs favor oxygen alkylation under the same conditions where "soft" reagents (e.g. CH_3I) favor C-alkylation.

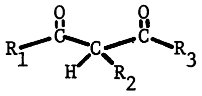
Despite the reasonable implication of ion-pairs or other aggregates as controlling factors in enolate alkylation there have been relatively few physicochemical studies that have deliberately tried to measure the degree of enolate ion dissociation and relate it to the rate or to product formation. The recent authoritative review by Jackman and Lange (4) integrates a wealth of physical data with the results of product analysis and provides most of the necessary background for those who wish an up-to-date summary. We draw particular attention to the work of Bränström (9) and of Reutov (10) which employ conductance data for the resolution of alkylation kinetics of β-ketoesters through the Acree treatment of ion-pairing.

The work discussed here was performed primarily in dimethyl sulfoxide (DMSO). Although this medium is not ideal for synthetic purposes, it is frequently employed when a dipolar aprotic solvent is desired in order to provide good cation solvation in the absence of hydrogen bonding to the anion. A variety of physico-chemical studies of salts have already been done in this medium providing a rather broad background for relating conditions of synthetic importance to well defined physical properties. Of particular interest to us, is the opportunity to study "carbon-transfer" reactions from one anion to another by comparison of the thermodynamics for alkylation reactions to those for proton transfer. Bordwell's group (11) has by now developed pKa values in DMSO for the deprotonation of over 500 Brönsted acids with an enormous range of strengths and leaving groups. This is probably the most extensive collection of acid-base data in the literature which is directly relevant to organic chemistry. Some parallel thermochemical studies have been reported from this laboratory (12) which show a remarkably good agreement between the variation of free energy and enthalpy of ionization for several series of acids. The thermodynamics of ionization for the enolate anions provide a valuable backlog of factual data for comparison with the kinetics and thermodynamics of alkylation.

We will discuss here results from our studies of the structures, the thermodynamic and kinetic reactivities of a few carefully chosen β-ketoenolate anions and ion-pair systems. Some of our data should have been published elsewhere (13) by the time this article appears in print. Others are new and incomplete but suggest patterns that are relevant to this discussion.

Structures of β-Ketoenolate Anions and Ion Pairs

The ionization of a β-diketone by a base such as an alkali metal hydroxide in water or by alkali dimsyl in DMSO can produce a highly complicated system in which one must consider the degree of enolization of the neutral diketone and the important conformations of both species. These may be



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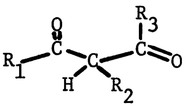

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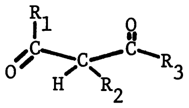

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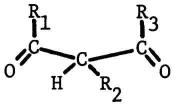

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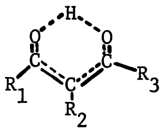

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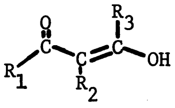

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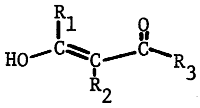

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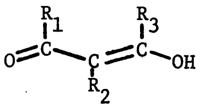

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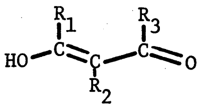

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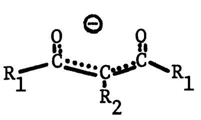
Some of this complexity can be reduced by the use of symmetrical compounds in which R_1=R_3. The corresponding structures for the enolate anions in this case are



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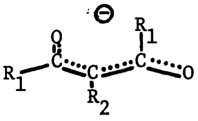

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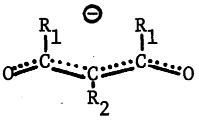


IX

Structures I, IV and VII are in the so called U-shape which is associated with the familiar chelate interaction of the proton (IV) or the metal counterion when it is placed between the oxygen atoms in structure VII. Structures II, V, VI and VIII are called the sickle form. Finally, structures III and IX are in the W-form. The U-shape may be stabilized by chelation but at the expense of dipolar repulsions between the parallel carbonyl groups. Such repulsion is relieved in the sickle- and W-conformations.

The systems we report here have been sharply simplified by using purified salts of the completely ionized symmetrical diketones and esters shown in Table I. In several cases the conformational problem has also been simplified. Thus, the dipivaloyl methide ion (DPM) is constrained by the bulky *t*-butyl groups to arrangements that can depart only slightly from the U-shape. The same is probably true of the dibenzoyl methide (DBM) ion. Correspondingly the ions derived from methyldimedone (MD) and isopropylidene methylmalonate (methyl Meldrum's acid) are restricted to the W-arrangement. This allows some control over comparisons of cyclic and acyclic systems. Raban (14) has shown that at low temperatures the simple acetylacetonate anion ($acac^-$) exists primarily as slowly interconverting U-shaped (Z,Z) and sickle-shaped (E,Z) conformers. Addition of lithium ion produced the triple anion species $Li(acac)_2^-$ which is frozen in the chelated U-shape. We expect that other enolate systems will also show different conformations for the enol, the free anion and the ion pair.

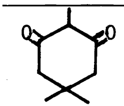
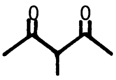
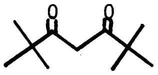
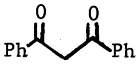
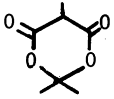
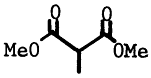
Table 1 provides some measures of the relative stabilities for several of the anions relative to the neutral diketones in DMSO. Because of the ability of this solvent to accept hydrogen-bonds, the neutral species are mostly enolized. Dimethyl methylmalonate is an exception (11b). The pKa's (determined by Bordwell's group) and the heats of deprotonation, ΔH_D, (12) both indicate a greater stability relative to the neutral precursors for the cyclic anions than for the acyclic. In accordance with this notion, our conductance experiments (and corresponding indicator measurements in Bordwell's laboratory) show that the cyclic anions are much more highly dissociated from their ion pairs than are the acyclic ions. We are not yet certain whether the cyclic ions are stabler than the acyclic ones although we note that the ring holds them in a favorable position for a planar conjugated arrangement with a minimum of dipolar repulsion. The U-shape which favors chelate ion pair formation is obviously precluded.

The ion-pair dissociation constants of the alkali DBM's, DPM's, and $acac^-$ show a reasonable sequence in terms of cation size. Likewise, the calculated Bjerrum distances from center to center of the ion-pairs are in the correct range (13). Using a 1% conductance bridge, the conductance of LiDBM and LiDPM were barely detectable (13). More recent studies with a high quality Jones bridge shows that the lithium, sodium and potassium salts of methyl dimedone are virtually completely dissociated. Extrapolation of the equivalent conductance of these solutions to infinite dilution and correction for the cation leads to a common value for the anion. Agreement between ion-pair dissociation constants as determined by conductance and by Bordwell's indicator method (11b) is excellent. There are clear differences between our values for the Li and Na salts of methylacac compared to Bordwell's values for the acac salts. It will be interesting to see whether the variations are attributable to the conformational changes resulting from the methyl group on the central carbon.

Spectroscopic studies of the alkali salts of DBM and DPM confirm that they are best represented as ion-pairs in equilibrium with ions that are essentially "free" by conductometric and kinetic criteria. There are slight secondary cation effects but the systems are represented very well for most purposes as a simple two-state equilibrium.

The far-infrared spectra of these salts showed bands between 350 cm^{-1} and 450 cm^{-1} that were both cation-and anion-dependent (15). These were assigned to the cation-oxygen stretching modes in the chelated ion pair. This frequency was shown by us to correlate in a linear manner with the reciprocal of the Pauling radii of the cations. This is strong support for the ion-pair model of the alkali chelates in DMSO solution. A similar correlation with reciprocal cation radius was found for the chemical shift of the methide proton. Again ^{13}C shifts for the carbonyl and methide carbons were consistent with the pattern of increasing upfield shifts as the ionic radius increased. The ^{13}C shifts were, however, remarkably small (16) again suggesting that the strongest interaction was through the carbonyl oxygens.

Table I. Thermodynamic and Kinetic Data for Proton Transfer, Alkylation and Ion Pairing in DMSO at 25°*.

Diketone	pKa	ΔH_D (2)	Alkali Salt	ΔH_{MeI} (3)	Rate Constants (4)	log K_D Conductance (5)	log K_D Indicator (1)
 Methyl-dimedone	11.71± 0.02	-33.93 ±0.49	Li	-24.7±2.5	$3x10^{-1}$	-1.77±0.05	
			Na	-25.8±1.3		-1.04±0.06	
			K	-28.7±1.3		-0.65±0.05	
 Methyl-acac	13.33^1 ±0.05	-30.33 ±0.23	Li	-35.4±3.2	0.8	-2.76±0.08	-4.77±0.01
			Na	-37.4±1.6	Fast	-1.16±0.19	-2.60±0.06
			K				-1.39±0.09
 Dipivaloyl-methane			Li				
			Na	Not measured		-3.47±0.02	
			K			-3.13±0.02	
			Cs			-2.43+0.02	
 Dibenzoyl methane	13.36^1 ±0.06	-33.18 ±0.45	Li			Very small	-5.86±0.01
			Na			-3.79±0.10	-3.97±0.04
			K		$3x10^{-1}$	-2.72±0.04	-2.76±0.07
			Cs			-2.17+0.03	
 Methyl Meldrum's Acid		-38	Li	-26 to -62			
			Na	-18 to -33	$6x10^{-2}$		
			K	-18 to -32			
 Dimethyl Methyl-malonate	16.37^1 ±0.06	-28.27 ±0.20	Li	-36.3±5.0	0.4		-4.46±0.07
			Na		Fast		-3.30±0.06
			K	-38.3±8.0	Fast		-2.31±0.02

1) These values were reported to us by Olmstead and Bordwell (11b) for pKa's and K_D in DMSO of the systems without methyl groups between the carbonyl carbons.

2) Heats of deprotonation in kcal/mole using K^+ $DMSYL^-$ in DMSO.

3) Heats of alkylation in kcal/mole on enolate carbon using methyl iodide (see text).

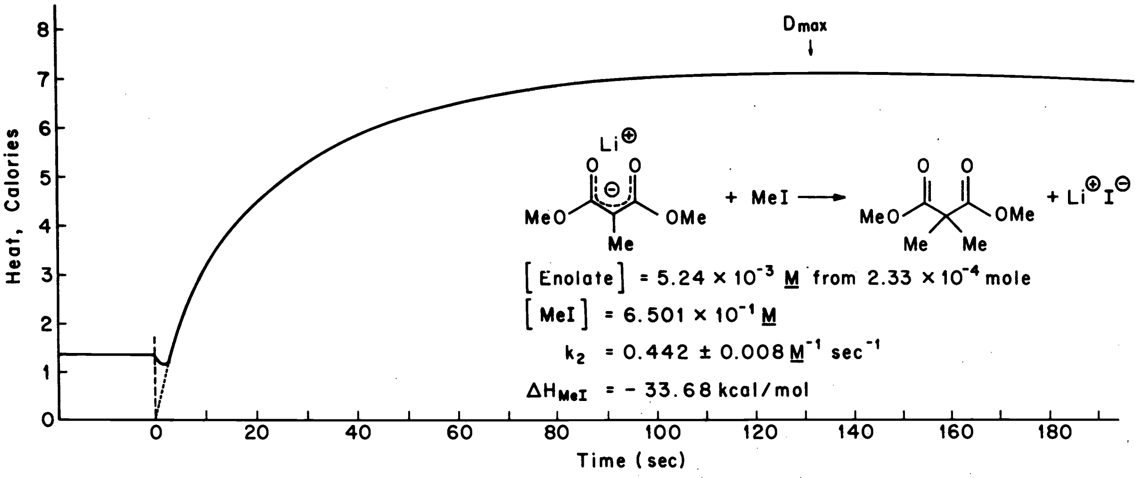
4) Estimated second order rate constants in $M^{-1}sec^{-1}$ for reaction of the anion with CH_3I. For the highly dissociated cyclic compounds k_i is equivalent to the observed second order rate constant k_2. For the acyclic compounds k_i is obtained by plotting k_2 versus α which in turn is determined from K_D (2, 10, 13).

*The data in this table were assembled for presentation at this Conference in honor of Professor Szwarc. The work is clearly incomplete as of this date. The reader should not conclude that there are major technical difficulties in obtaining the missing data or in refining some of the less precise values given here. We are actively engaged in making the appropriate measurements.

The infrared spectra in the normal carbonyl region were not especially enlightening nor were the U.V. spectra (13).

Ion Pairing and Reactivity: We have approached the reactivity of β-ketoenolate systems by two criteria which can be obtained conveniently from a single experiment. If one suddenly introduces a sample of alkylating agent into a DMSO solution of alkali enolate in a solution calorimeter a curve such as that shown in Figure 1 may be produced. Since the amount of heat change at any given point can be taken as a measure of the extent of reaction at that time after sample introduction, the rate of the reaction can be determined from the curve. Correspondingly, the heat change at completion of the reaction may be converted into the molar heat of reaction. The necessary corrections for treatment of the data have been described clearly (17). The method works best for reactions that are slow enough to permit good heat transfer within the calorimeter but not so slow that heat leaks will lead to erroneous recorder displacements. In our system the convenient range of rate study is reactions with half lives between about 20 and 1000 seconds.

Fig. 1. Simultaneous calorimetric determination of heat of reaction, ΔH_{MeI}, and second order rate constant, k_2, for carbon methylation of Li dimethyl methyl malonate in DMSO at 25°.



Using methyl iodide in DMSO, pure carbon alkylation was observed in every case, as demonstrated by NMR spectra. For potassium dibenzoylmethide (KDBM) the second order rate constants obtained at a series of initial KDBM concentrations showed a dependence which could be resolved within experimental error through the Acree equation. This requires that there be a linear relationship between the rate constant and the degree of dissociation, α, obtained from the conductance experiments. The slope of such a plot yields k_i, the rate constant for reaction of methyl iodide with the unpaired anion. The intercept is k_{ip}, the corresponding rate constant for the ion pairs (2, 3, 13). Again, in conformity with the conductance results, we find virtually no cation or concentration effects on the second order rate constants for alkylation of the salts of methyldimedone. This is what would be expected if they were dissociated completely. Nearly the same result is found for the salts of methyl Meldrum's acid. In this case however, a remarkable variation of the heat of alkylation (ΔH_{MeI}) as a function of enolate concentration is found. We are looking forward to examining the conductance of these solutions as a possible clue to this extraordinary behavior.

The results in Table I are incomplete and are in many cases quite crude. However, some rough relationships may be seen between the stability of enolate anions, as measured against protons by pKa and ΔH_D, their stabilities against cations as measured by log K_D for ion pair dissociation and their reactivity against methyl iodide.

The two cyclic compounds, methyl dimedone and methyl Meldrum's acid have the lowest pKa's, the highest degrees of ion pair dissociation, the lowest heats of alkylation, the largest heats of deprotonation and the slowest rates of alkylation.

By each of these same criteria the four acyclic anions are less stable both thermodynamically and kinetically. Undoubtedly, the superior chelating ability of the U-shaped anions gives them an advantage in ion pair formation and this effect seems to be worth at least 3 to 4 kcal/mol. Thermodynamics of deprotonation in terms of pKa and ΔH_D show only rather modest differences between the six compounds.

In sharp contrast are the enormous differences between the heats of methylation on the enolate carbon of the unpaired anion. It is perhaps not too surprising that such heats of alkylation are not related directly to the heats of deprotonation since in DMSO the proton is probably transferred from enol oxygen, while alkylation by CH_3I occurs on carbon. Oxygen alkylation of the anion can be effected cleanly by appropriate "hard" reagents such as $(CH_3)_2S\text{-}O^+CH_3$(13). It will be interesting to see whether the thermodynamics of this reaction follow enol deprotonation more closely than does carbon alkylation.

The large magnitudes and differences in the heats of alkylation are noteworthy. They are paralleled by only modest rate differences for anion alkylation. The overall behavior seems to be describable in terms of Hammond's postulate and Reactivity Selectivity Principles which suggests that these enolate anions are highly reactive species towards methyl iodide. In these terms the alkylation reaction is highly exothermic and the transition state for attack by the anion comes very "early" so that there is not nearly as much discrimination in the energetics of forming the transition state as there is in product formation.

Finally, we wish to point out that the present discussion has been largely developed around the theme of anion reactivity. Comparisons with ion pair reactivity can be made through dissection of the overall rate constant using the Acree equation. Considerable advances have been made in recent years by "liberating" anions in solution from encumbrance by hydrogen bonding or cation-pairing. The use of aprotic solvents, crown ethers, cryptands and phase transfer catalysis to produce "naked" anions has been almost exclusively in that direction. In contrast, much less work has been done on ion pairs and other electrostatic aggregates even though they may be more reactive than free ions in some cases. The reactivity and stereospecificity of ion pairs can be controlled to some extent by cation variation in many cases where that of "free" anions cannot. The basis for understanding the reactivity of ion pairs can only be established by solid physical-organic analysis of the kinetics of reactions which involve ions and ion aggregates. This symposium recognizes the advances which have been made already in this effort, especially by Michael Szwarc. We hope that the research outlined in the present article will also contribute to this development.

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