spectral features (^{1}H NMR, IR, MS) agreed satisfactorily with those previously reported.[36]

Photochemical experiments employed a 10-W Osram HNS 10W/U OZ low-pressure mercury lamp or the pulses (193 nm, ~10 ns, 20–100 mJ, 0.5-Hz repetition rate) from a Lumonics TE-861M excimer laser filled with an argon/fluorine/helium mixture. The low-pressure Hg lamp was surrounded by a metal case which incorporated a 1-in. port to contain the sample cell and filter. The filter consisted of a 25 × 3 mm LiF disk (Harshaw VUV grade) which had been irradiated with ca. 1.7 Mrad of γ-radiation from a ^{60}Co source.[10] The transmittance spectrum of the filter was monitored quite closely during photolysis experiments, as the transmittance at 254 nm tends to increase slowly after prolonged exposure to (185 + 254)-nm light.[10] A freshly prepared filter typically has an optical density of ~0.5 at 185 nm and ~5 at 254 nm.[10c] The lamp was given a 20-min warmup period before each photolysis and cooled with a stream of nitrogen.

Photolyses were carried out in 10 × 25 mm cylindrical Suprasil quartz UV cells (Hellma) or in rectangular cells constructed from 10 × 20 mm rectangular Suprasil quartz tubing (Vitro Dynamics) at ambient temperature (ca. 23 °C). In the lamp runs, the sample was agitated with a small magnetic stirrer, while in the laser runs, the sample cell was contained in a mechanical shaker which provided constant, gentle agitation of the solution between laser pulses. Solutions were deoxygenated by bubbling dry nitrogen through the cooled (to ~0 °C) solutions for 5–15 min. The products obtained from photolysis of **3** and **4** were identified by coinjection with authentic samples on at least two VPC columns. Quantum yield determinations were carried out by cyclooctene actinometry, using approximately matched cells and alternately irradiating the substrate and actinometer solutions for identical, short periods of time.

Photolyses were generally carried to <2% conversion, with aliquots being withdrawn at suitable time intervals for VPC analysis. Product yields were determined relative to reacted starting material from the slopes of concentration vs. time plots constructed for all components of the mixtures relative to internal standard. Typical concentration vs. time plots, obtained from the photolysis (185 nm) of **4** in pentane, are shown in Figure 1. Quantum yields were obtained in similar fashion, after calculating the light flux from a concentration vs. time plot for the formation of *trans*-cyclooctene from the cis isomer. A value of 0.32 was employed for the actinometric quantum yield.[11b]

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Carbon Acidity. 72. Ion Pair Acidities of Phenyl Alkyl Ketones. Aggregation Effects in Ion Pair Acidities

Michael J. Kaufman and Andrew Streitwieser, Jr.*

Contribution from the Department of Chemistry, University of California, Berkeley, California 94720. *Received February 13, 1987*

Abstract: Equilibrium cesium ion pair acidities of acetophenone, propiophenone, isobutyrophenone, and *o*-methoxyacetophenone and the lithium ion pair acidity of *o*-methoxyacetophenone in tetrahydrofuran have been determined by an indicator method. For all of these compounds, the observed pK_a values decrease as the equilibrium enolate concentration is increased. It is proposed that this concentration dependence is a consequence of the aggregation of the enolates, and a method is described whereby average aggregation numbers can be determined from the acidity data. The results indicate that the extent of aggregation of enolate ions is influenced by both electronic and steric factors. In addition, internal solvation is found to be important for the lithium, but not the cesium enolate of *o*-methoxyacetophenone.

It is well established that alkyl- and aryllithium compounds form molecular aggregates in ethereal solvents.[1] Over the past several years, evidence has accumulated to indicate that many alkali-metal derivatives of ketones, esters, nitriles, and other carbon derivatives may exist as aggregates in solution.[2] Interpretations of reaction mechanisms of such derivatives must ultimately address the issue of whether monomers or aggregates are involved. Although many mechanistic hypotheses have been advanced to rationalize the regio- and stereochemical outcome of enolate ion reactions, these theories usually regard the monomeric ion (or ion pair) as the sole active nucleophile.[3] While it is probably true that monomeric enolate ions are the active species in solvents of high ionizing power (e.g., Me_2SO),[4] the role that aggregates play in carbanion reactions conducted in solvents of low polarity, such as ethers, is not well understood. From the above discussion, it is clear that a more complete knowledge of the state of aggregation of enolate ions in ethereal solution is needed; however, relatively few such studies are available. This paucity of data undoubtedly reflects the fact that the classical techniques for determining molecular association are difficult to apply to the highly air- and moisture-sensitive solutions of enolate ions. Despite such experimental difficulties, several workers have successfully applied the techniques of ebulioscopy,[5-7] osmometry,[8,9] and cryoscopy[10,11]

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to the study of the state of aggregation of carbanionic reagents. NMR spectroscopy has been used with notable success to probe the structures of lithium enolates.[12] However, the substrate concentrations used for these studies have generally been rather high—ca. 10^{-1}–10^{-2} M.

Alternatively to colligative property measurements, X-ray crystallography has been used to study enolate aggregation.[13-20] Crystallographic studies have the advantage of providing a complete description of molecular geometry. Unfortunately, structures in the crystal do not always accurately represent the solution-phase structures.[10,21] For example, the lithium derivatives of phenylacetonitrile and benzyl phenyl sulfone are monomeric in tetrahydrofuran (THF) at normal concentrations[22] but crystallize as dimers.[13-15] In the present paper we report how measurements of equilibrium ionn pair acidity can provide information on aggregation even in rather dilute solutions (down to 10^{-5} M). This technique can be a useful addition to those methods applicable to more concentrated solutions. Moreover, the dilute solution is clearly relevant to synthetically important concentrated solutions. For example, if a reagent is found to be aggregated even in highly dilute solutions, the monomeric species is less likely to be the active reagent at concentrations used in syntheses.

Recently, we have communicated equilibrium ion pair acidities in THF of a series of benzylic carbon acids stabilized by an adjacent cyano, carboalkoxy, and sulfonyl substituent.[22] The relative ion pair acidities of these compounds were determined by monitoring the position of the transmetalation equilibria (eq 1, $M^+ = Li^+, Cs^+$) using hydrocarbon indicators, InH, of known pK_a values in THF.[23] Since these indicator anions are known

$$RH + In^-M^+ \rightleftharpoons R^-M^+ + InH \qquad (1)$$

to exist exclusively as monomeric ion pairs in THF,[23] the indicator technique can be used to detect the presence of substrate carbanion ion pair aggregates. Thus, if an enolate ion pair is aggregated, the associative equilibrium (eq 2) will have the effect of "pulling" equilibrium 1 to the right. This results in an observed pK value

$$n(R^-M^+) \rightleftharpoons (R^-M^+)_n \qquad (2)$$

that is lower than the true value that would be observed in the absence of aggregation. Moreover, the stoichiometry of eq 2 is such that the relative proportion of enolate monomer to aggregate is dependent on the total enolate concentration, with the aggregated specie(s) being favored at higher total enolate concentration. Consequently, the effect of enolate aggregation is to increase the observed acidity of a carbonyl derivative as the total enolate concentration is increased. In this paper, we apply these principles to study the degree of aggregation of the enolate ions derived from a series of homologous aryl alkyl ketones in THF solution. We find that observed pK values do show a concentration dependence, and we describe how these data can be used to deduce an average aggregation number (n in eq 2).

Results

Description of Procedure. As we have previously described,[23] the acidity difference between two compounds RH and InH can be determined by measuring the position of the equilibrium shown in eq 1. In the present context, RH represents the carbonyl compound whose acidity is to be determined, and InH is a fluorene derivative of known relative ion pair acidity in THF. The corresponding acidity (pK) of RH is then calculated from eq 3. The

$$pK_a(RH) = pK_a(InH) - \log K \qquad (3)$$

true Brønsted acidities as defined by acid dissociation to free ions are too low to measure for these compounds in THF. For convenience, the numbers assigned as "pK_a" values are those relative to an arbitrary reference chosen as that of fluorene in dimethyl sulfoxide as determined by the Bordwell group.[24] Relative pK's for highly delocalized indicator hydrocarbons compare well in both series; however, this choice of fluorene instead of the H_- value of 9-phenylfluorene is a departure from our previous practice. The change involved is small and the reasons are detailed in a forthcoming paper.[25] Note that the cesium scale involves contact ion pairs[22] whereas the lithium scale involves solvent-separated ion pairs.[26]

In our previous work, both ion pairs involved in equilibrium 1 exhibited distinct visible absorption spectra so that the concentration of the organometallic species could be calculated by application of Beer's law. In contrast, the lithium and cesium salts of the carbonyl compounds used in the present study do not have absorption maxima in the visible region. Although the enolate ion pairs do exhibit distinct absorptions in the UV, this region of the spectrum is difficult to analyze quantitatively due to the large number of overlapping peaks arising from the indicators. Consequently, we used a "single-indicator technique".[27] The spectrum of a fluorenyl salt of known pK_a was recorded, and the initial indicator anion concentration $(In^-M^+)_i$ was determined from the absorbance at the appropriate λ_{max}. A measured amount of the substrate RH was then added and the spectrum of the resulting solution was recorded. The equilibrium concentration of the indicator anion was determined directly from the new absorbance value, and the equilibrium enolate ion concentration was evaluated by eq 4. From the known amounts of InH and RH used in the

$$[R^-M^+]_{eq} = [In^-M^+]_i - [In^-M^+]_{eq} \qquad (4)$$

experiment, the equilibrium concentration of the two protonated species can be calculated and K can then be evaluated.

Although the single-indicator technique has been used successfully in our laboratories in the past, the method does have two important limitations. The first concerns the stability of the indicator anion. Any decomposition of this anion occurring after the initial spectral scan will result in a decrease in absorbance that cannot be distinguished from the decrease expected from the addition of the test acid; the end result of this effect is that an

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Table I. Cesium Ion Pair Acidity of Acetophenone (ACP) at 25.0 °C

indicator	$10^4[ACP^-Cs^+]_t$[a]	K_{exptl}[b]	pK(ACP)[c]
Fl[d]	0.203	0.0435	24.44
Fl	0.252	0.0347	24.54
Fl	1.60	0.190	23.80
Fl	4.05	0.337	23.55
Fl	4.23	0.332	23.55
2,3-BF[e]	4.24	0.820	23.55
2,3-BF	4.90	0.877	23.52
Fl	6.59	0.398	23.48
Fl	6.83	0.518	23.36
2,3-BF	7.68	1.46	23.30
Fl	19.3	1.07	23.05
Fl	32.3	1.31	22.96
Fl	38.8	1.50	22.90
Fl	52.7	2.01	22.77

[a] Total enolate concentration in M. [b] Defined by eq 5 in text. [c] On a per-hydrogen basis. Least-squares linear correlation: pK(ACP) = $-0.716 \log [ACP^-Cs^+]_t + 21.138$; $r^2 = 0.991$. [d] Fluorene, pK_a = 22.90.[23,25] [e] 2,3-Benzofluorene, pK_a = 23.64.[23,25]

Table II. Acidity of Propiophenone (PRP) at 25.0 °C

indicator	$10^4[PRP^-Cs^+]_t$[a]	K_{exptl}[b]	pK(PRP)[c]
DBF[d]	1.56	3.10	23.35
DBF	1.73	3.19	23.34
DBF	2.23	3.55	23.29
DBF	2.62	3.80	23.26
2,3-BF	2.89	2.52	23.24
2,3-BF	3.15	2.57	23.23
DBF	4.35	4.69	23.17
2,3-BF	5.50	3.53	23.09
DBF	6.31	6.48	23.03
4,5-MP[e]	7.02	0.781	23.02
4,5-MP	8.62	0.862	22.97
2,3-BF	10.2	4.93	22.95
4,5-MP	15.8	1.27	22.81

[a] Total enolate concentration in M. [b] See note *b*, Table I. [c] On a per-hydrogen basis. [d] 2,3;6,7-Dibenzofluorene, pK_a = 23.84.[25] [e] 4,5-Methylenephenanthrene, pK_a = 22.91.[23,25]

erroneously low pK_a value for the test acid is obtained. However, it was found that the alkali-metal salts of the relatively acidic fluorene indicators are stable in THF for several hours when air and moisture are rigorously excluded. More importantly, it was possible to measure the relative acidity of most of the carbonyl compounds against more than one indicator; the internal consistency of the pK_a values obtained in this way (vide infra) is powerful evidence that indicator anion decomposition is not an important source of error in our work.

The second limitation of the single-indicator technique concerns the manner in which the equilibrium enolate concentration is calculated. Note that the application of eq 4 allows the calculation of the total enolate ion concentration, but does not provide any information regarding the aggregate form of the species involved. We will consider this point in further detail in a later section of this paper.

Acidity Measurements. The acidity of the homologous series of ketones, acetophenone (ACP), propiophenone (PRP), and isobutyrophenone (IBP), was studied by using lithium and cesium counterions. We have also studied the acidity of *o*-methoxyacetophenone (MACP). The results of the acidity measurements are summarized in Tables I–IV.

Some observations regarding the stability of equilibrium solutions of these enolates are of interest. In determining the acidity of carbonyl compounds, it is necessary to simultaneously maintain an equilibrium concentration of both the carbonyl compound and its derived anion. This presents a potential problem since enolate ions generally add to their conjugate acids (aldol addition). Furthermore, addition of the indicator anion to the carbonyl group may also occur. Either of these subsidiary reactions would perturb the position of the acid–base equilibrium, resulting in erroneous and irreproducible pK_a assignments. For this reason, we began our study with cesium as the counterion; our previous work had

Table III. Acidity of Isobutyrophenone (IBP) at 25.0 °C

indicator	$10^4[IBP^-Cs^+]_t$[a]	K_{exptl}[b]	pK(IBP)[c]
2,3-BF	0.616	0.0847	24.71
DBF	0.808	0.158	24.64
2,3-BF	0.832	0.0971	24.65
DBF	0.984	0.170	24.61
DBF	1.12	0.182	24.58
DBF	1.43	0.220	24.50
2,3-BF	2.03	0.173	24.40
DBF	2.33	0.297	24.37
DBF	3.04	0.340	24.31
2,3-BF	3.61	0.230	24.28
2,3-BF	5.04	0.279	24.20
2,3-BF	6.65	0.314	24.14
2,3-BF	7.58	0.336	24.11

[a] Total enolate concentration in M. [b] See note *b*, Table I. [c] On a per-hydrogen basis.

Table IV. Acidity of *o*-Methoxyacetophenone (MACP) at 25.0 °C

indicator	$10^4[MACP^-Li^+]_t$[a]	K_{exptl}[b]	pK(MACP)[c]
	Lithium Counterion		
9-Ph-3,4-BF[d]	0.628	0.299	16.67
9-Ph-3,4-BF	0.749	0.325	16.64
9-Ph-3,4-BF	0.910	0.348	16.60
9-Ph-3,4-BF	2.11	0.524	16.43
9-Ph-3,4-BF	2.43	0.641	16.34
9-Ph-3,4-BF	3.81	0.741	16.28
9-Ph-3,4-BF	4.44	0.752	16.27
9-Ph-3,4-BF	4.48	0.885	16.20
9-Ph-3,4-BF	5.02	0.952	16.17
9-Ph-3,4-BF	6.71	1.04	16.13
9-Ph-3,4-BF	9.08	1.19	16.07
	Cesium Counterion		
DBF	0.707	0.847	24.09
DBF	1.11	1.19	23.94
2,3-BF	2.82	1.43	23.66
DBF	2.90	2.19	23.69
DBF	3.59	2.64	23.59
DBF	4.54	3.37	23.49
2,3-BF	11.2	2.91	23.35

[a] Total enolate concentration in M. [b] See note *b*, Table I. [c] On a per-hydrogen basis. [d] 9-Phenyl-3,4-benzofluorene, pK_a = 15.67.[32]

shown that proton-transfer equilbria are attained much more rapidly with cesium compared to lithium counterion.[26] In addition, whenever possible more than one indicator was used to measure the acidity of the ketones. The fact that consistent results were obtained with different indicators is added evidence that carbonyl addition reactions are not an important source of error in this work.

For reactions involving cesium salts, addition of the ketone to a THF solution of the indicator anion resulted in an immediate decrease in the optical density of the solution measured at the λ_{max} of the indicator. In all cases, this initial decrease in absorbance was followed by much slower changes in absorbance. For example, in a typical experiment the addition of acetophenone to a THF solution of fluorenylcesium resulted in an immediate decrease in the optical density of the solution from an initial value of 1.034 at 364 nm to 0.561; after 10 min the absorbance had increased to $A = 0.566$. We interpret the initial decrease in absorbance as being due to the establishment of the proton-transfer equilibrium. The subsequent smaller changes in absorbance are undoubtedly due to side reactions involving carbonyl addition reactions. For cesium salts these side reactions occur much slower than proton transfer and do not present a problem in obtaining reliable acidity data. This was particularly true for the sterically hindered ketones PRP and IBP.

The reactions involving lithium salts exhibited much different behavior. For all four aryl alkyl ketones, proton transfer from the ketone to the lithium indicator was much slower than for cesium salts and resulted in only gradual decreases in absorbance readings with time. However, in contrast to the results obtained with the benzylic system,[22] only the reactions with MACP were observed to reach a stable equilibrium end point. Indeed, the

equilibria with MACP were found to remain stable for periods of time at least as long as those described for the benzylic systems. However, for ACP, PRP, and IBP, carbonyl addition reactions apparently occur at rates comparable to the proton transfer and resulted in absorbance readings that changed indefinitely with time. When runs with ACP, PRP, and IBP were performed at a lower temperature (−10 °C), both the proton transfer and the side reactions were greatly retarded in rate, but stable equilibrium end points were still not observed. This imposes a rather severe restriction on our studies since it appears probable that many simple lithium enolates are too reactive relative to proton transfer to be studied by these methods.

Discussion

The acidity data in Tables I–IV show variations in pK_a values that are consistent with all four ketone enolates existing as aggregates in THF solution. Note, however, that the sensitivity of pK_a values to changes in enolate concentration varies among these compounds. Indeed, it is possible to use these acidity–concentration profiles to derive an average aggregation number n for each of the enolates. Before doing so, however, it is necessary to carefully define the various concentration terms involved in the equilibrium expressions. As described above, the equilibrium enolate ion concentration is calculated from the difference in initial and equilibrium indicator anion concentration (eq 4). This difference gives the total enolate ion concentration without regard to aggregate form; we shall denote this total enolate concentration as $[R^-M^+]_t$. The observed apparent equilibrium constants K_{exptl} presented in Tables I–IV were calculated from the equilibrium expression shown in eq 5. The true relative acidity of RH and InH is denoted K_a and is given by eq 6, where $[R^-M^+]$ refers to a monomeric enolate ion pair. Comparison of eq 5 and 6 show that the values of K_{exptl} and K_a are related by eq 7.

$$K_{exptl} = [R^-M^+]_t[InH]/[RH][In^-M^+] \quad (5)$$

$$K_a = [R^-M^+][InH]/[RH][In^-M^+] \quad (6)$$

$$[R^-M^+] = (K_a/K_{exptl})[R^-M^+]_t \quad (7)$$

To continue with this treatment, we note that the average degree of aggregation of an enolate ion pair is the result of several discrete associative equilibria, viz.

$$2(R^-M^+) \rightleftharpoons (R^-M^+)_2$$

$$3(R^-M^+) \rightleftharpoons (R^-M^+)_3$$

$$\vdots$$

$$n(R^-M^+) \rightleftharpoons (R^-M^+)_n$$

The equilibria shown above are characterized by equilibrium constants $K_2, K_3, \ldots, K_n$. Thus, the concentration of each aggregate species can be expressed in terms of the concentration of monomeric enolate (eq 8). Additionally, mass balance requires the

$$[(R^-M^+)_n] = K_n[R^-M^+]^n, \qquad n = 1, 2, \ldots \quad (8)$$

$$[R^-M^+]_t = \sum n[(R^-M^+)_n] \quad (9)$$

relationship given by eq 9, which includes the fundamental assumption that the spectroscopic method used measures each R^-M^+ unit independent of its occurrence in a monomer or aggregate. Substitution of (8) into (9) gives

$$[R^-M^+]_t = \sum nK_n[R^-M^+]^n \quad (10)$$

Multiplication of eq 10 by the ratio $[InH]/[In^-M^+][RH]$ leads to

$$K_{exptl} = \sum nK_nK_a[R^-M^+]^{n-1} \quad (11)$$

Substitution of (7) into (11) gives

$$K_{exptl} = \sum nK_nK_a^n([R^-M^+]_t/K_{exptl})^{n-1} \quad (12)$$

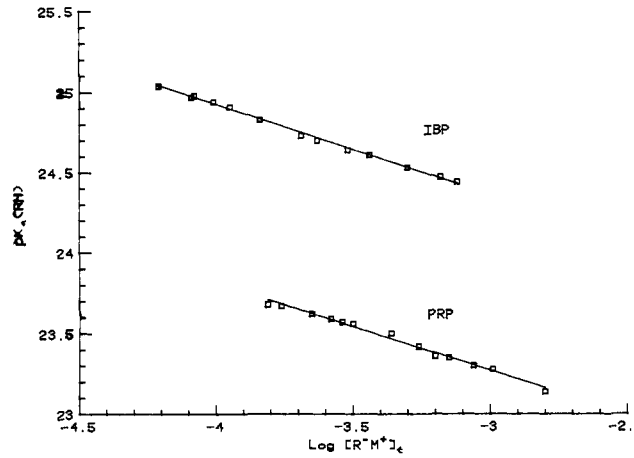

Figure 1. Data from Tables II and III plotted as pK_a vs. log $[R^-M^+]_t$. Isobutyrophenone (IBP): $pK_a = -(0.562 \pm 0.010)$ log $[IBP^-Cs^+]_t + (22.34 \pm 0.03)$, $r^2 = 0.997$. Propiophenone (PRP): $pK_a = -(0.540 \pm 0.017)$ log $[PRP^-Cs^+]_t + (21.33 \pm 0.06)$, $r^2 = 0.989$.

On a macroscopic level, the summation over discrete aggregates can be replaced by an average aggregation number $\bar{n}$; thus

$$K_{exptl} = \bar{n}K_nK_a^{\bar{n}}([R^-M^+]_t/K_{exptl})^{\bar{n}-1} \quad (13)$$

Taking logarithms and rearranging gives

$$\log K_{exptl} = (1/\bar{n}) \log (\bar{n}K_nK_a^{\bar{n}}) + [(\bar{n} - 1)/\bar{n}] \log [R^-M^+]_t \quad (14)$$

This equation provides an experimentally useful relationship between the measurable quantities K_{exptl} and $[R^-M^+]_t$. However, at any given value of $[R^-M^+]_t$, the value of K_{exptl} will depend upon the indicator used in the measurement. This dependence can be removed by assigning an "absolute value" to the pK_a of RH as defined in eq 3 and discussed above.[25] On substitution of (3) into (14), the final equation takes the form

$$pK_a(RH) = [(1 - \bar{n})/\bar{n}] \log [R^-M^+]_t + b \quad (15)$$

where $b = pK_a(InH) - (1/\bar{n}) \log (\bar{n}K_nK_a^n)$.

This approach assumes, of course, that the indicator systems are monomeric ion pairs in the concentration region used. This assumption appears to hold for the lithium and cesium indicators used in this study on the basis of the independence of indicator pK's to concentration[23,26] and from recent conductivity studies.[26]

The relationship described by eq 15 is complicated by the fact that $\bar{n}$ is a complex and unknown function of the total enolate concentration unless the compound is present as a single discrete aggregate. Nevertheless, a plot of observed pK_a values vs. log $[R^-M^+]_t$ should yield a curve whose tangent at any given enolate concentration is equal to $\bar{n}$. In practice, $\bar{n}$ (or, more precisely, the function $[1 - \bar{n}]/\bar{n}$) changes rather slowly with changing enolate content; consequently, $\bar{n}$ may be treated as a constant over a limited concentration range, and eq 15 takes the form of a linear relationship. This is illustrated by the data for propiophenone and isobutyrophenone which are plotted in Figure 1. Similar linear correlations were obtained for the other ketones employed in this study. Moreover, least-squares analysis of the plots allows the calculation of $\bar{n}$ values; these results are presented in Table V. Table V also includes aggregation data for some benzylic compounds for which we have communicated results[22] but did not previously analyze according to eq 15.

Factors Affecting Aggregation Numbers. Several features of the aggregation data contained in Table V are of interest. First, we note that the benzylic salts appear to exist as simple monomeric ion pairs in THF solution,[28] while the aryl alkyl ketones are all found to form higher aggregates. This difference between benzylic and non-benzylic ion pairs is best interpreted as resulting from

(28) The lithium salt of phenylacetonitrile has been reported to exist as a monomer in THF from cryoscopic measurements: Bauer, W.; Seebach, D., unpublished results quoted in ref 13.

Table V. Average Aggregation Numbers for Ion Pairs in THF[a]

compound	$\bar{n}$[b] Li+	$\bar{n}$[b] Cs+
tert-butyl phenylacetate	1.1	1.1
phenylacetonitrile	0.9_5	1.1
(*p*-methoxyphenyl)acetonitrile	1.0	1.0
benzyl phenyl sulfone	1.0_5	1.0
acetophenone		3.5
o-methoxyacetophenone	2.1	2.7_5
propiophenone		2.2
isobutyrophenone		2.3

[a] pK_a's for the first four compounds have appeared in a preliminary communication.[22] [b] Average aggregation number (see text). Estimated errors are ±10%.

the different electronic structures of the two groups. The formation of aggregate species provides additional electrostatic stabilization of the ion pair dipoles in ethereal and other low dielectric solvents. Since the driving force for aggregate formation is electrostatic stabilization, we can expect this stabilization to be greatest for enolate ions in which the negative charge is more strongly localized. Conversely, the additional charge dispersal provided by an adjacent phenyl group will lower the electron density at the enolate oxygen atom, resulting in a lower net energy decrease upon aggregation. The present results indicate that the charge delocalization provided by a single phenyl substituent is sufficient to completely inhibit aggregate formation at these concentrations. Note that this delocalization effect of a phenyl group is not inhibited even with a *p*-methoxy substituent in the case of phenylacetonitrile.

The cesium salt of acetophenone appears to be mostly tetrameric even at rather high dilutions. The average aggregation number is obtained as a slope that determines $(\bar{n}-1)/\bar{n}$. As $\bar{n}$ increases this slope gets closer to unity and $\bar{n}$ becomes difficult to measure with precision. For $\bar{n}=3.5$, the function $(\bar{n}-1)/\bar{n}=0.71$, only slightly different from the slope 0.75 given for $\bar{n}=4$. Thus, the salt of acetophenone may well be present almost wholly as tetramers and those of PRP and IBP may be wholly dimers. The estimated reliability of the values determined for $\bar{n}$ is about 10%. The experimental differences are sufficiently great as to demonstrate that the cesium salts of both propiophenone and isobutyrophenone are significantly less aggregated than that of acetophenone. The most reasonable explanation for these results is that increasing steric bulk among this series of compounds inhibits the packing of monomer units into higher aggregates.[26,29] It is interesting to note that the introduction of a single α-methyl group into acetophenone results in a large decrease in aggregation, but that further methyl substitution has little additional effect. For comparison, NMR studies indicate lithioacetaldehyde to be tetrameric in THF;[30] similarly, lithioisobutyrophenone is predominantly tetrameric in ethers such as dioxolane and THF but the dimer is also important in glyme even at high concentrations.[12a] Cryoscopy shows the lithium enolate of cyclopentanone to be a mixture of dimer and tetramer in melting THF.[10]

In addition to electronic and steric effects, the results with *o*-methoxyacetophenone suggest that a third effect may influence aggregate formation, as indicated by the comparison of *n* values for MACP using lithium and cesium counterions. Normally, it is expected that aggregate formation would be promoted by changing from the larger, more polarizable cesium ion to the smaller lithium cation. To account for the observed decrease in aggregation on changing from cesium to lithium, we propose that MACP$^-$Li$^+$ exists as an internally solvated complex. The results show that this lithium salt exists primarily as a dimer, and examination of molecular models indicates that dimerization can occur without introducing any serious nonbonded interactions. Moreover, models suggest that while the methoxy methyl groups in the dimer effectively shield one "face" of each lithium atom, the other sides of the cations are quite free to accept a solvent molecule to fill the fourth coordination site. We therefore propose the structure (MACP$^-$Li$^+$)$_2$·2THF for this complex. A similar internally coordinated dimeric structure has been observed for lithiated 2-(carbomethoxy)cyclohexanone dimethylhydrazone.[11] On the basis of a range of other known lithium coordination structures, the proposed structure is unexceptional.[32] Moreover, it is significant that MACP is the only compound whose lithium enolate was sufficiently unreactive in aldol additions to be studied by our acidity methods. This lack of reactivity implies a mode of stabilization that is not available to the other phenyl alkyl ketones. Additional evidence for an internal solvate structure comes from a comparison of the observed acidities of the MACP enolate toward lithium and cesium (Table IV). At comparable enolate concentrations, MACP is found to be more acidic by a factor of 10^8 with lithium as gegenion compared to cesium. In fact, since the cesium enolate is more highly aggregated, the true acidity difference is actually greater. This is one of the largest cation effects ever encountered in acidity measurements and clearly suggests that some special form of anionic stabilization is operative in the lithium, but not the cesium enolate. Apparently, the cesium cation is too large for internal coordination to be important. Recall that the lithium pK_a is compared to an indicator lithium salt *present as a solvent-separated ion pair*; the increased electrostatic interaction of a lithium enolate contact ion pair would alone provide enhanced relative acidity of the corresponding ketone.

Ion Pair Acidities. We communicated previously that the monomeric benzylic systems have cesium ion pair p*K*'s that are similar to the ionic p*K*'s in dimethyl sulfoxide.[22] For example, cesium ion pair p*K*'s, corrected to the fluorene reference and on a per-hydrogen basis, are 22.7 for phenylacetonitrile and 23.8 for *tert*-butyl phenylacetate. The corresponding values in dimethyl sulfoxide are 22.2[24a] and 23.9,[24e] respectively. The p*K*'s of the ketones are "apparent" values that vary with concentration. The apparent values may be treated as "effective" p*K*'s for a given concentration as a measure of relative basicity of the ion pair aggregates. Conversion to true p*K*'s requires knowledge of the ion pair association constants and can be derived from eq 15. The effect is that the p*K*'s of the monomers are higher than those of the aggregates. For example, if at our lowest concentration, 10^{-4} M, the cesium salt of propiophenone is 1% dissociated to monomeric ion pairs, the true p*K* would be 26.5. The value in Me_2SO is 24.7.[24a] Thus, unlike the delocalized hydrocarbon indicators and the monomeric benzylic systems above, the ketones appear to have acidities in THF significantly lower than those in Me_2SO. If dissociation is less, the true p*K* is still higher; the effect is additive: one p*K* unit for each power of ten in dissociation constant. One would have expected the reverse; enolate ions are less delocalized than the hydrocarbon indicators and should produce stronger ion pairs with *lower* effective p*K*'s. We conclude from this analysis that the association constants of cesium enolates cannot be too large and that monomers are probably present to some extent at the dilute end of the concentrations studied but in amounts too small to register with the technique used.

Concluding Remarks. In this paper we have described a technique for assessing the extent of aggregation of carbanion ion pairs. The principal limitation of our method is that many lithium enolates are too reactive toward carbonyl addition to be studied. Another drawback is that precise data over wide concentration ranges are required for reliable determinations of *n* values.

For enolates that are not too reactive to be studied, our method does have some advantages compared to colligative property

(29) Steric inhibition to aggregation has been observed for some hindered lithium phenoxides; see ref 8 and: Shobatake, K.; Nakamoto, K. *Inorg. Chim. Acta* **1970**, *4*, 485. The aggregation of the *tert*-butyl ester of lithioisobutyrate is reported to be less than that of the methyl or ethyl esters in THF; see ref 9.

(30) Wen, J. Q.; Grutzner, J. B. *J. Org. Chem.* **1986**, *51*, 4220.

(31) Setzer, W. N.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, *24*, 353–451.

(32) Note that the pK_a of 9-phenyl-3,4-benzofluorene has not been determined in THF, and we have assumed the value of 15.67 obtained from studies in cyclohexylamine (CHA).[33] This assumption is warranted by the close correspondence between pK_a values in THF and CHA for hydrocarbons yielding highly delocalized anions.

(33) Streitwieser, A., Jr.; Juaristi, E.; Nebenzahl, L. L. In *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: New York, 1980.

measurements. Although we have limited our initial studies to THF solutions at 25 °C, the method can in principle be applied to other solvents and other temperatures. Also, aggregation studies by our technique are generally limited to dilute (10^{-3}–10^{-4} M) solutions; in this respect the method is complementary to colligative measurements, which are generally conducted at higher substrate concentrations. Synthetic chemistry is normally done at higher concentrations but it is clearly important and relevant to understand the dilute solution.

Previous research has established that a tetrameric structure is favored for several lithium enolates at concentrations of ca. 0.1 M,[7,9,12,29] although dimers appear to be favored at low temperature.[10] The present work shows that the cesium enolate of acetophenone is substantially tetrameric even in dilute solutions. In contrast, the cesium enolates of propiophenone and isobutyrophenone are found to exist predominantly as dimers. At present, it is not known what effect the deaggregation of cesium enolates compared to their more common lithium counterparts will have on the reaction chemistry of these important synthetic reagents.

Finally, the true relative pK_a's of the monomeric ion pairs are still not known but are established as greater than those of the aggregates reported. The "effective" pK_a's of the aggregates are readily evaluated by the procedure discussed in this paper, at least over the concentration range for which the n values reported in Table V are constant. These effective pK_a's vary with concentration and such variation may have synthetic significance. However, comparison of these pK's with values in Me_2SO suggests that the association constants of cesium enolates to higher aggregates cannot be very large and that the true ion pair pK values are no more than a few units higher than the apparent values.

Experimental Section

Indicator Acids. The hydrocarbon indicators used in this work either were available from our previous studies, or were synthesized by published procedures. All of the indicators were carefully purified prior to use by repeated recrystallization followed by vacuum sublimation.

Carbonyl Compounds. Acetophenone, propiophenone, isobutyrophenone, and *o*-methoxyacetophenone were obtained from commercial suppliers. All of the ketones were fractionally distilled under vacuum two times and degassed prior to use. The purity of the compounds was determined by vapor-phase chromatography; all compounds gave analyses indicating a purity of at least 99%. All compounds also gave satisfactory elemental analyses.

Acidity Determinations. The procedures used in the acidity determinations have been previously described in detail.[23,26] The cesium ion pair indicator pK_a's used are those of the revised scale.[25]

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Registry No. ACP, 98-86-2; ACP^-Cs^+, 109839-78-3; PRP, 93-55-0; PRP^-Cs^+, 109839-79-4; IBP, 611-70-1; IBP^-Cs^+, 109839-80-7; MACP, 579-74-8; $MACP^-Li^+$, 109839-81-8; $MACP^-Cs^+$, 109839-82-9.

Iminium Ion and Acyliminium Ion Initiated Cyclization Reactions of Vinylsilanes. Regiocontrolled Synthesis of Tetrahydropyridines and Related Heterocycles[1]

Chris Flann, Thomas C. Malone, and Larry E. Overman*

Contribution from the Department of Chemistry, University of California, Irvine California 92717. *Received March 6, 1987*

Abstract: 1,2,5,6-Tetrahydropyridines containing substituents at positions 1, 2, 3, and 4 can be prepared in useful yields, with *complete regioselectivity*, by the cyclization of iminium ions derived from 4-(trimethylsilyl)-3-butenylamines. The general sequence is illustrated in Scheme I. Three methods for generating the iminium ion intermediate are described. Tetrahydropyridines containing a 1-substituent are most easily prepared by the reaction of N-substituted (*Z*)-4-(trimethylsilyl)-3-butenylamines with aldehydes in the presence of <1 equiv of a sulfonic acid (see eq 4 and Table I). Alternatively, tetrahydropyridines of this type can be prepared from the reaction of α-cyanoamines **20** with silver salts (see eq 5 and Table II). This latter more costly procedure is useful when the aldehyde component is precious or, in the case of formaldehyde, when the cyclization reaction is slow. Tetrahydropyridines unsubstituted at position 1 can be prepared in modest yields by the cyclization of nonenolizable imines **23a–c** with excess trifluoroacetic acid (see eq 6 and Table III). The cyclization of the 5-(trimethylsilyl)-4-pentenylamine **26** to give hydroazepine **28** demonstrates that allylically unsaturated heterocycles other than six-membered can also be prepared in this way (eq 7). Acyliminium ion–vinylsilane cyclizations are also successful and can be utilized for the regiocontrolled synthesis of indolizidinones and quinolizidinones 44. The functionalized indolizidinone **44c** was employed as the key intermediate in a short synthesis of the racemic *elaeocarpus* alkaloids, elaeokanines A and B (see Scheme IV). Several lines of evidence indicate that vinylsilane and allylsilane iminium ions **29** and **32** equilibrate (via a cationic aza-Cope rearrangement) more rapidly than either cation cyclizes to the tetrahydropyridine product.

Electrophilic cyclization reactions of iminium ions and related intermediates (Mannich cyclizations) constitute some of the most important methods for preparing nitrogen heterocycles.[2] In two of the more venerable of these procedures, the Pictet–Spengler and Bishler–Napieralski reactions,[3] an aromatic ring is the nucleophilic reaction component (cyclization terminator). Cyclization reactions of simple alkenes with iminium ions, although well-known, have received much less attention.[4] In part this neglect is due to the fact that the carbonium ion intermediate produced

(1) A mechanistic study of these cyclization reactions is described in the following paper of this series: McCann, S. F.; Overman, L. E. *J. Am. Chem. Soc.*, following paper in this issue.

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