K(actual) = 0.02 atm. The standard free energy change is then ΔG° = 2300 cal/mole and ΔS° = 23 cal/mole deg.

Our preliminary estimate of 10.2 kcal/mole for the activation energy for the decomposition of triphenylperoxy radical to triphenylmethyl and oxygen is consistent with the observed value of 9 kcal/mole for the heat of decomposition for the triphenylperoxy radical. At this time the difference between these values may fall within the error of our determinations. However continued work is expected to improve these values.

Preliminary experiments with 9-phenylfluorene-9-carboxylic, diphenylacetic, 2,2-diphenylpropionic, and 2,2-diphenylbutyric acids have given esr spectra attributed to the hydrocarbon radical. Exposure to air has given the peroxy radical in the first two cases. Experiments with other stable free radicals, *e.g.*, tris(*p*-nitrophenyl)methyl radical, are in progress.

Oxygen-17 Nuclear Magnetic Resonance Studies of the Equilibria between the Enol Forms of β-Diketones

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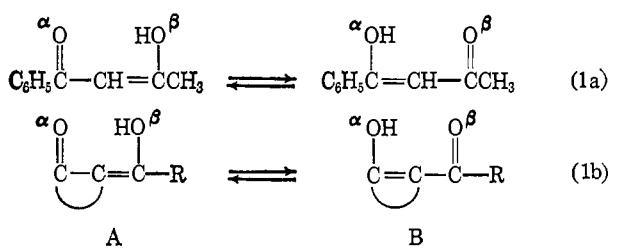
Contribution from the Organic Chemistry and Isotope Departments of the Weizmann Institute of Science, Rehovoth, Israel. *Received November 12, 1966*

Abstract: A method for determining the relative concentrations of the two enol tautomers A and B of asymmetric β-diketones (eq 1a and b) using ^{17}O nmr spectroscopy is described. The ^{17}O spectra of eight ^{17}O-enriched asymmetric β-diketones were studied. Two sets of lines were observed: (a) one broad peak in the range −500 to −600 ppm (downfield from $H_2{}^{17}O$) due to the keto tautomer, and (b) two peaks in the range 0 to −500 ppm due to the two nonequivalent oxygens of the enol tautomers. From the chemical shift of the enol peaks the equilibrium constant, K = [B]/[A], is calculated. The results show a small but systematic effect of ring size and substituents on K: (i) six-membered rings favor endocyclic double bonds while five-membered rings favor exocyclic double bonds; (ii) structure A is increasingly stabilized when R is changed from methyl to hydrogen to phenyl.

The equilibrium between keto and enol forms of β-diketones has been the subject of many extensive studies.[1-3] The most common method used to study this equilibrium is proton magnetic resonance spectroscopy (pmr).[4] Since the rate of the keto–enol interconversion is usually slow, separate signals of the protons due to the enol and keto forms may be observed and by intensity measurements the relative ratio of the two forms can be determined.

In a symmetrically substituted β-diketone (*e.g.*, acetylacetone) there is only one distinguishable enolic form. When the substituents on the β-diketone are not identical, two different enolic forms are possible, A and B.



In general the two forms will have different thermodynamic stabilities and the equilibrium constant

$$K = [B/[A] \quad (2)$$

will be different from unity. The determination of this equilibrium constant is, however, impossible by classical chemical methods because the two enolic forms are in rapid dynamic equilibrium. Their interconversion involves merely an intramolecular proton transfer with a concomitant change in the electron distribution in the molecule. The rate of this proton transfer is fast even on the time scale of nuclear magnetic resonance frequency and therefore only one set of lines is displayed in the pmr spectra by the two enolic forms.[4] The rate of interconversion between the two enol forms is, however, slow on the time scale involved in ultraviolet[5] and infrared[6] spectroscopy. In fact ultraviolet measurements have been employed to determine K in a number of α-benzoyl ketones, but since the absorption maxima of the separate forms were not known, the results cannot be considered reliable.[5b] Another attempt to estimate K using a chemical method was based on the relative yield of formation of derivatives of one or the other tautomeric forms upon reaction with diazomethane.[7] The results depend, however, on the relative reaction rates of the two forms, which again are not known, and therefore this method cannot be used for quantitative calculations.

(1) L. N. Ferguson, "The Modern Structural Theory of Organic Chemistry," Prentice-Hall Inc., Englewood Cliffs, N. J., 1964, pp 368–379.

(2) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Reinhart and Winston Inc., New York, N. Y., 1959, pp 376–384.

(3) G. S. Hammond in "Steric Effects in Organic Chemistry," M. S. Neuman, Ed., John Wiley and Sons, Inc., London 1956, pp 445–454.

(4) (a) H. S. Jarrett, L. S. Sadler, and J. N. Shoolery, *J. Chem. Phys.*, **21**, 2092 (1953); (b) N. Bhar, *Arkiv Kemi*, **10**, 223 (1957); (c) L. W. Reeves, *Can. J. Chem.*, **35**, 1351 (1957); (d) L. W. Reeves and W. G. Schneider, *ibid.*, **36**, 793 (1958); (e) J. L. Burdett and M. T. Rogers, *J. Am. Chem. Soc.*, **86**, 2105 (1964).

(5) (a) D. W. Barnum, *J. Inorg. Nucl. Chem.*, **21**, 221 (1961); (b) R. D. Campbell and H. M. Gillow, *J.Am. Chem. Soc.*, **82**, 5427 (1960).

(6) S. Forsen, F. Merenyi, and M. Nilsson, *Acta Chem. Scand.*, **18**, 1208 (1964).

(7) E. D. Campbell and H. M. Gillow, *J. Am. Chem. Soc.*, **84**, 1440 (1962).

The most successful method employed up to date is due to Garbisch using pmr spectroscopy.[8] The method is based on the fact that the pmr frequency of the aldehydic proton in the enol forms of aldehydo ketones (R = H, equilibrium 1b) will be the weighted average of its frequencies in forms A and B; K can be calculated provided these frequencies are known. Unfortunately the quantitative application of this method is limited to aldehydo ketones since the chemical shifts of protons further removed from the carbonyl group differ too little in the two enolic forms.[6]

In the present paper we describe a method for determining the equilibrium constant K using ^{17}O nmr spectroscopy. The approach is very similar to that of Garbisch.[8] The advantage here is the large differences found in the chemical shifts of the ^{17}O resonances. Christ, *et al.*,[9] have measured the ^{17}O chemical shifts of a large number of organic compounds. The shifts cover a range of 1000 ppm which is divided into intervals characteristic of the functional group containing the oxygen atom. It was found that the chemical shifts of hydroxylic oxygens fall in the range of ±40 ppm, while those of carbonyl oxygen fall in a narrow range around −550 ppm, both relative to water.

Methods of Calculation

Consider equilibrium 1; if the rate of equilibration is slow, each enol form should show two ^{17}O resonance lines, one at a low field corresponding to the carbonyl oxygen, and the other at a higher field corresponding to the hydroxyl oxygen. Since the chemical shift of ^{17}O within a given bond is only slightly dependent on a neighboring substitution, the carbonyl resonances of the two forms A and B will fall very close to each other or even coincide. The same applies, of course, to the hydroxyl resonances. On the other hand when the two enol forms interconvert at a rate much faster than the difference in the chemical shift between the carbonyl and hydroxyl resonances (*i.e.*, much faster than 10^4 sec^{-1} in a magnetic field of 14,000 gauss), each oxygen (α or β) will show only one resonance line at a frequency corresponding to the weighted average frequencies of the carbonyl and hydroxyl resonances. This is in fact the case for the group of β-diketones under consideration. Thus the observed chemical shift of oxygen α, δ^α, will be

$$\delta^\alpha = \delta^{COH}[B] + \delta^{CO}[A] \quad (3)$$

and similarly

$$\delta^\beta = \delta^{CO}[B] + \delta^{COH}[A] \quad (4)$$

where δ^{COH} and δ^{CO} are the chemical shifts of the hydroxyl and carbonyl oxygens of the "frozen" enol compounds (assumed to be independent of the substitution), and [A] and [B] are the mole fractions of forms A and B. Thus, if δ^{COH} and δ^{CO} were known, the equilibrium constant, K = [B]/[A], could be calculated from either δ^α or δ^β. It will be shown below that δ^{COH} and δ^{CO} can be evaluated to a high degree of certainty. In order to make use of δ^α and of δ^β we shall derive an expression for K involving both. From eq 3 and 4 and remembering that [A] + [B] = 1, it follows that

$$\delta = [A](\delta^{CO} - \delta^{COH}) - [B](\delta^{CO} - \delta^{COH}) = \Delta(2[A] - 1) \quad (5)$$

where $\Delta = \delta^{CO} - \delta^{COH}$ and $\delta = \delta^\alpha - \delta^\beta$. Thus

$$[A] = {}^1/_2(1 + \delta/\Delta) \quad (6a)$$

and similarly

$$[B] = {}^1/_2(1 - \delta/\Delta) \quad (6b)$$

and

$$K = [B]/[A] = (\Delta - \delta)/(\Delta + \delta) \quad (7)$$

The values of δ can be obtained experimentally; Δ will be considered a constant for all the compounds studied and is estimated to be 460 ppm. This estimate is based on the following consideration. From the results obtained by Christ, *et al.*,[9] and additional data obtained in this laboratory, the chemical shift of the carbonyl oxygen of simple ketones (Table I) is found to vary in the narrow range 540–570 ppm relative to water,[10,11] with an average at 555 ppm. To estimate the value of δ^{CO} in the enol form one should take into account the fact that the carbonyl oxygen in this form is internally hydrogen bonded with the hydroxyl proton. Hydrogen bonding to carbonyl oxygen shifts the oxygen resonance to a higher field. This was demonstrated for acetone for which an upfield shift of *ca.* 60 ppm was found upon dissolving it in water.[12] A similar effect of H bonding to the carbonyl oxygen is exhibited by an upfield shift of 60 ppm of the carbonyl resonance in salicylaldehyde as compared to benzaldehyde.[12] Taking this effect into consideration we estimate δ^{CO} at 555 − 60 = 495 ppm.

Table I. ^{17}O Chemical Shifts[a,b] of Mono- and 1,2-Diketones

Compound	δ, ppm
Acetone[c]	572
Acetaldehyde[c]	595
Cyclohexanone[c]	559
Cyclopentanone[c]	548
Acetophenone	546
Camphor	514
Tropolone	250
1,2-Cyclohexadione	495 (C=O); 52 (COH)

[a] Chemical shifts are given in ppm downfield from $H_2{}^{17}O$ (ref 11). [b] The spectra were done on the neat liquid except for the last three compounds which were measured in benzene. [c] Reference 7.

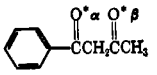
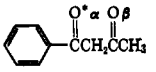
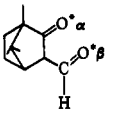
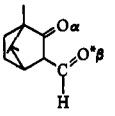
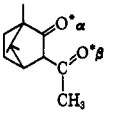
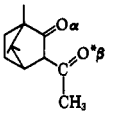
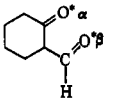
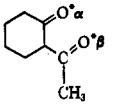
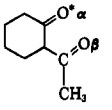
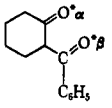
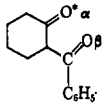
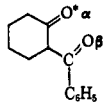
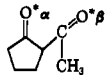
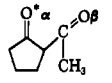
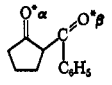
From eq 3 and 4, the average $\delta_{1/2}$ of δ^{CO} and δ^{COH} should also be the average of the measured shifts δ^α and δ^β.

$$\delta_{1/2} = {}^1/_2(\delta^{CO} + \delta^{COH}) = {}^1/_2(\delta^\alpha + \delta^\beta) \quad (8)$$

We assigned the value of 265 ppm to $\delta_{1/2}$, which is the mean value obtained for the compounds studied (Table II, column 7). Substitution in eq 8 gives δ^{COH} = 35 ppm. The latter value is consistent with the chemical shift found for hydroxylic oxygens. Therefore, Δ = 495 − 35 = 460 ppm. In view of the approximation involved in estimating Δ, its value should be

(8) E. W. Garbisch Jr., *J. Am. Chem. Soc.*, **85**, 1696 (1963).
(9) H. A. Christ, P. Diehl, H. R. Schneider, and H. Dahn, *Helv. Chim. Acta*, **44**, 865 (1961).
(10) The exceptionally high-field shift of camphor (Table I) will be considered when discussing camphor derivatives.
(11) Since we shall be concerned only with lines falling at low field relative to $H_2{}^{17}O$ we shall for the sake of convenience denote low-field shifts by positive numbers.
(12) H. A. Christ and P. Diehl, *Helv. Phys. Acta*, **36**, 170 (1963).

Table II. ^{17}O Nmr Spectra[a] of β-Diketones in Benzene Solution

No.	Method of labeling	β-Diketone[b]	δ^{α} [c]	δ^{β} [d]	δ^{K} [e]	$\delta_{1/2}$	[A]	[B]	K = [B]/[A]
I[g]	Neutral solution	$CH_3\overset{O^*\alpha}{\overset{\|\|}{C}}CH_2\overset{O^*\beta}{\overset{\|\|}{C}}CH_3$	274 (115)[f]		566 (240)	274	0.50	0.50	1.00
IIa	Neutral solution		233 (220)	291 (240)	...	262	0.44	0.56	1.29
IIb	Specific labeling		234	...	...				
IIIa	Acidic solution		430 (250)	88 (250)	α 514 β 587	259	0.87	0.13	0.15
IIIb	Neutral solution		...	88	... β 585				
IVa	Acidic solution		408 (470)	108 (220)	α 520 β 570	258	0.83	0.17	0.21
IVb	Neutral solution		...	108	560 (670)				
V	Acidic solution		205 (170)	360 (170)	...	283	0.33	0.67	2.02
VIa	Neutral solution		175...[h]	359 (300)	...	267	0.30	0.70	2.34
VIb	Specific labeling		179	...	...				
VIIa	Acidic solution		231 (315)	295 (350)	553 (830)	263	0.43	0.57	1.32
VIIb	Specific labeling		231	...	*i*				
VIIc	Neutral solution		232	...	560				
VIIIa[f]	Neutral solution		354 (170)	169 (160)	545 (480)	262	0.70	0.30	0.43
VIIIb	Specific labeling		354		544				
IX	Acidic solution		395 (270)	121 (200)	542 (670)	258	0.80	0.20	0.25

[a] The chemical shifts are given in ppm downfield from $H_2{}^{17}O$ (ref 11). [b] The oxygen atoms marked by a star are labeled with ^{17}O. [c] ^{17}O chemical shift of the α oxygen in the enol form. [d] ^{17}O chemical shift of the β-oxygen in the enol form. [e] The ^{17}O shift of the oxygens of the keto form. [f] The numbers in brackets are the full line width at half maximum intensity ($1/\pi T_2$) given in cps. [g] Spectrum of neat liquid. [h] This line appears as a doublet in the neat liquid (see text). [i] No line due to the keto form was observed (apparently due to its low concentration).

considered reliable to ±45 ppm. In systems where K is of the order of unity, $|\delta/\Delta| \ll 1$, and the error in determining [A] and [B] is less than the error in Δ, *i.e.*, better than 10%. However, when one of the enol forms is dominant, $|\delta/\Delta|$ is close to 1, the calculated values for the concentration of the minor form, and thus for K, will be much less reliable.

Experimental Section

Synthesis of Unlabeled Compounds. All unlabeled compounds studied were prepared and purified by standard techniques.

Preparation of ^{17}O-Enriched β-Diketones.[13] Two kinds of ^{17}O-labeled compounds were prepared: (a) "totally labeled" compounds where both carbonyl groups were labeled, and (b) "specifically labeled" compounds in which one of the two compounds was marked.

"Totally labeled" compounds were prepared by exchange with ^{17}O-enriched water.[14] The rate of exchange is acid catalyzed and varied from compound to compound. In the present work no kinetic measurements on the exchange rate were attempted, and a unified enrichment procedure for all substances was adopted. The compound was mixed with an excess of $H_2{}^{17}O$, molar ratio 1:4, containing approximately 3 atom % of ^{17}O. The enriched water had been normalized to the natural abundance of hydrogen isotopes. Enough dioxane was added until a clear solution was obtained, the solution was refluxed overnight under nitrogen, and the labeled compound was recovered by distilling off the solvent and subsequently purified. The pmr spectra of the ^{17}O-enriched compounds were always identical with the normal compounds. Under these conditions, the oxygen atoms of acetylacetone (I), benzoylacetone (II), acetylcyclohexanone (VI), acetylcyclopentanone (VIII), and 1,2-cyclohexadione exchange both oxygen atoms with $H_2{}^{17}O$. On the other hand, tropolone did not exchange sufficiently to show a detectable ^{17}O resonance and formyl- and acetylcamphor (III and IV) and benzoylcyclohexanone (VII) incorporated ^{17}O into one of their two carbonyl groups only. For these compounds acid catalysis was resorted to; one drop of concentrated hydrochloric acid was added to the reaction mixture to make the solution acidic to *ca.* 0.05 *N*. After refluxing overnight the product was extracted with absolute ether and purified.

"Specifically labeled" compounds were prepared by synthesis from monoketones labeled with ^{17}O by exchange with ^{16}O-enriched water. Cyclohexanone and cyclopentanone exchanged in neutral solution while camphor and acetophenone needed acid catalysis. The labeled compounds were treated with sodium hydride in dry ether, and then with either ethyl acetate or benzoyl chloride. To prevent oxygen scrambling, the reaction mixture was worked up under anhydrous conditions; the sodium enolate was decomposed with ethanolic hydrogen chloride and the sodium chloride was filtered off under reduced pressure and washed with absolute ether. The combined solvents were evaporated *in vacuo*, and the products were purified. The diketones thus obtained proved to be pure except for benzoylcyclohexanone, which was contaminated with benzoic acid. The latter was removed by adding an ethereal solution of diazomethane and subsequent distillation of the methyl benzoate formed.

Nmr Measurements. The ^{17}O nmr spectra were recorded on a V-4200 Varian wide-line spectrometer operating at 8.13 Mc/sec. The derivative of the absorption lines were recorded using 40-cps sweep modulation. Calibration was done by the side-band technique. All the spectra were taken in a solution of spectroscopic benzene (10–20% by weight) except for acetylacetone (I) and acetylcyclopentanone (VIII), which were measured as neat liquids. The probe temperature was 27°. For the measurements, the solutions were placed in 13-mm i.d. test tubes which served as the nmr sample holder. The chemical shifts were measured relative to $H_2{}^{17}O$ as an external standard. The accuracy of the chemical shift values varies between ±2 and ±5 ppm depending on the width of the resonance band in question. When appreciable overlap between lines occurred, the position of the peaks was determined by comparing the spectrum with theoretically constructed doublets. For the sake of completeness we have also measured the line width of the ^{17}O peaks. In these measurements care was taken not to saturate the lines, and the data given in Table II were corrected for overmodulation. The reported line widths, $1/\pi T_2$, are the full width at half maximum intensity of the absorption mode. Measurements of the line widths were done only for the compounds "totally labeled" with ^{17}O.

Results

The Chemical Shifts of Monoketones and 1,2-Diketones. In Table I are listed the chemical shifts of some mono- and 1,2-diketones. The values for acetaldehyde, acetone, cyclohexanone, and cyclopentanone are taken from the work of Christ, *et al.*,[9] and are used for comparison. The other results are from the present work.

The ^{17}O spectrum of 1,2-cyclohexadione in benzene shows two equally intense signals at 52 and 495 ppm assigned respectively to the hydroxyl and carbonyl oxygens of the enol form (see Table I). No signal due to the keto form was observed. The ^{17}O shifts observed in the enol form support our assignment of δ^{COH} and δ^{CO} discussed above (35 and 495 ppm, respectively). The fact that two ^{17}O lines are observed indicates that interconversion between the two possible symmetric enol forms is slow. This finding is consistent with the pmr spectrum of 1,2-cyclohexadione in benzene; no signals due to a keto form were observed, and a sharp low-field triplet due to the enol vinylic hydrogen indicates slow interconversion. It is not surprising that in this compound interconversion between the two symmetric enol forms is slow; here interconversion cannot proceed by a mere proton jump between the two oxygens, but must also involve an exchange of α-hydrogen atoms.[15] On the other hand, tropolone which also exists entirely in its enol form[16] shows only one ^{17}O signal. Here the two symmetric forms can interconvert through a fast transfer of the hydrogen between its two oxygen atoms. The appearance of only one ^{17}O signal and its chemical shift is consistent with such a fast interconversion.

The Chemical Shifts of the Keto Tautomers of the β-Diketones. These results are summarized in Table II, column 6 (δ^{K}). As expected, these values fall in the range of 500–600 ppm typical for monoketones; most of them, however, are in the narrow range between 540 and 580 ppm. A keto tautomer of an asymmetrically substituted β-diketone would be expected to show two ^{17}O resonances but, as already discussed, substitution has only a small effect on the ^{17}O chemical shift. Indeed, in most cases only one comparatively broad line was observed. The two camphor derivatives, III and IV, however, are exceptional, and two keto signals were observed in each. Here the difference in the chemical shift between the two carbonly oxygens seems to be large enough to allow resolution into two peaks. This larger difference is due to the position of the resonance of the camphor oxygen which falls at a considerably higher field than the ^{17}O carbonyl resonance of simple ketones and aldehydes (see Tables I and II).

No resonance in the range 500–600 ppm was observed in benzoylacetone (II), formylcyclohexanone (V), and acetylcyclohexanone (VI) due to the low concentration of the keto forms. The relative concentration of enol

(13) Concerning methods for labeling oxygen atoms see: D. Samuel and B. L. Silver, *Advan. Phys. Org. Chem.*, 3, 147 (1965).

(14) $H_2{}^{17}O$ was obtained from the enrichment plant of this institute.

(15) The triplet due to the vinylic proton is also observed in methanolic solution and does not change on addition of acids. However when base is added the components of the triplet broaden, indicating a fast interconversion between the two symmetrical forms.

(16) T. Nozoe in "New Benzenoid Aromatic Compounds," D. Ginsburg, Ed., Interscience Publishers, Inc., New York, N. Y., 1959, p 339.

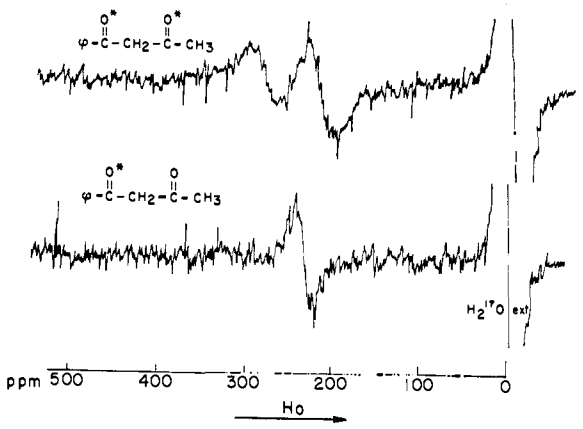


Figure 1. ^{17}O spectra of benzoylacetone (II): upper trace, both oxygen atoms labeled with ^{17}O; lower trace, one oxygen atom labeled.

to keto forms was not determined from the ^{17}O spectra; this may be done more accurately by pmr.

The Chemical Shifts of the Enol Tautomers of β-Diketones. The main part of the present work concerns the quantitative interpretation of the chemical shifts of the enol tautomers. The results are summarized in Table II, columns 4 and 5. Acetylacetone (I), the only symmetrically substituted β-diketone studied, shows a single resonance line of its enol form, indicating a fast interconversion of the two identical forms. Its chemical shift at 274 ppm is in agreement with $\delta_{1/2}$ values for the other β-diketones (these vary from 258 to 283 ppm) (Table II, column 7).[16a]

All the other β-diketones studied are asymmetrically substituted. As a representative compound, we consider first benzoylacetone (II). The spectrum of this compound when totally labeled with ^{17}O (IIa) is shown in the upper trace of Figure 1. No lines due to a keto form are observed, and the two peaks at 233 and 291 ppm correspond to the "average" chemical shifts of α and β oxygen atoms in the enol forms A and B, which are evidently in nonequal concentrations. The peak at 233 ppm corresponds to the oxygen which is predominant in the COH from and the peak at 291 ppm to the oxygen atom that is predominantly in the C=O form. On the basis of this spectrum it is not possible to assign the two peaks to the specific oxygens α or β. To solve this problem we have synthesized benzoylacetone specifically labeled at oxygen α, *i.e.*, the one adjacent to the phenyl ring. The ^{17}O spectrum of this compound (IIb) consists of a single line centered at 234 ppm (lower trace of Figure 1). Thus the α oxygen is predominantly in the hydroxylic form and equilibrium 1 tends to the right. The fractional concentration of the two forms and the equilibrium constant may now be calculated easily using eq 6 and 7.

(16a) Note Added in Proof. From the line width of this peak (Table II) it is possible to set a lower limit to the exchange rate between the two (symmetrical) enol forms; using the equation for "fast exchange" (J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, Chapter 10), a chemical shift of $460 \times 8.13 \times 2\pi = 2.35 \times 10^4$ radians sec^{-1}, and an upper limit to the "excess broadening" of $115 \times \pi = 360$ sec^{-1}, the lower limit to the exchange rate turns out to be $\sim 2 \times 10^5$ sec^{-1}. Since, however, the observed width of this signal is of the same order as other ^{17}O lines,[9] the excess width used must have been highly overestimated and consequently the lower limit to the exchange rate may confidently be increased by at least one order of magnitude and quite possibly much more. The same considerations apply to the other β-diketones.

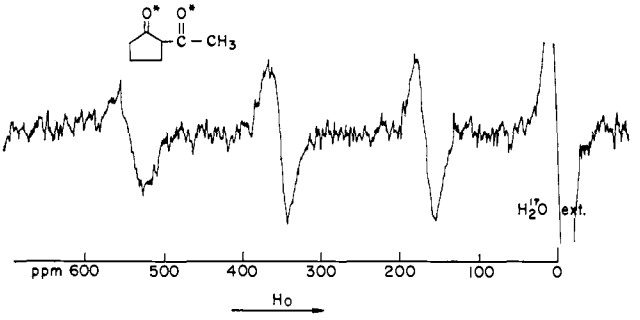


Figure 2. The ^{17}O spectrum of acetylcyclopentanone (VIII) with both oxygens labeled with ^{17}O.

In a similar manner, the dominant enol forms and equilibrium constants for acetylcyclohexanone (VI), benzoylcyclohexanone (VII), and acetylcyclopentanone (VIII) were established. The spectrum of VIII "totally labeled" with ^{17}O is shown in Figure 2.

It is generally accepted that the dominant form of 3-formylcamphor (III) is the 3-hydroxymethylene tautomer. Thus the lines at 430 and 88 ppm observed in the spectrum of this compound may be identified with oxygens α and β, respectively (see Table II), of its enol form. In order to prove this, we have tried to label one of the two oxygen atoms by synthesis, but unfortunately did not succeed. An alternative method of specifically labeling one of the two oxygens was discovered when the spectra of III after exchange in neutral and acidic solution were compared. In the former spectrum two peaks were observed at 88 and 585 ppm and in the latter four peaks at 88, 430, 514, and 587 ppm. It has been concluded that in neutral solution only one oxygen exchanges, and the low-field chemical shift at 585 indicates it to be the aldehydic one. It is known that the aldehydic oxygen exchanges very rapidly[13] while the camphor oxygen is very slow to react in neutral solution. It follows that the peak at 88 ppm corresponds to the "averaged" resonance of oxygen β in the enol forms.

Using eq 6 and 7 and the value $\Delta = 460$ ppm, the concentrations of the enolic forms A and B of formylcamphor (III) were calculated (Table II). However, this value of Δ may be unsuitable for the latter compound, since the ^{17}O resonance for camphor oxygen is at an exceptionally high field, and that for an aldehyde oxygen has a rather low-field value when compared with other carbonyl oxygens. A better estimate of δ^{CO} for the α oxygen is 454 ppm (its value in camphor less 60 ppm for hydrogen bonding), and for the oxygen β is 530 ppm (the value of acetaldehyde less 60 ppm). Substituting the above values and $\delta^{COH} = 35$ ppm in eq 3 and 4, one obtains [B] = 0.06 and 0.13, respectively. Thus the concentration of B in the equilibrium mixture may be 0.10 ± 0.05. This result justifies the basic assumption adopted by Garbisch[8] in his evaluation of the relative concentration of the enolic forms of β-aldehydo ketones.

Acetylcamphor (IV) also gave different ^{17}O spectra after exchange in neutral or in acidic solutions. The assignment of the peaks was done in an analogous manner to formylcamphor (III), and the fractional concentrations of the enolic forms A and B were calculated from eq 6. The error in this estimate may also be con-

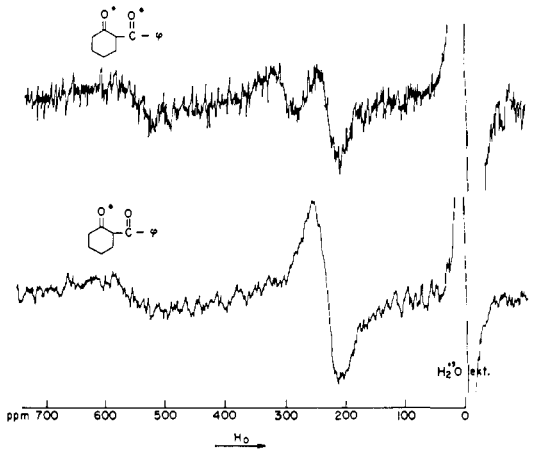


Figure 3. ^{17}O spectra of benzoylcyclohexanone (VII): upper trace, both oxygen atoms labeled (from an enrichment in an acidic solution); lower trace, only the α oxygen is labeled (enrichment in neutral solution).

siderable, and when one uses eq 3, substituting δ^{CO} = 454 ppm, one arrives at [B] = 0.12 instead of 0.17 given in Table II.

The ^{17}O spectrum of formylcyclohexanone (V) showed only two peaks assigned to the oxygens of the enol forms. No specific labeling of this compound was carried out, since the dominant enol form had already been determined.[8] The results for the fractional concentrations of A and B are close to but not identical with those obtained from pmr spectra by Garbisch.[8]

Different ^{17}O spectra were obtained when benzoylcyclohexanone (VII) was exchanged in neutral (VIIc) or acidic (VIIa) solutions (*cf.* Figure 3). The spectrum of the enol form obtained by exchange in a neutral solution was the same as that obtained by specifically labeling oxygen α (VIIb). Thus in neutral solutions oxygen β, *i.e.*, that adjacent to the phenyl ring, did not exchange, as was also observed in neutral solutions of acetophenone.

^{17}O-labeled benzoylcyclopentanone (IX) was prepared by exchange in acid solution only, and all expected lines were observed. The identification of the lines was based on the results of acetylcyclopentanone for, as shown below, substitution of the methyl by a phenyl group has only a small effect on the equilibrium position.

^{17}O–^{1}H Spin–Spin Coupling. The ^{17}O resonance of a hydroxyl group is expected to be split into two components due to spin–spin coupling with the proton. In the enol form, fast intramolecular proton transfer between the two oxygens occurs and, therefore, the expected splitting of the oxygen in the fast exchange limit, J', is given by

$$J' = [N]J \qquad (10)$$

where [N] is the fraction of time that this oxygen is hydroxylic and J is the oxygen–proton, spin–spin coupling in the hydroxyl group. A similar equation was used by Garbisch[8] to discuss the observed splitting of the aldehydic proton in the β-aldehydo ketones. It should be noted that eq 10 holds only if the proton exchange is intramolecular and no spin exchange of the proton occurs.

In the case of ^{17}O, the greater line width of the resonance prevented, in most cases, the detection of ^{17}O–^{1}H spin–spin splitting. In one case, however, *i.e.*, neat acetylcyclohexanone (VI), a structure due to a spin–spin coupling with the hydroxyl proton could be observed, in the resonance of the α oxygen, when low sweep modulation amplitude was used (Figure 4). There is a high degree of overlap between the two components of the doublet, and the values for J' and the line width were derived by a graphical procedure outlined by Christ and Diehl.[12] The analysis gave J' = 54 cps and $1/\pi T_2$ = 77 cps. Using eq 10 and identifying [N] with [B] one obtains J = 76 cps, which is of the same order of magnitude as that observed previously in water and in methanol.[17]

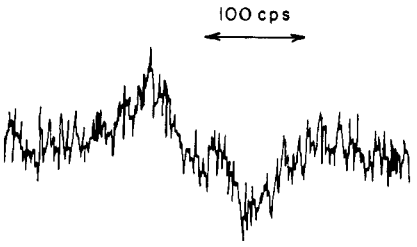


Figure 4. ^{17}O spectrum of oxygen α of the enol form of acetylcyclohexanone (VI). The structure is due to ^{17}O-^{1}H spin–spin coupling.

Discussion

The K values for equilibrium 1 of the β-diketones studied in the present work and in ref 8 fall all in the relatively narrow range of 0.1–10. Thus, change in substitution of the β-diketones does not have a marked effect on the relative stabilities of either one or the other of the tautomers A and B. However, the results indicate certain systematic trends in the effect of substituents on the K of equilibrium 1. It is possible to distinguish three major factors. These are listed and discussed below in the order of their relative importance.

(i) An endocyclic double bond predominates in the enol tautomers of cyclohexanone derivatives while the cyclopentanone derivatives favor an exocyclic double bond. This tendency is closely related to and is in accordance with the generalization of Brown, Brewster, and Shechter,[18] *i.e.*, that exocyclic double bonds stabilize a five-membered ring and destabilize a six-membered ring. This generalization could be explained qualitatively in terms of the I-strain effect. A quantitative theory was recently put forth by Garbisch.[19]

(ii) The phenyl group as compared to a methyl group or a hydrogen atom tends to stabilize the enol tautomer $C_6H_5C(OH)=C(CO)$ (form B of equilibrium 1a) relative to $C_6H_5(CO)C=C(OH)$ (form A). This tendency is in the direction predicted by simple MO calculations. Forsen,[20] assuming that the difference in stabilities of forms A and B is due only to π electron delocalization energies, has calculated the relative stabilities of these forms by the Hückel MO method and indeed found that form B is more stable than A. The quantitative ap-

(17) (a) J. Reuben, A. Tzalmona, and D. Samuel, *Proc. Chem. Soc.*, 353 (1962); (b) S. Meboom, *J. Chem. Phys.*, 34, 375 (1961); (c) J. Reuben and D. Samuel, *Israel J. Chem.*, 1, 279 (1963).

(18) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Am. Chem. Soc.*, 76, 467 (1954).

(19) E. W. Garbisch, *J. Am. Chem. Soc.*, 87, 505 (1965). This paper came to our attention only after submitting the present manuscript.

(20) S. Forsen, *Arkiv Kemi*, 20, 1 (1963).

plication of this theory seems, however, to be premature; the calculated relative stability is about 2 kcal/mole as compared to about 0.2 kcal/mole found experimentally. It seems that other effects, such as modification of the σ electrons and H-bond energies, should also be considered.[20]

(iii) Finally, there seems to be a small but systematic tendency of a methyl group, relative to a hydrogen atom, to stabilize that enol form in which the methyl is adjacent to a carbonyl group.

Acknowledgment. We wish to thank J. Reuben for help in recording some of the ^{17}O nmr spectra.

Intramolecular Catalysis. X.[1] Facilitation of Acylation of Tertiary Hydroxyl Groups in Alicyclic 1,3-Diaxial Glycols[2,3]

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Abstract: Evidence is presented for a facilitation of acylation of tertiary hydroxyl groups in alicyclic 1,3-diaxial diols, and for the argument that, in suitable systems, the acylation may be subject also to intramolecular catalysis by a tertiary nitrogen atom. Treatment of the perhydrobenzo[*b*]quinolizine tetrol **1** with acetic anhydride in pyridine at room temperature yielded the triacetate **3** in practically quantitative yield, and similar acetylation of the triol **36** gave the diacetate **37**. Potentiometric, spectroscopic, and chemical evidence for the configuration of **1** and its derivatives is presented. Treatment of **1** with phosgene yielded the 9,10a-carbonate **19**. An alternate route to **19** proceeded *via* conversion of **1** to the ethyl tetrol carbonate **7** and conversion of **7** to **19** by base treatment. Acetylation of **19** yielded the diacetate **20**. Acylation of **19** with ethyl chloroformate gave the 9,10a-carbonate 8-ethyl carbonate **23**. Acetylation of **7** yielded the 6a,8,9-triacetoxy-10a-ethyl carbonate **8**. Acetylation of **1** with acetic anhydride–perchloric acid, followed immediately by termination of the reaction with excess methanol, gave the 8,9,10a-triacetate **5**; reaction for a longer period gave the tetraacetate **9**. Methanolyis of **3** at room temperature smoothly yielded the diacetate **4** and similar solvolysis of **5** gave **6**. Oxalic acid hydrolysis of enol ether **30** gave the unsaturated ketone **33**, and hydrogenation of **33** followed by hydroxylation with performic acid gave triol **36**. Mineral acid hydrolysis of **30** gave **31**. Lithium and ammonia reduction of **31**, followed by chromic acid oxidation, gave **41**. Reduction with lithium aluminum hydride gave the β-equatorial alcohol **34**, whereas catalytic hydrogenation with ruthenium gave a mixture of **34** and **39**. Treatment of triol **36** with 1 molar equiv of acetic anhydride yielded the 6a-monoacetate **38**, and similar acylation of **19** yielded **21**. Arguments are advanced in support of the view that the facile acylation of the C-6a tertiary hydroxyl group is a bifunctionally catalyzed direct acylation. The buffer ratio–rate profile indicated *intermolecular* basic catalysis of the pseudo-first-order solvolysis of **3**, **5**, and **22** over the pH′ range studied. A similar study of the solvolysis of the triol monoacetate **38** indicated *intramolecular* basic catalysis, and rate enhancement approximately 10,000-fold over that expected. Possible mechanisms for the facile acylations and deacylations among perhydrobenzo[*b*]quinolizine polyol derivatives are discussed.

Facilitation of the alkaline solvolysis of an alicyclic axial acetate by a hydroxyl group bearing a 1,3-diaxial juxtaposition to the acetate is a well-established fact.[5–10] Furthermore, in suitably constituted molecules, the solvolysis may be subject also to intramolecular general base catalysis by a tertiary nitrogen atom.[1,11] We report herewith our observation of facilitation of acylation of tertiary hydroxyl groups in alicyclic 1,3-diaxial diols and evidence for the argument that, in suitable systems, the acylation may be subject also to intramolecular catalysis by a tertiary nitrogen atom.

Treatment of 1,3,4,6,6a,7,8,9,10,10a,11,11a-dodecahydro-2*H*-benzo[*b*]quinolizine-6a,8,9,10a-tetrol (**1**)[12,13] with acetic anhydride in pyridine at room temperature yielded the 6a,8,9-triacetate **3**, in practically quantitative yield. Acetyl determination indicated that **3** was a triacetate, and the nmr spectrum shows three acetate methyl signals, at τ 7.91, 7.97, and 7.99. The infrared spectrum in Nujol shows carbonyl absorption nicely resolved into three bands at 5.74, 5.80, and 5.90 μ.

(1) Part IX: S. M. Kupchan, S. P. Eriksen, and Y.-T. S. Liang, *J. Am. Chem. Soc.*, **88**, 347 (1966).

(2) This work was presented, in part, at the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, Abstracts, p 101K.

(3) This investigation was supported by Public Health Service Research Grant HE-02275, from the National Heart Institute.

(4) National Institutes of Health Predoctoral Fellow, 1963-1966.

(5) S. M. Kupchan and W. S. Johnson, *J. Am. Chem. Soc.*, **78**, 3864 (1956).

(6) H. B. Henbest and B. J. Lovell, *Chem. Ind.* (London), 278 (1956); *J. Chem. Soc.*, 1965 (1957).

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(12) S. M. Kupchan, G. R. Flouret, and C. A. Matuszak, *J. Org. Chem.*, 31, 1707 (1966).

(13) All asymmetric synthetic products described are racemic mixtures. Only one optical antipode for each is drawn for convenience of representation and discussion. In the representation of the quinolizidine derivatives the electron pair on nitrogen is understood to project downward, and a heavy-line bond to the 11a hydrogen indicates the *trans*-quinolizidine configuration.