conformational flexibility even in the low-temperature region. This last observation may appear surprising in view of recent data presented for enkephalins. For these compounds, which also possess two aromatic residues spaced by two glycyl residues, a type I β turn has been proposed as the most stable conformation in solution[41,42] and this structure has been observed in the crystalline state by X-ray analysis.[43] However, enkephalins contain another bulky residue (Leu, Met) at the C end, which could change the conformational preferences. Another possible reason for this difference may arise from the different solvent systems.

A general question is to what extent the data obtained in our work for tryptophyl residues are valid for other aromatic residues. We expect to partly answer this question by investigation of other peptide families, i.e., H-Gly-X-(Gly)$_n$-Trp-Gly-OH (n = 0, 1, 2), where X = Phe, Tyr, and His, which we have already prepared and characterized.

Acknowledgment. This research has been supported by the Swiss National Foundation, Grant 2.892-0.77.

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NMR Studies of Enolate Anions. 6. A ^{13}C NMR Study of Alkali Metal Chelation by 3-Alkylacetylacetonates[1]

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Abstract: The low-temperature ^{13}C NMR spectra of the sodium salts of 2,4-pentanedione, 2,4-hexanedione, 3-methyl-2,4-pentanedione, and 3-ethyl-2,4-pentanedione are presented. At the temperatures at which spectra were measured torsion about carbon–carbon partial double bonds is slow on the NMR time scale and resonances of *Z,Z*, *E,Z*, and *Z,E* diastereomers or topomers are distinguishable. Addition of lithium iodide (configurational titration) was used to assign resonances and to study chelation of lithium ion by enolate anions. The effects of steric bulk on chelation are described and the effects of gegenion and stereochemistry on ^{13}C NMR chemical shifts are discussed. The ^{13}C NMR spectra of 2,4-pentanedione, 2,4-hexanedione, 3-methyl-2,4-pentanedione, and 3-ethyl-2,4-pentanedione are also reported and the enol chemical shifts compared with those of the enolates.

Introduction

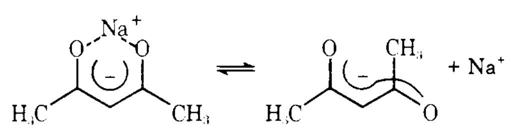
Reactions of resonance-stabilized carbanions, notably enolate anions, are among the most important class of reactions in synthetic and mechanistic organic chemistry.[2] Although numerous authors[3] have suggested that ion pairing and the stereochemistry of β-keto enolates have an important effect on their regiospecificity, stereoselectivity, and rates of alkylation, it has been possible, only recently, to study these properties directly. The solid-state structures of several alkali metal salts of β-dicarbonyl compounds have been reported recently[4-7] and low-temperature ^{1}H NMR spectroscopy has been shown to be useful for directly studying stereochemistry and associ-

0002-7863/79/1501-5178$01.00/0

ation with alkali metals in solution.[8,9] We have extended our previous ^{1}H NMR work on acetylacetonate to carbon magnetic resonance (^{13}C NMR) in order to investigate the effect of alkyl substitution at the 3 position on the configurational disposition and ability to chelate alkali metals in methanol solution.[10] The availability of low-temperature ^{13}C NMR spectra also allows us to comment on room temperature ^{13}C NMR spectra of enolate anions which have been described recently.[12-16]

Results and Discussion

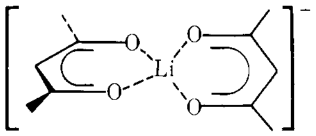
Low-temperature ^{1}H NMR spectroscopy of sodium acetylacetonate (**1**) indicated that the equilibrium expressed by eq 1 obtains in methanol-d_4. The existence of this equilibrium is also evident in low-temperature (ca. −60 °C) ^{13}C NMR spectra in methanol. The spectrum features two equally intense carbonyl resonances for the *E,Z* form and a single less intense carbonyl resonance for the *Z,Z* form. Two resonances are observed for the methine carbon (C-3) in the two forms and three resonances correspond to the acetyl methyl carbon atoms (Scheme I). The relative amounts of the two forms could be determined from ratios of intensities (or integrated intensities)[17] of carbonyl or C-3 resonances.[18] Both sets of resonances afforded the same mole fraction of *Z,Z*-**1**, i.e., 0.25, in good agreement with the value obtained from ^{1}H NMR spectroscopy,[9] viz., 0.23, and allow us to conclude that errors from differential NOE effects, relaxation times, and line widths are not large. The internal consistency in measured mole fraction of *Z,Z*-**1** and the agreement with the value derived from ^{1}H NMR spectra provide a justification of the validity of this procedure.



(1)

Z,Z-1-Na *E,Z*-1

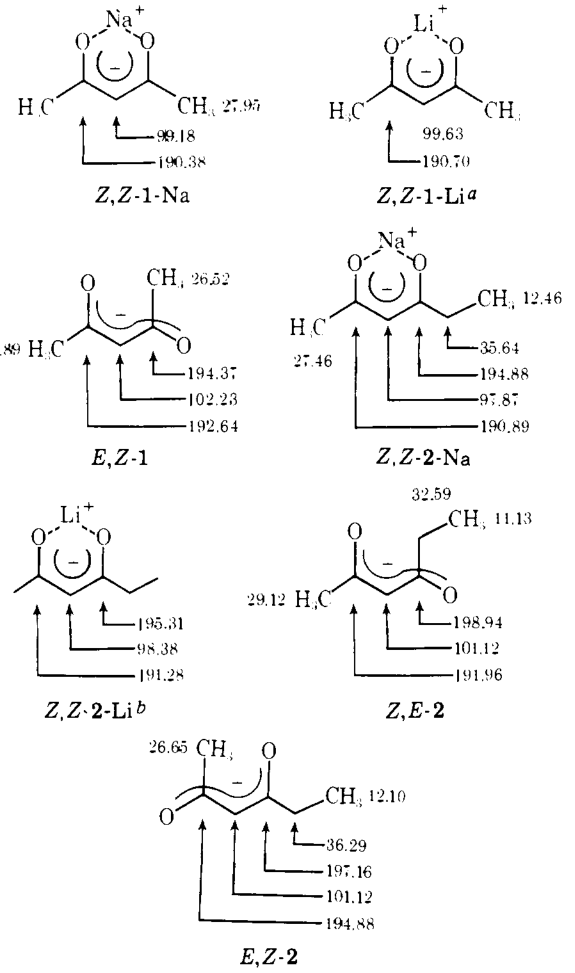
Addition of measured amounts of lithium ion (as (LiI) effects significant changes in the ^{13}C NMR spectrum. The C-3 and carbonyl resonances corresponding to the *E,Z* form diminish as the amount of lithium ion is increased while those of the *Z,Z* form increase and exhibit small downfield shifts. A plot of the mole fraction of *Z,Z*-**1** as a function of added lithium ion extrapolates to complete conversion to the *Z,Z* form upon addition of 0.5 mol of lithium ion signaling the presence of the bischelated triple ion, **3**, in accord with the results from a previous ^{1}H NMR study.[9,19]



3

Lithium triple ions related to **3** have been observed in the solid-state structures determined by X-ray diffraction.[5,7] One of these structures,[7] that of a *β*-keto ester, features a distorted tetrahedral array for the four oxygen atoms. In the other structure,[5] that of lithium 2,4-pentadioate, the four oxygen atoms and the lithium ion are coplanar. However, this second structure also features lithium ions which bridge separate triple ions and it seems likely that the spatial requirements for bridging can distort the triple ion geometry giving rise to a distorted square planar (distorted D_{4h}) array. For this reason we favor the nonplanar structure **3** as the more likely structure in solution. The observation of both forms in solid-state structures suggests that the energy difference between them is not great. This is in accord with the model for the structure of these chelates which postulates metal oxygen interactions which are essentially ionic. Coulombic forces should favor a tetrahedral array but not as strongly as the hybridization factors which are responsible for the tetrahedral rigidity of covalent methane.

Scheme I. ^{13}C NMR Assignments for 2,4-Pentanedione and 2,4-Hexanedione Enolates



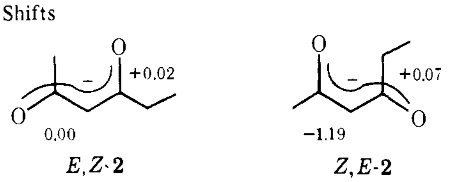
[a] Spectrum of **1**-Na + 0.69 equiv of LI. [b] Spectrum of **2**-Na + 0.82 equiv of LiI.

The observation of negligible downfield shifts for the carbonyl and methine carbon atoms of the *E,Z* form (0.00, 0.07, and 0.07 ppm, respectively) upon addition of 0.34 equiv of lithium ion, but substantial shifts for the carbonyl and methine carbon atoms of the *Z,Z* form (0.15 and 0.36 ppm), is in accord with the type of equilibrium indicated in eq 1. The *E,Z* form is thought to be essentially dissociated ions and the addition of lithium iodide has only a negligible effect on the bulk solvent properties.[20] By contrast, *Z,Z*-**1** is a tight ion pair and the change of the gegenion from Na$^+$ to Li$^+$ as the titration proceeds is reflected in chemical-shift changes which are well outside of experimental error. Further, the observation of a gradual change in chemical shift rather than a broadened or doubled signal (especially for the C-3 resonance) indicates that exchange of gegenion is rapid on the NMR time scale even at these low temperatures.

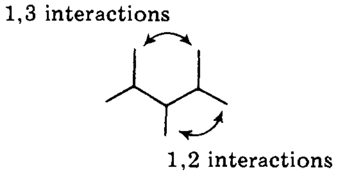
Similar behavior was observed for the sodium salt of the unsymmetrical diketone, 2,4-hexanedione (**2**). The low-temperature spectra indicate the presence of three diastereomers having the *Z,Z*, *E,Z*, and *Z,E* configurations in a ratio of 3:5:2. The chemical shift assignments are given in Scheme I.

The spectrum features five resonances in the carbonyl region. The two corresponding to the *Z,Z* form were easily identified on the basis of the lithium titration as those at δ 190.89 (C-2) and 194.88 (C-4), since the carbonyl resonances

Scheme II. Deviations of Observed from Calculated Carbonyl Chemical Shifts



Scheme III. 1,2 and 1,3 Interactions



of the sodium and lithium chelates are very similar as in **1**. Addition of 0.46 equiv of LiI to **2**-Na resulted in almost complete conversion to the *Z,Z* form indicating that a triple ion analogous to **3** is also formed by this enolate.

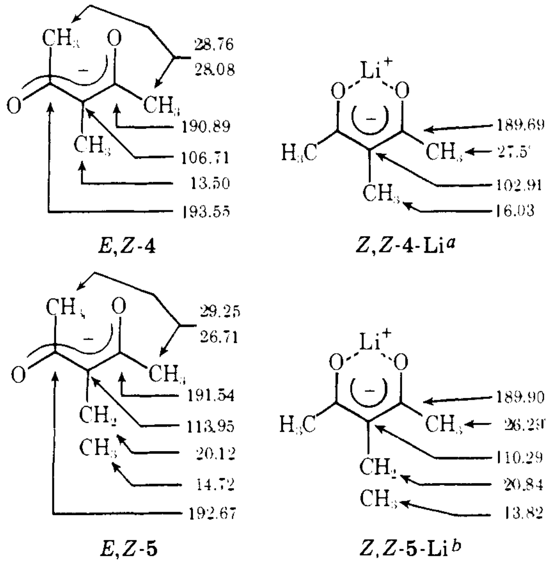
Predicted values for the chemical shifts in the *E,Z* and *Z,Z* isomers were calculated on the basis of the spectrum of **1**. Thus, the differences in the resonances of the two carbonyl groups in *E,Z*-**1** and the single resonance in *Z,Z*-**1**-Na are 194.37 − 190.38 = 3.98 ppm and 192.64 − 190.38 = 2.25. These increments were added to the identified resonances of *Z,Z*-**2**-Na to produce predicted values of δ 193.15, 194.88, 197.14, and 198.87 which were matched with the experimental values using peak intensities as a guide. The minor isomer was assigned the *Z,E* configuration since in this isomer the more bulky ethyl group is in the more congested environment. It may be noted that one of the calculated values exactly coincides with one of the resonances of *Z,Z*-**2**-Na, accounting for the observation of only five resonances for the six distinguishable carbonyl groups. The deviations of the observed from calculated shifts are illustrated in Scheme II. Negligible shifts are observed for all but the C-2 carbon in *Z,E*-**2**, the minor isomer. This is in accord with our assignment. Apparently, the close contact between the carbonyl oxygen and the ethyl group not only destabilizes this isomer relative to the *E,Z* form but also gives rise to an upfield shift relative to the predicted value. The remaining shifts in **2** were assigned in routine fashion. The observation of a downfield shift for the acetyl methyl group and an upfield shift for the acetyl carbonyl in *Z,E*-**2** (relative to those in *E,Z*-**2**) made possible the assignments of the *E* and *Z* acetyl resonances in *E,Z*-**1** as given in Scheme I.

The mole fraction of the chelated *Z,Z* form is greater for hexane-2,4-dione than for pentane-2,4-dione (0.33 vs. 0.25 for a 0.4 M solution). The increased amount of the *Z,Z* form is due entirely to the destabilization of the *Z,E* diastereomer. The ratio of the mole fractions of *Z,Z*-**2**-Na to *E,Z*-**2**, viz., 0.69, is essentially the same as the ratio of *Z,Z*-**1**-Na to one of the *E,Z*-**1** topomers, viz., 0.67.

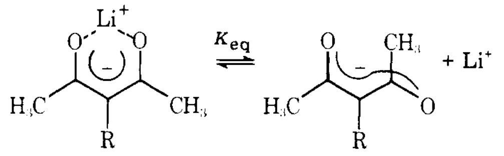
While 1,3 steric interactions (resulting from substitution in the 1 position in **1**) destabilize dissociated *E,Z* forms relative to the *Z,Z* chelate, 1,2 interactions have the opposite effect and lead to very significant destabilization of the sodium chelate (Scheme III).[21] As a result, the ^{13}C NMR spectra of the 3-methyl and 3-ethyl derivatives, **4**-Na and **5**-Na, in methanol exhibit only two, equally intense carbonyl resonances signaling the sole presence of the *E,Z* configuration.

Lithium chelation is, however, more favorable than sodium chelation and addition of lithium iodide results in the growth of new resonances attributable to the *Z,Z* chelate (Scheme IV). The titration curves[19] for **4** and **5** are quite different from that of **1** and feature more gradual increases in the content of the *Z,Z* configuration. More than 1.5 equiv of LiI is required before the resonances of the *E,Z* form become weak enough that they can no longer be observed. Because the enolate is converted to the *Z,Z* form much less readily we do not postulate the existence of triple ions as described for **1** and **2**. The effect of lithium ion on the configurational distribution can be analyzed using eq 3, which can be derived for the kind of equilibrium shown in eq 2. K_{eq} represents the dissociation constant for the lithium contact ion pair, C is the concentration of enolate (total), L is the number of equivalents of lithium iodide added, and R is the ratio of mole fractions of the *Z,Z* to *E,Z* configurations. Rearrangement of eq 3 produces

Scheme IV. ^{13}C NMR Assignments for 3-Methyl-2,4-pentanedione and 3-Ethyl-2,4-pentanedione Enolates



[a] From the spectrum of a 0.4 M solution of 4-Na containing 2.4 equiv of LiI. [b] From the spectrum of a 0.4 M solution of **5**-Na containing 1.7 equiv of LiI. [c] Resonance overlaps with a resonance from acetone-d_6.



(2)

R = CH_3, CH_2CH_3

$$K_{eq} = \frac{CL}{R} - \frac{C}{1 + R} \tag{3}$$

$$CL - \frac{CR}{1 + R} = K_{eq}R \tag{4}$$

which was suitable for linear least-squares analysis. Plots[19] of $CL - ((CR/1 + R))$ vs. R afforded reasonably linear plots with slopes equal to the dissociation constants: **4**, $K_{eq} = 8.0 \pm 1.0 \times 10^{-2}$, $R = 0.94$; **5**, $K_{eq} = 8.1 \pm 0.9 \times 10^{-2}$, $R = 0.95$. These values are about two orders of magnitude greater than the value estimated for the dissociation of lithium acetylacetonate.[9] Since the electronic effect of alkyl substitution would be expected to increase the bascity of the carbonyl oxygen atoms we would judge that this represents a lower limit for the steric effect involved in the double 1,2 interactions in the chelate form of the 3-alkyl acetylacetonates.

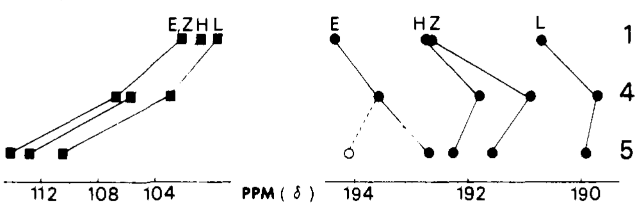
Qualitatively we would judge the 1,2-methyl *n*-alkyl interaction as less destabilizing than the 1,3-methyl methyl interaction since we find no evidence for any of the *E,E* form being present. The *E,E* configuration seems better on electronic grounds and is the preferred configuration for malonaldehyde anion,[24] in which steric interactions are minimized. Finally we may note that the steric factors which destabilize the *Z,Z*

Table I. Gegenion Effects on ^{13}C NMR Chemical Shifts in Enolates

ketone (solvent)	^{13}C NMR shift change[a] gegenion change	α carbon	C=O	ref
phenylacetone (DME)	Li → Na	−1.9	+4.6	12
2,2-dimethylpentan-3-one (dioxane)	Mg → Na	−17.3	+9.9	13
dibenzoylmethane (Me_2SO)	Li → Na	−0.4	−0.4	14
dipivaloylmethane (Me_2SO)	Li → Na	−1.1	−1.0	14
2,4-pentanedione, **1**	H → Li	−1.1	−2.0	*b*
(methanol)	Li → Na	−0.5	−0.5	*b*
	Li → free enolate	+3.0	+2.6[c] (1.7, 3.5)	*b*
2,4-hexanedione, **7**	H → Li	−1.22	−1.3, −1.5[d]	*b*
(methanol)	Li → Na	−0.5	−0.4, −0.4[d]	*b*
	Li → free enolate	+3.8	+2.1, 2.7[d,e]	*b*
3-methyl-2,4-pentanedione **4**	H → Li	−2.8	−2.11	*b*
(methanol)	Li → free enolate	+3.8	+2.8[c] (1.5, 4.0)	*b*
3-ethyl-2,4-pentanedione **5**	H → Li	−2.5	−2.4	
(methanol)	Li → free enolate	+3.7	+2.4[c] (1.8, 2.9)	*b*

[a] Chemical shifts for X → Y are defined as $\delta_Y - \delta_X$, i.e., downfield shifts are positive. [b] This work. [c] Average shifts. Values in parentheses are the separate shifts for *Z* and *E* carbonyl groups. [d] Shifts are for C-2 (acetyl) and C-4 (propionyl), respectively. [e] Average shifts.

Scheme V. Comparison of C-3 (■) and Carbonyl Chemical Shifts (●) in **1**, **4**, and **5**[a]



[a] The expected position for the *E* carbonyl resonance is indicated by an open circle (○). The shifts of the lithium chelate (L), the enol (H), and the *E,Z* form (*E,Z*) are given.

chelate relative[2] to the *E,Z* configuration also seem to be responsible for the decreased amount of enol found in equilibrium with the keto form for both diketones relative to acetylacetone.

The changes in chemical shifts during the configuration titration[19] of **4** and **5** differ from those described above for **1** and **2**. The shifts in the carbonyl and C-3 resonances of the chelate upon addition of ca. 1 equiv of lithium iodide are downfield and quite small: *Z,Z*-**4**, 0.3-1.4 equiv of LiI, C=O, 0.12 ppm, C-3, 0.13; *Z,Z*-**5**, 0.3-1.6 equiv of LiI, C=O, 0.13, C-3, 0.03. This difference in behavior from **1** and **2** is in accord with our interpretation of the lithium ion induced shifts as reflecting a change from a sodium to a lithium chelate. In the present case, we find no evidence for a sodium chelate and the *Z,Z* configuration of **4** and **5** is always solely due to the lithium chelate.

The lithium ion shifts for the *E,Z* configuration are more difficult to interpret. Two of the resonances exhibit small shifts while one, that which we assign to the *E* carbonyl carbon atom, is significantly affected: *E,Z*-**4**, 0-1.4 equiv of LiI, *E*-C=O, 0.42 ppm, *Z*-C=O, −0.04, C-3, 0.21; *E,Z*-**5**, 0-1.6 equiv of LiI, *Z*-C=O, 0.46, *Z*-C=O, 0.12, C-3, 0.29. One possible explanation for this behavior would involve partial coordination of the *E,Z* isomer with lithium ion or solvent methanol at the sterically more accessible *E* carbonyl group. However, no reliable conclusion can be drawn from this limited information.

The assignments of specific resonances in the spectra of the three alkyl derivatives which are detailed in Scheme IV were derived from a comparison of shifts in derivatives of **1**, **4**, and **5** which is illustrated in Scheme V. The carbonyl shifts in the lithium chelate (L), the enol[19] (H), and the free enolate (*E* and *Z*) are plotted as well as the C-3 resonances (L, H and *E,Z*).

As indicated in the scheme the replacement of hydrogen by methyl results in a downfield shift for C-3 and further replacement of methyl by ethyl results in a further, somewhat larger, shift in the same direction. These shifts are in the direction and of the relative magnitude anticipated for α and β alkyl substitution. The shifts for all three resonances parallel those in keto forms of the corresponding ketones: **1**, 58.24; **4**, 61.71; **5**, 69.86 ppm.

The behavior of the carbonyl resonances is more complicated and the behavior of the enol and enolate resonances is quite different from that in the corresponding ketones.[19] In the ketones, replacement of the C-3 hydrogen with methyl results in a downfield shift (β substituent) while changing the 3-alkyl group from methyl to ethyl results in a smaller upfield shift (γ substituent): **1**, 204.66; **4**, 207.38; **5**, 206.48 ppm. The enol/enolate carbonyl resonances exhibit just the reverse for replacement of the C-3 hydrogen with a methyl group, i.e., an upfield shift, and three of them (H, *Z*, and L) then undergo small downfield shifts upon the replacement of the 3-methyl group by ethyl. An exception to this behavior is found for the *E*-carbonyl resonance of the *E,Z* configuration of 3-ethyl-2,4-pentanedionate, which suffers a shift of about 1 ppm from the position which would be expected (open circle in Scheme V) if the shifts for the other carbonyl resonances were followed. This anomaly is reminiscent of that described above for the *Z* carbonyl of (*Z,E*)-2,4-hexanedionate (Scheme II). There is a structural similarity in the two cases since both feature ethyl groups which can approach the carbonyl closely, and it is possible that the two discrepancies have a similar origin.

Several of the recent investigations of ^{13}C NMR spectra of enolates have involved the measurement of chemical-shift changes attendant upon change of gegenion (Li → Na or Mg → Na) and these changes have been interpreted in terms of π-electron densities and their effects on the shifts at carbonyl and α carbon atoms. All of these studies were performed at room temperature or have involved simple enolates, and, as a consequence, it was not possible to observe equilibrating contact ion pairs and free ions as separate species.

Both House et al.[12] and Fellmann and Dubois[13] report M → Na shifts (M = Mg or Li) in simple enolates which are downfield for the carbonyl carbon atom and upfield for the α carbon. In both cases, they regarded these shifts as reflective of increased π density at the α carbon atom since the sodium salts were regarded as being more similar to the dissociated enolate. Arnett and DePalma[14] came to similar conclusions about the Li → Na shifts in enolates of β-diketones, although they observed upfield shifts for both the α and carbonyl carbon atoms.

In the present work we have examined the enolates of 2,4-

pentanedione and 2,4-hexanedione in four different states of coordination, the *Z,Z* enolate chelating hydrogen, lithium, and sodium and the free *E,Z* enolate, and the enolates of 3-methyl- and 3-ethyl-2,4-pentanedione in three of these (excepting the sodium chelate). Our results are compared with those of previous works in Table I.

Examination of the data in Table I indicates the variability of results obtained in different systems. This variability suggests that drawing general conclusions about the origins of these chemical-shift changes may be premature. Examination of some of the discrepancies in Table I may be instructive.

Fellmann and Dubois noted the much larger α carbon shift obtained in their system (for Mg → Na) relative to that in phenylacetone (for Li → Na) and attributed this to their use of a dialkyl ketone, while in the experiments of House et al. the α carbon was in conjugation with the phenyl ring leading to less accumulation of charge on the α carbon. However, comparison of the results for β-diketone enolates does not indicate a further large diminution in the shift when the more strongly conjugating carbonyl group is present.

While there is some consistency in the shifts for the carbonyl groups either in the simple enolate group or the β-keto enolate group, the behavior of these two groups is reversed, i.e., the M → Na (M = H, Mg, or Li) shifts are downfield for simple enolates but upfield for the β-keto enolates. Thus explanations for the direction of carbonyl shifts which do not take into account the specific differences between the two systems cannot be valid.

The most striking feature of our data in Table I is the difference between the Li → Na (or H → Na) and Li → free enolate shifts for **1**, **2**, **4**, and **5**. While, in agreement with the results of Arnett and DePalma, we find upfield shifts for Li → Na, removal of the gegenion (Li or Na → free enolate) results in downfield shifts. Arguments based upon π density and canonical structures would lead to the reverse prediction. Further, we note that the shifts in the enols are not very different from those in the sodium and lithium chelates. While we find the anticipated order of chemical shifts ($\delta_H > \delta_{Li} > \delta_{Na}$), these differences are smaller than the difference between chelated and dissociated enolates. We must conclude that, if π densities play a role in determining ^{13}C NMR chemical shifts in enolates, this factor is less important than stereochemistry or other factors in these systems, and that considerably more data are necessary before conclusions drawn from one system can be safely generalized to others.

Experimental Section

Variable-temperature ^{13}C nuclear magnetic resonance spectra were measured at 15.04 MHz on a JEOL FX-60 spectrometer. The NM 5471 variable-temperature controller was modified to use nitrogen gas which passed through coils cooled in liquid nitrogen. Spectra were measured on 0.4 M solutions in methanol in 10-mm tubes which contained a sealed 5-mm coaxial insert containing 5% tetramethylsilane (Me_4Si) in acetone-d_6. Chemical shifts are reported in δ units relative to external Me_4Si. Temperatures were measured at the end of the accumulation by replacement of the sample tube with an open tube containing methanol and a copper-constantan thermocouple. The decoupler was turned off and the temperature measured as quickly as possible before thermal equilibrium was reestablished. Duplicate measurements agreed within ±3 °C. Approximately 2000 FID were collected using 16 384 data points and a window of 4 kHz. The pulse width was 3 μs corresponding to a flip angle of 30°. Decoupled spectra were recorded with 1-kHz width broad band noise decoupling.

Acetylacetone (pentane-2,4-dione) and hexane-2,4-dione were obtained commercially. 3-Methylpentane-2,4-dione and 3-ethylpentane-2,4-dione were prepared as previously reported.[25,26]

The sodium salts were prepared by the dropwise addition of the β-diketone (11 mmol) in benzene or pentane to a benzene or pentane slurry of oil dispersed sodium hydride (0.547 g, 10 mmol, 57% oil dispersion). The mixture was stirred until the evolution of hydrogen gas ceased. The precipitate was filtered, washed with benzene, and dried and stored in vacuo.

Supplementary Material Available: An appendix containing a listing of chemical shifts of carbonyl and C-3 resonances in **1**, **4**, and **5** in the presence of various amounts of lithium iodide (Table A1), as well as plots of composition as a function of equivalents of LiI added (Figures A1, A2, and A3), plots of eq 4 for **4** and **5** (Figures A4 and A5) and a listing of chemical shifts in the ketones corresponding to **1**, **2**, **4**, and **5** (Figure A6) (8 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) Previous papers in this series: part 1, E. A. Noe and M. Raban, *J. Am. Chem. Soc.*, **96**, 6184 (1974), correction *ibid.*, **98**, 641 (1976); part 2, E. A. Noe and M. Raban, *J. Chem. Soc., Chem. Commun.*, 165 (1976); part 3, G. Yamamoto and M. Raban, *Inorg. Nucl. Chem. Lett.*, **12**, 949 (1976); part 4, ref 9; part 5, M. Raban and D. Haritos, *J. Chem. Soc., Chem. Commun.*, 965 (1978). (b) Part 5 of this series is a preliminary report of some of this work. (c) Abstracted from the M.S. Thesis of D. P. Haritos, Wayne State University, 1978. (d) This work was supported by the National Science Foundation and the National Institutes of Health.

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(17) The use of intensities rather than integrated intensities in general gave more internally consistent results and results throughout this paper are based on peak intensities. For intense peaks the same value was obtained either from intensities or integrated intensities. However, when *S/N* ratios are low, measured integrated intensities are greatly affected by the assignment of the base line and anomalous (internally inconsistent) results were obtained.

(18) Intensities of acetyl methyl resonances could not be accurately measured because of overlap with the resonances of acetone-d_6 which was used to maintain the internal lock.

(19) See paragraph at end of paper regarding supplementary material.

(20) Based upon the point-to-point resolution (0.03 ppm),[3] the effect of the exponential window, and possible errors in phasing we estimate our resolution and chemical shift errors to be ±0.04 ppm.

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