tion studies.[3] Ribonuclease dissolved in 6 *M* GuHCl has been shown to possess the titration behavior expected of a randomly coiled polypeptide chain, without important noncovalent interactions. Twenty-nine of the 32 titratable groups are titrated exactly in accord with the limiting ideal curve, based on expected p*K* values and an absence of any interactions between titratable groups. Some phenolic groups have a somewhat higher p*K* than the others, but the difference is no greater than 0.4 p*K* unit, and there is no difficulty in visualizing weak interactions, which could remain in a random structure, to account for it. One anomalous group was titrated per molecule, but was shown to represent a chemical reaction which is probably common to most unfolded proteins which retain intact disulfide bonds.

A Nuclear Magnetic Resonance Study of the Reversible Hydration of Aliphatic Aldehydes and Ketones. I. Oxygen-17 and Proton Spectra and Equilibrium Constants

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Abstract: Oxygen-17 nuclear magnetic resonance spectra of aqueous solutions of a number of aliphatic carbonyl compounds enriched in ^{17}O are reported. It is shown that the resonances of the unhydrated carbonyl species and of the hydrated *gem*-diol species fall in two different regions. The carbonyl oxygen resonance falls in the range -520 to -560 ppm (relative to $H_2{}^{17}O$), and that of the *gem*-diol falls close to the water line, often being concealed by it. Proton magnetic resonance spectra have also been studied and used to determine equilibrium constants, K_d, for the hydration–dehydration reaction of the carbonyl group. It is shown that a good correlation between K_d values, which span a range of seven orders of magnitude, and $\Sigma\sigma^*$ is obtained provided account is taken of the number of aldehydic protons in the molecule. The following free-energy relationship between K_d and $\Sigma\sigma^*$ is proposed, $-\log K_d = \rho^*\Sigma\sigma^* + B\Delta + C$, where ρ^*, B, and C are constants, and Δ is the number of aldehydic hydrogens in the molecule. A best-fit analysis gave $\rho^* = 1.70 \pm 0.07$, $B = 2.03 \pm 0.10$, and $C = -2.81 \pm 0.13$. These results are discussed in terms of adjacent bond interaction.

The reversible hydration–dehydration (reaction 1) of carbonyl compounds in aqueous solutions has, because of its great chemical importance, been the subject of a great number of scientific publications.[1]

$$R_1R_2C(OH)_2 \rightleftharpoons R_1R_2C{=}O + H_2O \tag{1}$$

This reaction represents one of the simplest addition reactions to the carbonyl group and is of great importance in understanding many organic reactions. Previous studies have shown that the extent of hydration varies over a wide range and depends strongly on the nature of the substituents directly bonded to the carbonyl group. Equilibrium constants[1]

$$K_d = [R_1R_2C{=}O]/[R_1R_2C(OH)_2] \tag{2}$$

ranging from 10^{-4} to 10^3 for simple aliphatic carbonyl compounds have been reported. The rates of the hydration–dehydration reaction are usually too fast to allow the determination of K_d by isolating one of the compounds, and it is therefore necessary to apply methods which do not perturb the equilibrium. Moreover, in many cases the equilibrium concentration of one of the components may be so small as to be detectable only by very sensitive spectroscopic methods. In ref 1, the various methods of studying reaction 1, the results obtained, and their significance are thoroughly reviewed. The most common methods to determine K_d are ultraviolet spectroscopy and proton magnetic resonance (pmr), although in a few cases other methods have been employed.

The main features of the pmr spectra of aqueous solutions containing a mixture of free and hydrated carbonyl compounds have been described by several authors.[2-5] When the equilibrium constant, K_d, is between $\sim 10^{-2}$ to $\sim 10^{+2}$, it is usually possible to observe two sets of lines corresponding to the hydrated and unhydrated species. Regularities in the chemical shifts of the aldehydic and α-protons of these two species have been observed. It is found that the resonance due to the protons bonded to the *gem*-diol carbon atom in the hydrated species is shifted 4.6 to 5.0 ppm upfield relative to the aldehydic hydrogen in the unhydrated form. Similarly, α-protons in both hydrated aldehydes and ketones are found to be shifted +0.7 to +0.9 ppm relative to the corresponding unhydrated compounds. β-Protons are also found to shift upon

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(1) For a recent comprehensive review which will serve as a key to earlier literature, see R. P. Bell, *Advan. Phys. Org. Chem.*, **4**, 1 (1966).

(2) (a) E. Lombardi and P. G. Sogo, *J. Chem. Phys.*, **32**, 635 (1960); (b) Y. Fujiwara and S. Fujiwara, *Bull. Chem. Soc. Japan*, **36**, 574 (1963); (c) M.-L. Ahrens and H. Strehlow, *Discussions Faraday Soc.*, 112 (1965); (d) P. G. Evans, G. R. Miller, and M. M. Kreevoy, *J. Phys. Chem.*, **69**, 4325 (1965).

(3) (a) J. Hine, J. G. Houston, and J. H. Jensen, *J. Org. Chem.*, 30, 1184 (1965); (b) J. Hine and J. G. Houston, *ibid.*, 30, 1328 (1965).

(4) (a) M. Becker, *Ber. Bunsenges. Physik. Chem.*, **68**, 663 (1964); (b) V. Gold, G. Socrates, and M. R. Crampton, *J. Chem. Soc.*, 5888 (1964).

(5) (a) W. Knoche, H. Wendt, M.-L. Ahrens, and H. Strehlow, *Collection Czech. Chem. Commun.*, 31, 388 (1966); (b) K. Moedritzer and J. R. Van Wazer, *J. Phys. Chem.*, 70, 2025 (1966).

hydration but to a lesser extent (+0.14 to +0.20 ppm). These differences in the chemical shift of the two kinds of species seem to be quite general and therefore provide a means of identifying hydrated and nonhydrated species in equilibrium. The equilibrium constant, K_d, can then be determined by intensity measurements.[2-5] As a part of the present work we have supplemented the available data by determining some equilibrium constants not reported hitherto and remeasured others by the pmr technique.

The main part of the experimental results reported here is concerned with the ^{17}O nuclear magnetic resonance (omr) spectra of aqueous solutions of aliphatic carbonyl compounds. Such spectra have not been published previously, and it is shown that the ^{17}O resonance of the hydrated molecules is significantly removed from that of the carbonyl compounds and may therefore also provide a method of studying reaction 1. The ^{17}O spectra of a large number of liquid organic compounds have been studied by Christ, Diehl, Schneider, and Dahn.[6] Their data provide the basis for the systematization of the ^{17}O chemical shift. They showed that the ^{17}O resonances of neat aldehydes and ketones fall in the range −530 to −595 ppm relative to $H_2{}^{17}O$ as an external standard, while the ^{17}O resonances of the hydroxyl group of alcohols fall near the water line (+37 to −70 ppm). In aqueous solutions of carbonyl compounds, known to be hydrated, an ^{17}O resonance due to the *gem*-diol grouping should appear and is expected to fall in the range of the ^{17}O shift characteristic of the hydroxylic oxygen. Indeed we were able to detect signals in this range due to the hydrated species of a number of carbonyl compounds. Admittedly the quantitative determination of K_d from the intensity of the ^{17}O resonances is less accurate than either the pmr or ultraviolet methods. This is due to the fact that the ^{17}O spectra, in the present work, were recorded as the derivative of the absorption mode, and intensity measurements require double integrations which are more tedious and less accurate than the other methods. Nevertheless, omr spectroscopy can sometimes be used for identification of components in reaction mixtures. For this reason we have undertaken the survey of the ^{17}O spectroscopy of these compounds.

In the last section we shall try to correlate the available equilibrium constants by a free-energy relationship. Within the classes of ketones and aldehydes a good correlation with $\Sigma\sigma^*$ values is obtained. An extra stabilization of the carbonyl group is attributed to alkyl substitution. This is interpreted in terms of the adjacent bond interaction theory.

Experimental Section

All materials used were obtained commercially, most of them of pure grade, and were used without treatment. Some were of practical grade and were distilled prior to use. The purities of biacetyl and of monochloroacetone were also checked by vpc and found to be above 99% pure. An elementary analysis of the monochloroacetone used was also done. *Anal.* Calcd: C, 38.94; H, 5.45; Cl, 38.32. Found: C, 38.77; H, 5.30; Cl, 38.63.

The solutions for omr spectra were prepared by dissolving known amounts of the carbonyl compound in $H_2{}^{17}O$ to make up about 2 ml of 1 to 3 *M* solutions. For pmr, isotopically normal water was used and the concentration was usually 1 *M*. The $H_2{}^{17}O$ was obtained from the Institute's enrichment plant and contained ~4 atom % of ^{17}O. For biacetyl and acetaldehyde, water containing 8 atom % ^{17}O was used. Sufficient time was allowed for the hydration equilibrium and oxygen exchange to be established. This did not amount to more than a few minutes for all the compounds studied except acetone, for which oxygen exchange in neutral aqueous solution has a half-life of about 10 hr.

The omr spectra were recorded on a V-4200 Varian broad-line nuclear magnetic resonance spectrometer, operating at 8.13 Mc/sec, the derivative of the absorption line being recorded. The chemical shift was measured relative to the $H_2{}^{17}O$ solvent line and is reported in the text in units of ppm. Calibration of the field sweep was done by the side-band technique. For the sake of completeness we have also measured the line widths. In these measurements care was taken to minimize saturation, and the reported line widths (in cps at half-maximum height of the absorption mode, $1/\pi T_2$) are corrected for overmodulation and saturation. The probe temperature for the ^{17}O measurements was 27° ± 1.

The pmr spectra were recorded on a Varian A-60 spectrometer, the probe temperature being 25 ± 2°.

Results

The ^{17}O chemical shifts (and line widths) of the peaks observed in aqueous solutions of the carbonyl compounds studied are summarized in the left part of Table I. The proton chemical shifts of the aldehydic and α- (and in some cases β-) proton peaks are given in the right part of the table. The shifts are in ppm relative to the solvent water peak. The proton chemical shifts are concentration dependent. Most of those given in the table are for 1 *M* solutions. For that reason the data for the proton shifts can serve only as a guide to the general pattern of the spectra. Spin–spin splittings are, of course, also observed, but these are not included. As discussed below, the ^{17}O shifts are also concentration dependent.

Most of the results of the table are self-evident, but, for the sake of clarity and in order to point out some special features, we shall describe below the spectra of some of the compounds in detail.

The pmr of aqueous acetaldehyde (II) has been described and studied extensively[2] and will therefore not be described here. The omr spectrum of a 5.5 *M* solution of CH_3CHO in water enriched to 8 atom % ^{17}O is shown in Figure 1. In addition to the strong solvent water resonance at the high-field part of the spectrum, two other signals at −71 and −558 ppm ascribed respectively to the hydrated and unhydrated molecules are observed. From the known value[1] of K_d, for acetaldehyde (0.7), the relative integrated intensities of the carbonyl and *gem*-diol resonances are expected to be ~1:3. The smaller height of the hydrated molecule signal is due to its much greater width. Since the signal heights of the derivatives of absorption peaks are inversely proportional to the square of their heights, this peak appears much smaller than that due to the unhydrated molecules. The ^{17}O spectrum of propionaldehyde (III) can be understood in the same manner. Formaldehyde (I), which is known to be nearly completely hydrated in aqueous solution,[1] indeed shows only a single ^{17}O resonance at −51 ppm due to the *gem*-diol grouping. On the other hand, acetone (IX), which exists over 99% in the unhydrated form, shows only a line due to the carbonyl oxygen at −523 ppm. However, in the pmr spectrum of a 20% acetone–water mixture, Hine[7] was able to detect a very weak signal due to hydrated acetone and to estimate its concentration to be 0.2% of total acetone.

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[6] H. A. Christ, P. Diehl, H. R. Schneider, and H. Dahn, *Helv. Chim. Acta*, 44, 865 (1961).

[7] J. Hine, quoted by Bell in ref 1.

Table I. ^{17}O and ^{1}H Nuclear Magnetic Resonance Spectra[a] and K_d Values for Aqueous Solutions of Some Carbonyl Compounds

		Omr chemical shifts, ppm		Pmr shifts of hydrated species, ppm		Pmr shifts of unhydrated species, ppm		
No.	Compound	*gem*-Diol oxygens	Carbonyl oxygen	Aldehydic proton	α- and β-protons	Aldehydic proton	α- and β-protons	K_d[c]
I	CH_2O	−51 (140)[b]	*e*	~0.0[h]	...	*e*	...	5.0 × 10⁻⁴
II	CH_3CHO	−67 (190)	−550 (45)	−0.48	α +3.45	−4.90	α +2.57	0.7
III	CH_3CH_2CHO	−65 (245)	−538 (70)	−0.17	α +3.26 β +3.92	−4.91	α +2.23 β +3.78	1.4
IV	$CH_3(CH_2)_2CHO$							2.1
V	$(CH_3)_2CHCHO$[d]			−0.19	α +3.40 β +3.89	−4.89	α +2.40 β +3.70	2.3
VI	$(CH_3)_3CCHO$			*e*	β +3.92	−4.72	β +3.75	4.1
VII	CH_2ClCHO			−0.43	α +1.21	*e*	α +0.40	2.7 × 10⁻²
VIII	CCl_3CHO	−56 (360)	*e*	−0.53	...	*e*	...	3.6 × 10⁻⁵
IX	CH_3COCH_3	*e*	−523 (90)	...	α +3.40[f]	...	α +2.60	5 × 10²
X	$CH_2ClCOCH_3$	*e*	−528 (235)	...	α-CH_2Cl +1.17 α-CH_3 +3.30	...	α-CH_2Cl +0.29 α-CH_3 +2.51	9.1
XI	$(CH_2Cl)_2CO$	−67 (525)	−521 (440)	...	α +1.01	...	α +0.24	0.10
XII	$Cl_2CHCOCH_3$							0.35
XIII	$CH_3COCOCH_3$	−59 (595)	−530[g]	...	α +3.30	...	α +2.48[g]	0.50
XIV	$CH_3COCOOCH_3$			...	α +3.24 OCH_3 +0.98	...	α +2.32 OCH_3 +0.78	0.32
XV	$CH_3COCOOH$	−68 (~480)	−555 (780) COOH −245 (400)	...	α +3.40	...	α +2.51	0.42
XVI	$CH_3COCOONa$	*e*	−534 (410)	...	α +3.28	...	α +2.37	18.5

[a] Solutions of 1–3 *M* were used for the omr spectra. The shifts are given in ppm relative to solvent $H_2{}^{17}O$. Estimated reproducibility of ^{17}O shifts is ±4 ppm. Pmr spectra of some of the compounds have been reported previously.[2a,b,4a] However, these were measured at greatly varying concentrations and reported relative to different references. The proton shifts reported here are for 1 *M* solutions (except for compounds V and VI which were 0.15 *M*) and given in ppm relative to solvent water as an internal reference. [b] The numbers in brackets are the full width at half maximum intensity of the absorption mode, $1/\pi T_2$, of the corresponding line; estimated accuracy, ±10%. [c] Equilibrium constants for the dehydration of the carbonyl hydrates. For sources see discussion in Comments on K_d Values section. [d] The proton chemical shift of the β-protons is from the present work for a solution of 0.15 *M*. We were unable to detect the α-protons and aldehydic protons of the hydrated species. The values given for these shifts are from ref 2a, corrected for water as an internal standard.[2b] [e] Not detected. [f] Taken from ref 7. [g] This peak is a superposition of two lines, and therefore the shift represents the average of the two. The line width for the ^{17}O resonance was not determined. [h] For a full discussion of the pmr spectrum of formaldehyde see ref 5b.

The omr shifts of the carbonyl oxygen and to a lesser extent those of the *gem*-diol grouping were found to shift to high field upon dilution. For example, the carbonyl peak of acetaldehyde shifts from −574 ppm in a 33 mole % solution to −550 ppm in a 3.6 mole % solution. In the same interval the *gem*-diol peak shifts from −75 to −67 ppm. The high-field shift of the carbonyl group upon dilution in water has already been observed for acetone by Christ and Diehl[8] and interpreted in terms of hydrogen bonding.

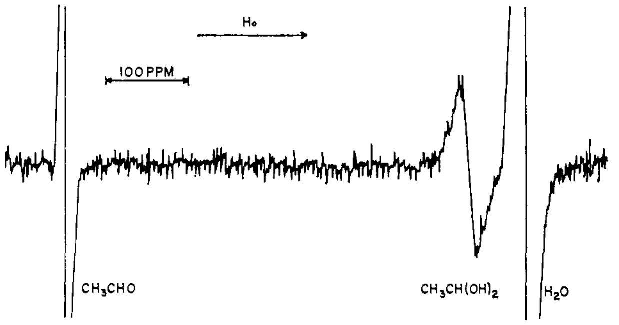

Figure 1. Omr spectrum of a 5.5 *M* solution of CH_3CHO (II) in water enriched to 8 atom % ^{17}O.

The pmr spectrum of monochloroacetone (X) is shown in Figure 2. In addition to the strong solvent peak two sets of two lines are observed. The two more intense lines are ascribed to the unhydrated compound and the two weak lines to the hydrated molecules. At high resolution the CH_3 line of the unhydrated compound appears as a triplet with a splitting of 0.5 cps, and the CH_2Cl lines appear as a quartet with the same splitting. This splitting is due to long-range spin–spin coupling enhanced by the intervening carbonyl group and has been observed previously in neat monochloro-

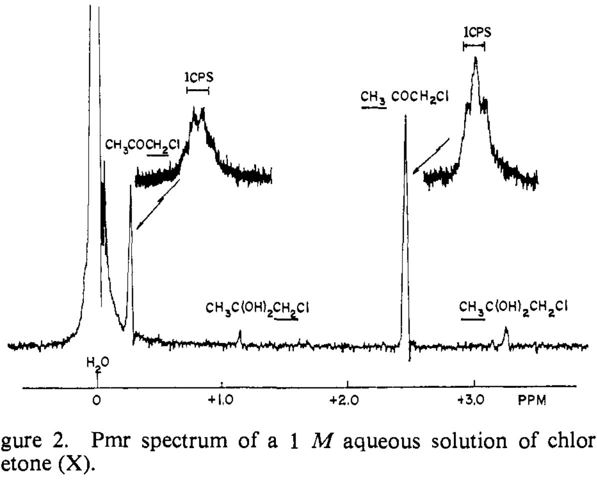

Figure 2. Pmr spectrum of a 1 *M* aqueous solution of chloroacetone (X).

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(8) H. A. Christ and P. Diehl, *Helv. Phys. Acta*, 36, 170 (1963).

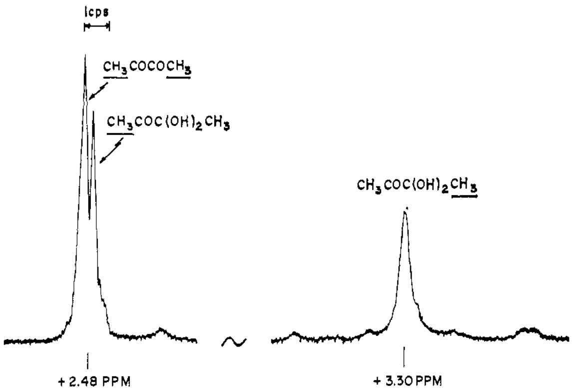

Figure 3. Pmr spectrum of a 1 M aqueous solution of biacetyl (XIII). The numbers below the peaks indicate the chemical shifts in ppm from solvent water which is not shown.

acetone.[9] From intensity measurements the equilibrium constant, K_d, was found to be 9.1 ± 0.9.

In the omr spectrum of a solution of monochloroacetone only a carbonyl oxygen signal was detected in addition to that of solvent water. The line due to the *gem*-diol oxygens of monochloroacetone hydrate could not be seen, probably because of its low intensity and proximity to the strong water line.

Chloral (VIII) is known to be practically completely hydrated in aqueous solutions.[1] Therefore in the omr spectrum of an aqueous chloral solution no peak was expected nor observed in the range corresponding to the carbonyl chemical shifts. Surprisingly, neither was there a line detected in the range corresponding to the hydroxyl group. Suspecting that this resonance had been covered by the much more intense water line, we employed the idea of Jackson, *et al.*,[10] of shifting the solvent water resonance by adding paramagnetic ions. When paramagnetic ions having a labile hydration shell are added to water, the water resonance is shifted due to the fast exchange between the free solvent molecules and the molecules in the hydration shell whose resonance is greatly shifted relative to that of free molecules. Following Alei and Jackson,[11] we have chosen $Dy(ClO_4)_3$ as the paramagnetic salt to shift the ^{17}O resonance. This salt will cause a large shift without appreciable broadening of the water peak.[12] Moreover, Dy^{3+} shifts the ^{17}O resonance of water toward high field, while the resonance of the hydrated chloral is expected, on the basis of other observed hydrate signals, to be on the low-field side of the water peak. Indeed, upon addition of $Dy(ClO_4)_3$ (to make up a 0.3 M solution in Dy^{3+}) to the chloral solution, the solvent water line was displaced upfield, and the hidden resonance due to the chloral hydrate appeared. The shift of this line was measured relative to an external $H_2{}^{17}O$ sample; both solution and reference were contained in spherical Pyrex bulbs.[12]

The pmr spectrum of an aqueous solution of *s*-dichloroacetone (XI) exhibits, in addition to the solvent peak, a weak and a strong line due respectively to the unhydrated and hydrated species (*cf.* Table I). Intensity measurements are quite inaccurate because the weak signal due to the nonhydrated species falls on the side of the strong water signal. A rough estimate in a 1 M solution gave K_d = 0.16 in fair agreement with the ultraviolet result (0.10).[13]

In the omr spectrum of *s*-dichloroacetone, a weak signal at −521 ppm due to the carbonyl oxygen and an unresolved line due to the hydrated molecules near the strong water line could be detected. Upon addition of Dy^{3+} the water line shifted and a well-resolved line due to the *gem*-diol oxygens was observed.

The hydration of biacetyl (XIII) has been studied by Bell and McDougall[13] using ultraviolet spectroscopy. However, as indicated by the authors, the ultraviolet spectrum of an aqueous solution of biacetyl is complicated and the results are uncertain. It should be noted that this compound could in principle form two kinds of hydrates: a monohydrate, $CH_3COC(OH)_2CH_3$ (M), and a dihydrate $CH_3C(OH)_2C(OH)_2CH_3$ (D). The ^1H and ^{17}O nmr indicate that the dominant form is M and show no evidence for the presence of form D. The pmr spectrum of an aqueous solution containing 1 M biacetyl under high resolution is shown in Figure 3 (the water line is absent from this figure). The two intimate lines at +2.48 ppm fall in the range characteristic of methyl protons adjacent to a carbonyl group, while the other line falls in the range of methyl protons adjacent to a hydrated carbonyl group. This spectrum can thus be interpreted as a superposition of the spectra of unhydrated and monohydrated biacetyl. One of the two lines at +2.48 ppm is ascribed to the methyl protons of the unhydrated diacetyl and the other to the methyl protons adjacent to the carbonyl group in the monohydrated form. The shift between these two lines is small as would be expected, since they occupy very similar magnetic environments. In addition, some weak lines can also be observed. These lines are not seen in the spectrum of neat biacetyl and their origin is not yet understood. We ascribe them tentatively to by-products formed by reaction with water.

The identification of the two lines at +2.48 ppm as shown in Figure 3 was based on intensity measurements as a function of temperature. Upon increasing the temperature, K_d is known[13] to increase. Indeed it was found that the line due to the hydrate at +3.30 ppm decreased in intensity upon raising the temperature. At the same time the high-field component of the intimate pair at +2.48 ppm also decreased and the low-field component of this pair increased in intensity, thus providing the identification of the lines as shown in the figure.

The equilibrium constant, K_d, was determined from the area under the methyl resonances and found to be 0.50. In the calculation, account was taken of the fact that the area under the peaks at +2.48 ppm corresponds to the two methyl groups of the unhydrated diacetyl plus one methyl group of the monohydrate, while the peak at +3.30 ppm corresponds to only one methyl group of the monohydrate.

The above interpretation of the proton resonance is borne out by omr. In Figure 4 is shown the ^{17}O resonance of a 3.7 M aqueous solution of biacetyl in

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(9) N. Van Meurs, *Spectrochim. Acta*, **19**, 1695 (1963).

(10) J. A. Jackson, J. F. Lemons, and H. Taube, *J. Chem. Phys.*, **32**, 553 (1960).

(11) M. Alei, Jr., and J. A. Jackson, *ibid.*, **41**, 3402 (1964).

(12) W. B. Lewis, J. A. Jackson, J. F. Lemons, and H. Taube, *ibid.*, **36**, 694 (1962).

(13) R. P. Bell and A. O. McDougall, *Trans. Faraday Soc.*, **56**, 1281 (1960).

water enriched to 8 atom % ^{17}O. In the upper trace the *gem*-diol oxygen resonance is partly covered by the solvent water line. The lower trace was recorded after the addtion of a small amount of $DyCl_3$, and the whole of the resonance due to the *gem*-diol group can now be observed. The carbonyl oxygen signal is seen to be a superposition of two lines. This is more clearly observed in the lower trace. One of the two peaks is ascribed to the carbonyl oxygen of the unhydrated biacetyl and the other to the carbonyl oxygen of the monohydrate. To check on this point the ^{17}O resonance of neat biacetyl enriched in ^{17}O (3 atom %) was studied and found to be a single structureless signal located at -566 ppm ($1/\pi T_2$ = 233 cps). The fact that a larger separation between the two carbonyl peaks is observed in the lower trace of Figure 4 may be ascribed to complexing with Dy^{3+}. If one of the two species complexes with Dy^{3+}, the carbonyl resonance of this species may be shifted relative to that of the other carbonyl group and thus yield a better resolved spectrum. The equilibrium constant, K_d, was also estimated from the ^{17}O resonance by double integration and found to be 0.48, in agreement with the pmr result.

The hydration of pyruvic acid and pyruvate anion (XV and XVI) has been studied previously by pmr.[4] Two peaks, separated by ~0.9 ppm, due to the methyl protons are observed corresponding to the hydrated and unhydrated forms. The pmr spectrum of methyl pyruvate (XIV), which was studied in the present work, shows two sets of two lines corresponding to the two kinds of methyl groups. It is interesting to note that (as shown in Table I) the carbomethoxy proton resonance is significantly shifted upon the hydration of the carbonyl group from which it is separated by four bonds.

The omr spectrum of an aqueous solution of pyruvic acid is described in Table I. In addition to the carbonyl and *gem*-diol grouping, there is a peak at -245 ppm which is within the range characteristic of the carboxyl group and is therefore ascribed to the carboxyl group of pyruvic acid. This peak is not observed immediately upon dissolving the compound in enriched water, but rather increases with time owing to slow oxygen exchange of the carboxyl group. The oxygen exchange of this group was complete within 2 hr at room temperature. The carbonyl oxygen resonance of pyruvate anion falls very close to that of pyruvic acid. No line due to the oxygens of the *gem*-diol group could be observed owing to its low concentration. Neither was there a peak due to the carboxylate oxygens. This is because the oxygen exchange of the carboxylate anion is very slow, its half-life in sodium pyruvate being longer than 24 hr at room temperature.

An interesting feature of the results of the omr spectra is the variation in the line widths. It is seen that within the groups of aldehydes and ketones the line widths of both the *gem*-diol and carbonyl resonances increase with increasing molecular size, the line widths of the ketones being greater than those of the aldehydes. ^{17}O nmr line widths in diamagnetic molecules are predominantly determined by quadrupole relaxation which results from the random modulation of the electric field gradient at the position of the oxygen nucleus *via* tumbling of the molecules. The line widths are proportional to the electric field gradient and the tumbling time of the molecules. Since the electric field gradient at the oxygen of the carbonyl group is not expected to change much between the various compounds, the variation in line width can be explained by the increase in tumbling time with increasing size of the molecules. Similarly Christ and Diehl[14] observed a linear dependence of the ^{17}O line widths on the calculated tumbling time of the molecules in a series of alcohols.

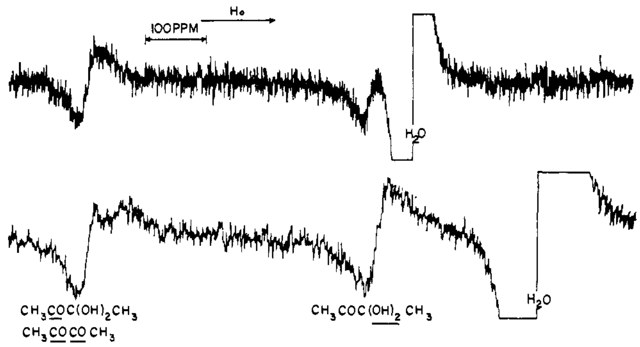

Figure 4. Upper trace: omr spectrum of a 3.7 *M* solution of biacetyl in water enriched to 8 atom % ^{17}O. Lower trace: the same spectrum, after addition of $DyCl_3$ to make up a 0.67 *M* solution of Dy^{3+}.

Comments on K_d Values

A considerable amount of data has now accumulated pertaining to the reversible hydration of the carbonyl group (reaction 1). The equilibrium constants, K_d, of the compounds studied in the present work are listed in the last column of Table I. A short discussion of these values seems to be in order.

The various studies of the hydration equilibria of formaldehyde (I) and acetaldehyde (II) have been critically reviewed by Bell.[1] The values given in the table are those recommended by him. The data for propionaldehyde (III), butyraldehyde (IV), isobutyraldehyde (V), and chloral (VIII) were taken from Gruen and McTigue[15] and those for *as*- and *s*-dichloroacetone (XII and XI) from Bell and McDougall,[13] both groups using ultraviolet spectroscopy. The values for pyruvic acid (XV) and pyruvate anion (XVI) were taken from Becker,[4a] who used pmr spectroscopy, and those for biacetyl (XIII) and methyl pyruvate (XIV) are from the present work.

The K_d value for pivalaldehyde (VI) is also from the present work and was determined from the relative intensities of the proton resonances of the methyl groups of the hydrated and unhydrated forms.

The equilibrium constant for chloroacetone (X) has been determined by Bell and McDougall[13] using ultraviolet spectroscopy and was found to be 1.60 at 25°. This value is more than a factor of 5 smaller than that determined from pmr as described above. This discrepancy is probably due to the fact that the method of determining K_d by ultraviolet spectroscopy depends on the constancy of ϵ_{max} in different solvents. It appears that ϵ_{max} is in many cases solvent dependent,[15a]

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[14] H. A. Christ and P. Diehl, *11th Colloq. Ampere, Eindhoven*, 224 (1962).

[15] L. C. Gruen and P. T. McTigue, *J. Chem. Soc.*, 5217 (1963).

[15a] NOTE ADDED IN PROOF. P. Greenzaid, Z. Rappoport, and D. Samuel, unpublished results. G. E. Lienhard and W. P. Jencks, *J. Am. Chem. Soc.*, **88**, 3982 (1966), have recently reported from ultraviolet

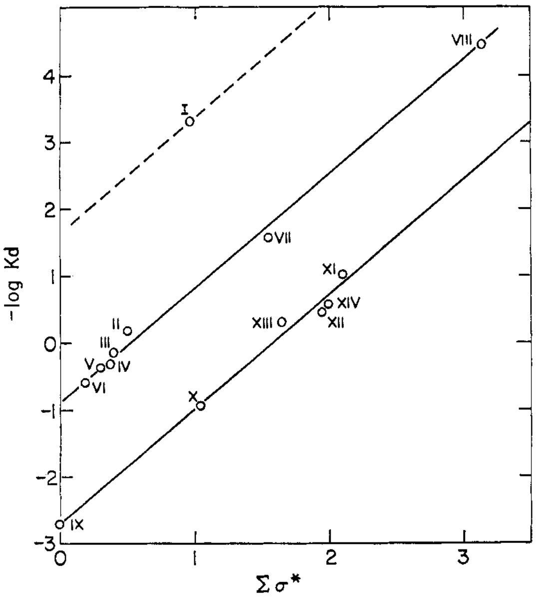

Figure 5. Plot of $-\log K_d$ *vs.* $\Sigma\sigma^*$. The numbering of the compounds is as in Table I.

and we therefore felt that the value determined by pmr is more reliable and it has been quoted in Table I.

The K_d value of acetone (IX) was estimated by Hine[7] from pmr spectroscopy as mentioned above. This measurement was done in a ~3 M (20%) solution of acetone. However, not much change is to be expected for a more dilute solution since Bell and McDougall[13] have found little change in the equilibrium constants on varying the proportion of dioxane in aqueous solutions of *s*-dichloroacetone.

Federlin[16] measured K_d for chloroacetaldehyde (VII) in a dioxane–water mixture at 20°. Extrapolating to 25° and to pure water, Bell[1] obtained K_d = 0.027. To check on this value we have studied the pmr spectrum of this compound in pure water. As seen from Table I, in addition to the lines due to the aldehydic and α-protons of the hydrated compound, a doublet due to the α-protons of the unhydrated chloroacetaldehyde was observed. This doublet is very weak, and the triplet expected due to the aldehydic proton of this species could not be detected. From peak intensities we estimated that chloroacetaldehyde is ~3.5% in the unhydrated form in agreement with the value of Bell which is quoted in Table I.

It should be noted that the K_d values listed in Table I were determined in solutions of different concentrations. However, all the results are for solutions 1 M or less and the concentration dependence of K_d in this range is not expected to be large.[2c,13]

Free Energy Correlation of K_d Values

From the values for the equilibrium constants quoted in Table I it is seen that, in general, K_d decreases with increasing electronegativity of the substituents bonded to the carbonyl group. This has been explained[17] as being due to an increase of positive charge on the carbonyl carbon, thereby making it more susceptible to a nucleophilic attack of water, while electron-donating substituents will decrease its electrophilicity and thus stabilize the carbonyl group. It is therefore natural to look for a correlation of K_d with σ^*, the aliphatic polar substituent constant,[18] which is a measure of the electron-donating power of the substituent. An attempt of this sort, which will be discussed shortly, has already been made by Bell.[1]

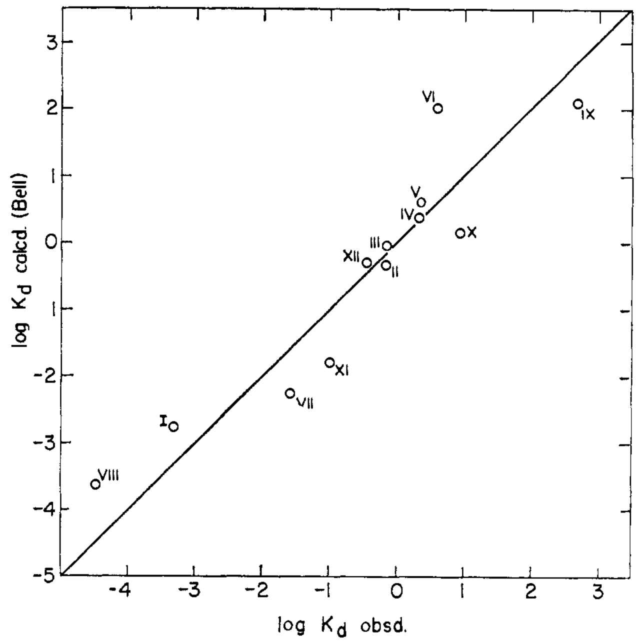

Figure 6. Plot of log K_d, calculated from eq 3, using parameters given in the text, *vs.* log K_d observed. The numbering of the compounds is as in Table I.

In Figure 5, $-\log K_d$ for the various aldehydes and ketones described above are plotted *vs.* $\Sigma\sigma^*$. Within the group of ketones and the group of aldehydes (excluding formaldehyde), a good correlation is observed, but the two groups fall on two nearly parallel lines. In order to fit all points on a single line by a $\Sigma\sigma^*$ correlation alone, it would be necessary to assume an unreasonable high error in the accepted value of σ^* for H. It therefore appears that $\Sigma\sigma^*$ alone is insufficient for correlating all of the carbonyl compounds, and additional parameters are necessary.

Bell[1] has attempted to correlate K_d by an equation containing two parameters, $\Sigma\sigma^*$ and ΣE_s, where E_s is the aliphatic steric substituent constant.[18] The relation proposed by Bell is

$$-\log K_d = \rho^*\Sigma\sigma^* + \delta\Sigma E_s + C \qquad (3)$$

where ρ^*, δ, and C are constants. Using K_d values from Table I, E_s and σ^* from ref 18, the following values for ρ^*, δ, and C were obtained by a multiple regression analysis: $\rho^* = 2.12 \pm 0.29$, $\delta = 1.12 \pm 0.26$, $C = -2.10 \pm 0.42$; $d = 0.79$, $r = 0.928$, where the errors represent standard deviations for the corresponding parameters, d the over-all standard deviation, and r the correlation coefficient.[19] In Figure 6 log K_d, as calcu-

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measurements of pivalaldehyde, $K_d > 10$, which differs markedly from our pmr value. This discrepancy as well as that for chloroacetone seems to stem from the same erroneous assumption of the constancy of ϵ_{max}.

[16] P. Federlin, *Compt. Rend.*, 235, 44 (1952).

[17] See, for example, J. Hine "Physical Organic Chemistry," 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 249.

[18] R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 13.

[19] The procedure is that of W. A. Pavelich and R. W. Taft, Jr., *J. Am. Chem. Soc.*, 79, 4935 (1957); E_s and/or σ^* values are not available for $COCH_3$, COOH, COO^-, and $COOCH_3$, and therefore biace-

lated from eq 3, is plotted *vs.* log K_d observed. Indeed it may be seen that most of the experimental points fall near the straight line of 45° inclination.

Summation of σ^* measures the total polar effect due to substituents. This procedure of evaluating the total polar effect has proved successful in many free energy correlations.[20,21] However, the assumption that steric effects are additive does not seem to be justified[21] as was also pointed out by Bell[1] himself and is not normally done. This can be understood if we consider the steric effect as being due to steric repulsion between two substituents. If one of the groups is removed or replaced by a much smaller substituent, practically all of the strain has been relieved and the removal of the second group should have a much smaller effect.

We have therefore tried a different approach of correlating the K_d values. Referring to Figure 5 it may be seen that the lines correlating the ketones and aldehydes are very nearly parallel, and it is therefore natural to assume that the dispersion between these two lines is due to a specific effect of substituting a C–H bond by a C–C bond upon going from aldehydes to ketones. With this approach formaldehyde may be considered as a point lying on a third line parallel to the other two and displaced, owing to an additional effect of a second hydrogen, by nearly the same amount as the aldehydes are displaced from the ketones. We therefore propose the following correlation between log K_d and $\Sigma\sigma^*$

$$-\log K_d = \rho^*\Sigma\sigma^* + B\Delta + C \qquad (4)$$

where B and C are constants and Δ is the number of aldehydic protons; it is zero for the ketones and one for aldehydes except for formaldehyde for which it is two. Like Bell's equation this is a two-parametric equation, but instead of considering the steric constant, E_s, due to the individual substituents, we consider the specific effect of substituting a C–C bond by a C–H bond.

A multiple regression analysis of the data of Table I gave the following values for the parameters of eq 4: $\rho^* = 1.70 \pm 0.07$; $B = 2.03 \pm 0.10$; $C = -2.81 \pm 0.13$; $d = 0.21$, $r = 0.995$. In Figure 7, log K_d, as calculated from eq 4, is plotted *vs.* log K_d observed. It thus appears that eq 4 gives a much better fit to the results than eq 3. Although this may be fortuitous, we believe that the parameters of eq 4 represent the reaction studied more truthfully. Perhaps the strongest support in favor of eq 4 comes from pivalaldehyde. This compound has a very large E_s value and according to eq 3 should have a log K_d value of +2.03 as compared to the experimental value of +0.6. On the other hand, the agreement with eq 4 as seen in Figure 7 is excellent.

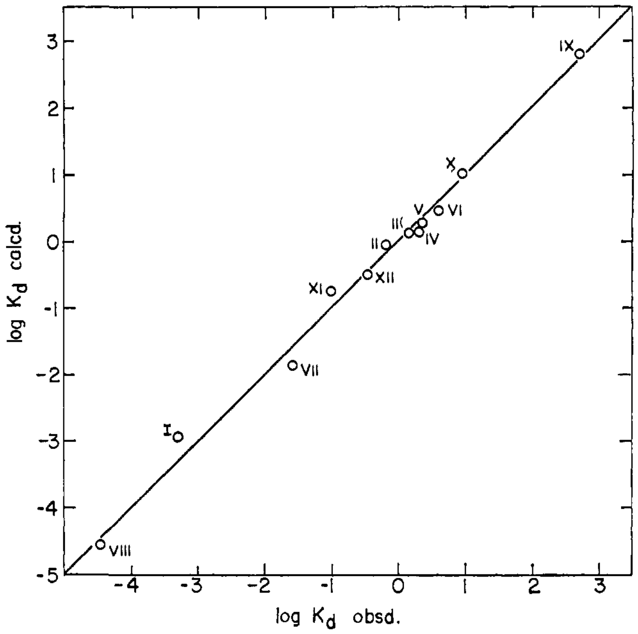

Figure 7. Plot of log K_d, calculated from eq 4, using parameters given in the text, *vs.* log K_d observed. The numbering of the compounds is as in Table I.

Discussion

It remains to interpret the empirical parameter Δ which contributes an extra additive term, over and above that measured by $\Sigma\sigma^*$. As is common in extrathermodynamic relationships, this is a "difficult, moot and vexing"[22] problem. It is quite clear from our results that there is a relative stabilization of the unhydrated carbonyl group due to substitution by an alkyl group. This stabilization amounts to $2.03 \times 2.3RT \cong 2.8$ kcal mole^{-1} per alkyl group. This effect, both in direction and in order of magnitude, is consistent with Dewar's theory of adjacent bond interaction.[23] According to this theory there is an extra stabilization of an R–S bond if alkyl groups are bonded to either atom R or atom S, the degree of stabilization depending on the hybridization of R (or S). The hydrogenation of ethylene and its alkylated derivatives involves the same changes in hybridization as in the present case. For substituted ethylenes, the increase in stabilization was about 2.7 kcal mole^{-1} per alkyl group, very similar to that found here for alkyl substitution in carbonyl compounds.

Similar effects of alkyl substitution of the carbonyl group have been previously observed.[20,24] Perhaps the best known example is that of the acid-catalyzed hydrolysis of acetals and ketals. Kreevoy and Taft[20] showed that when the rate constants for this reaction are plotted *vs.* $\Sigma\sigma^*$, the ketals fall on one line, the acetals fall on a second nearly parallel line, and formal is a deviant point. This point is separated from the acetal line at nearly the same distance as the acetal from the ketal line. These authors invoked a different approach to explain the effect of alkyl substitution. Using the concept of α-hydrogen hyperconjugation, they were able to correlate their results satisfactorily.[25] We have also tried a similar correlation of the K_d val-

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tyl, pyruvic acid, pyruvate anion, and methyl pyruvate were omitted from the least-squares calculations. The parameters of eq 3 derived by Bell[1] are $\rho^* = 2.6$, $\delta = 1.3$, and $C = -2.70$, differing somewhat from those quoted above. This is apparently due to the fact that for some compounds we have chosen different K_d values and also due to the inclusion of pivalaldehyde.

(20) M. M. Kreevoy and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **77**, 5590 (1955).

(21) P. R. Wells, *Chem. Rev.*, **63**, 171 (1963).

(22) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, p 233.

(23) (a) M. J. S. Dewar and R. Pettit, *J. Chem. Soc.*, 1625 (1954); (b) M. J. S. Dewar and H. N. Schmeising, *Tetrahedron*, **5**, 166 (1959); **11**, 96 (1960).

(24) R. W. Taft, Jr., and I. C. Lewis, *ibid.*, **5**, 210 (1959).

(25) Taft and Lewis[24] claimed to have further improved the precision of the correlation by introducing a term due to C–C hyperconjugation.

ues, but it turned out to be poor with a high standard deviation.[26]

In fact, a reexamination of the data on the acetal hydrolysis[20] showed that a correlation of the type of eq 4 gave almost as good a fit as that used previously.[20,27] As pointed out by Dewar,[23a] both approaches (adjacent bond interaction and hyperconjugation) would be equivalent if hyperconjugation energies for C–H and C–C (and even C–Cl) bonds are similar. Indeed in recent publications C–C hyperconjugation is gaining more importance.[24,28]

It should be noted that solvation effects may also play a role in determining the equilibrium constant K_d. It is likely that in aqueous solutions, the aldehyde hydrates are stabilized by hydrogen bonding to solvent water relative to ketone hydrates. A more complete understanding of the factors influencing the reversible hydration of the carbonyl group could, no doubt, be obtained from heats of formation. Unfortunately, reliable data are available only for a limited number of compounds.[13]

Acknowledgment. We are gratefully indebted to Professor R. P. Bell for sending us a copy of his article prior to publication and to Professor E. Grunwald, Dr. S. Brownstein, and Dr. Z. Rappoport for helpful comments regarding the discussion of the results.

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[26] With the nomenclature of Kreevoy and Taft[20] the following best-fit parameters were obtained.

$$-\log K_d =$$
$$(1.38 \pm 0.24)\Sigma\sigma^* - (0.53 \pm 0.12)(n - 6) - 2.83 \pm 0.51$$
$$d = 0.77 \quad r = 0.932$$

It is interesting to note that the coefficient of $(n - 6)$ that comes out of the present statistics, 0.53, is very close to the hyperconjugation energy per α hydrogen proposed by Kreevoy and Taft (0.54).[20]

[27] Using the data of Table I in ref 20, excluding those for neopentyl ketal and the α,β-unsaturated compounds, the equation of Kreevoy and Taft gave an over-all standard deviation of 0.31 while a correlation by eq 4 gave a standard deviation of 0.34. It is interesting to note that the B obtained (2.00 log units) is virtually the same as that in the present work (2.03 log units).

[28] Reference 22, pp 234, 349; see also R. S. Mulliken, *Tetrahedron*, 5, 253 (1959).

A Nuclear Magnetic Resonance Study of the Reversible Hydration of Aliphatic Aldehydes and Ketones. II. The Acid-Catalyzed Oxygen Exchange of Acetaldehyde

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Contribution from the Isotope Department, The Weizmann Institute of Science, Rehovoth, Israel. *Received September 13, 1966*

Abstract: The rate constant for the acid-catalyzed oxygen exchange between acetaldehyde and solvent water was determined from the broadening of the acetaldehyde ^{17}O nuclear magnetic resonance lines as a function of HCl concentration. For solutions 1.9 to 5.7 *M* in acetaldehyde, the acid catalysis rate constant is ~470 M^{-1} sec^{-1}. This result is compared with the acid-catalysis rate constant for the hydration of acetaldehyde. It is concluded that the oxygen exchange can be accounted for by the hydration–dehydration process. The rate of oxygen exchange of methylene glycol in a neutral aqueous solution was also measured and found to be similar to that of the dehydration of this compound.

The reversible hydration of acetaldehyde (reaction 1) has been the subject of extensive studies by various workers. The reaction was shown to be acid and base catalyzed, the half-life at room temperature in neutral solutions being of the order of 1 min and much shorter in acidic or basic solutions. Therefore, methods for studying fast reactions must be employed. The various techniques including pmr, thermal maximum, and chemical scavenging have been thoroughly reviewed in a recent article by Bell.[1]

$$CH_3CHO + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CH_3CH(OH)_2 \qquad (1)$$

If the water or the acetaldehyde are labeled with either ^{17}O or ^{18}O, reaction 1 provides a route for isotopic exchange. When the exchange is measured by isolating one component of this system and analyzing for its isotopic oxygen content, the observed rate constant should be at least equal to half the hydration rate constant. The factor of 2 is due to the fact that only in half of the events in which a C–OH bond of the *gem*-diol is broken will isotopic exchange occur. Isotope effects in oxygen are very small[2] and can be ignored in reactions of this type.

The only reported data on the oxygen exchange of acetaldehyde in aqueous solutions are by Herbert and Lauder[3] using ^{18}O, who found a half-life of about 2 hr at room temperature, a result which is inconsistent with the rate of hydration[1] of this compound. Another attempt to measure the rate of oxygen exchange was recently made by Byrn and Calvin,[4] who found that the exchange of a slightly acidic solution of acetaldehyde in a tetrahydrofuran–water solution was complete within 5 min. In order to elucidate the mechanism of oxygen exchange and to resolve the inconsistencies

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[1] R. P. Bell, *Advan. Phys. Org. Chem.*, 4, 1 (1966).

[2] L. Melander, "Isotope Effects in Reaction Rates," Ronald Press Co., New York, N. Y., 1960.

[3] J. B. M. Herbert and I. Lauder, *Trans. Faraday Soc.*, 34, 433 (1938).

[4] M. Byrn and M. Calvin, *J. Am. Chem. Soc.*, 88, 1916 (1966).