

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY, CHICAGO 16, ILL.]

Secondary Deuterium Isotope Effects in the Addition Equilibria of Ketones¹BY JOAN M. JONES AND MYRON L. BENDER²

RECEIVED JULY 15, 1960

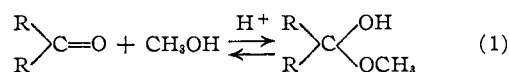
The equilibrium constants of reactions involving the addition of methanol to the ketones, acetone, acetone-*d*₆, cyclopentanone and cyclopentanone-2,2,5,5-*d*₄, to form their respective hemiketals have been determined. The ratio of hemiketal dissociation constants for the acetone and acetone-*d*₆ reactions in dioxane solution is $K_H/K_D = 1.29 \pm 0.09$. For the cyclopentanone and cyclopentanone-2,2,5,5-*d*₄ equilibria in methanol, the ratio, extrapolated to infinite dilution, is $K_H/K_D = 1.44 \pm 0.09$. These deuterium isotope effects indicate that the transformation of the trigonal carbonyl carbon atom of the ketone to the tetrahedral carbon atom of the hemiketal is facilitated by β -deuterium atoms. This result is in qualitative agreement with the reverse kinetic secondary deuterium isotope effect in the hydrolysis of ethyl acetate in which a trigonal carbon atom in the ground state is transformed into an approximately tetrahedral carbon atom in the transition state. A semi-quantitative correlation of frequency changes with deuterium isotope effects in carbonyl compounds indicates that the isotope effects need not be explained in terms of electronic effects but rather may be explained solely on the basis of mass effects on the fundamental vibrational frequencies of the molecules.

Introduction

In a previous paper¹ deuterium substitution on the carbon atom adjacent to the carbonyl group was shown to increase the rate of hydrolysis of ethyl acetate. This result is qualitatively the reverse of the effect of β -deuterium substitution in the S_N1 solvolyses of alkyl halides^{3,4} and acetyl chloride¹ which proceed through electron-deficient transition states and has been explained on the basis of the known mechanism of ethyl acetate hydrolysis involving a tetrahedral-like transition state which is less electron-deficient than the ground state containing a trigonal carbonyl carbon atom. In general, deuterium substitution leads to increased rate of reaction when the ground state is more electron-deficient than the transition state and leads to reduced rate of reaction when the transition state is more electron-deficient than the ground state. These results are compatible with the hypothesis that the β -hydrogen and β -deuterium can stabilize an electron-deficient center by hyperconjugation to different extents. Presumably a carbon-hydrogen bond can afford more hyperconjugative stabilization than can a carbon-deuterium bond because the former has a higher vibrational zero-point energy than the latter with a resultant lower dissociation energy.

Studies of the dissociation constants of cyanohydrins of aldehydes and ketones⁵ have suggested that hyperconjugative stabilization of the carbonyl group with respect to the tetrahedral cyanohydrin is one factor in the relative values of the dissociation constants obtained. When inductive and resonance effects on the equilibrium of *p*-substituted benzaldehydes and their respective cyanohydrins are evaluated separately by means of Taft's substituent constants, values for the contribution of hyperconjugation to the total free energy increase for the dissociation of the cyanohydrins can be obtained. These values range from 0.57 kcal./mole per C-H group in the *p*-substituent (C₂H₅)₃N⁺CH₂- to 0.07 kcal./mole for *p*-methyl and zero for *p*-*t*-

butyl, in a total free energy change of 2.55, 2.75 and 2.85 kcal./mole, respectively. Since the secondary isotope effect generally parallels the Baker-Nathan order, such as is found in the dissociation constants, a secondary deuterium isotope effect might be expected in equilibria of this type. In the equilibria studied here involving hemiketal formation, the trigonal carbon atom of the ketone carbonyl group becomes tetrahedral in the hemiketal, and ketones containing β -hydrogen atoms should be more stable relative to their hemiketals than the corresponding ketones containing β -deuterium atoms.



The formation of a tetrahedral addition product from ketone and methanol in this equilibrium is analogous to the formation of a nearly tetrahedral transition state from ester and hydroxide ion in the basic hydrolysis of ethyl acetate. Since the absolute reaction rate theory states that the ground state and the transition state are in equilibrium, and since the two reactants and the two addition compounds are chemically related to each other, the secondary deuterium isotope effect per deuterium atom would be predicted to be comparable in the ester hydrolysis reaction and the hemiketal equilibrium.

Experimental

Materials.—Acetone (reagent grade) was dried with sodium carbonate and distilled. Acetone-*d*₆ D/(D + H) = 96% was supplied by the Isotope Specialties Co., Inc. (Glendale, Calif.) in sealed ampoules. One sample was dried with sodium carbonate and one was used without treatment. No difference was observed in the results obtained.

Cyclopentanone (Eastman Kodak Co. white label) was dried with sodium sulfate and distilled. Cyclopentanone-2,2,5,5-*d*₄ was prepared by equilibration of cyclopentanone with D₂O in the presence of potassium carbonate.⁶ Density measurements (d^{25}_4 0.9888) indicated 4.0 D atoms/molecule.

Dioxane, m.p. 10.5–11°, was purified by refluxing with sodium followed by fractional distillation when the sodium was bright. The first fractions were rejected. Tetrahydrofuran (b.p. 64–66°) was dried with potassium hydroxide and distilled from lithium aluminum hydride. Methanol (reagent grade) was dried by refluxing with magnesium filings and distilled. Hydrogen chloride in dioxane, tetrahydrofuran or methanol was prepared by passing cylinder hydrogen chloride gas, washed in concentrated sulfuric acid, into the solvent.

(6) A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey and S. Suzuki, *THIS JOURNAL*, **80**, 2326 (1958).

(1) This research was supported by Contract At-(11-1)-295 of the U. S. Atomic Energy Commission. For the previous paper, see M. L. Bender and M. S. Feng, *THIS JOURNAL*, **82**, 6318 (1960).

(2) Alfred P. Sloan Foundation Research Fellow; present address, Department of Chemistry, Northwestern University, Evanston, Ill.

(3) E. S. Lewis and C. E. Boozer, *THIS JOURNAL*, **74**, 6306 (1952).

(4) V. J. Shiner, Jr., *ibid.*, **75**, 2925 (1953).

(5) D. P. Evans and J. R. Young, *J. Chem. Soc.*, 1310 (1954); J. W. Baker, *Tetrahedron*, **5**, 135 (1959).

It was prepared immediately before use and standardized by titration with carbonate-free sodium hydroxide.

Measurements of Hemiketal Equilibria.—Initial and equilibrium ketone concentrations were obtained by measuring the carbonyl absorption in the ultraviolet.⁷ Experiments were carried out at 25° on a Beckman DU spectrophotometer and at 25–27° in a Beckman DK2 spectrophotometer. Measurements of standard ketone solutions showed that Beer's law is obeyed over the experimental range of concentrations. For acetone and acetone-*d*₆, the maxima used were 274 and 277.5 μ , respectively, and the position and height of the maxima were unaffected, within experimental error, by a change in solvent from dioxane to methanol. The peak was somewhat broader in dioxane. For cyclopentanone and cyclopentanone-2,2,5,5-*d*₄, the maxima used were 295 and 297 μ , respectively, in dioxane and tetrahydrofuran and 287 and 288 μ in methanol. Shoulders clearly visible in the ether solvents were only inflections in methanol.

The dissociation constants (*K*) of the hemiketal in eq. 1 are given by: $K = (\text{acetone})(\text{methanol})/(\text{hemiketal}) = (\text{equilibrium ketone absorbance})/[(\text{moles methanol added}) - (\text{change in ketone absorbance})/(\text{extinction coefficient of the ketone})]/(\text{change in ketone absorbance})$. Measured amounts of ketone, methanol and a standard solution of hydrogen chloride in the reaction solvent were prepared at 25°.

Results

All experiments with acetone and acetone-*d*₆ were carried out in dioxane solution. It was found that the dissociation constant (*K*) was independent of the concentration of acid used as catalyst from 0.005 to 0.1 *M* hydrogen chloride, although the rate of attainment of equilibrium was proportional to the acid concentration; 0.05 *M* acid was used in subsequent experiments since equilibrium was reached in 4 minutes.

The equilibrium constant over a range of acetone and methanol concentrations is given in Table I. The low acetone concentrations were measured using 5- and 10-cm. absorption cells.

TABLE I
DISSOCIATION CONSTANTS OF ACETONE AND ACETONE-*d*₆
HEMIKETALS IN DIOXANE SOLUTION

Init. acetone concn., <i>M</i>	Init. methanol concn., <i>M</i>	<i>K</i>	Init. acetone concn., <i>M</i>	Init. methanol concn., <i>M</i>	<i>K</i>
Acetone			Acetone- <i>d</i> ₆		
0.00533	0.743	7.62	0.00536	0.496	5.47
.01066	.743	6.09	.00536	.743	4.33
.01066	.644	6.75	.0417	.743	5.21
.0482	.743	6.16	.0417	.618	4.87
.0482	.618	7.66	.0417	.996	4.47
.0964	.743	7.41	.0836	.743	6.30
.0966	.618	6.19	.0836	.618	6.40
.0964	.496	6.78			
		Av. 6.83 ± 0.22			Av. 5.29 ± 0.37

For acetone and acetone-*d*₆, $K_H/K_D = 1.29 \pm 0.09$. During the measurements on acetone-*d*₆, the absorption maximum was observed to drift slowly to short wave lengths. This may be due to isotopic exchange, or may be the slow shift observed in other ketones by Wheeler,⁷ and ascribed by him to condensation of the ketones. A shift of 1–1.5 μ in 16 hours was observed. A slow rise in absorbance, after the initial drop, was also observed in both acetone and acetone-*d*₆.

Preliminary experiments with cyclopentanone were carried out in dioxane and tetrahydrofuran as solvents, but the dissociation constant was too

large for accurate measurement. It was, therefore, decided to carry out the reaction in methanol. The dissociation constant is again independent of the acid concentration, and 0.05 *M* hydrogen chloride was again a suitable catalyst for rapid approach to equilibrium.

The equilibrium constants for different values of the initial cyclopentanone concentration are listed below in Table II. The figures are averages of two or three determinations.

TABLE II
DISSOCIATION CONSTANTS OF CYCLOPENTANONE AND CYCLOPENTANONE-2,2,5,5-*d*₄ IN METHANOL SOLUTION

Init. ketone concn., <i>M</i>	Final ketone concn., <i>M</i>	<i>K</i>	Init. ketone concn., <i>M</i>	Final ketone concn., <i>M</i>	<i>K</i>
Cyclopentanone			Cyclopentanone-2,2,5,5- <i>d</i> ₄		
0.0220	0.0050	7.0	0.0270	0.0052	5.8
.0407	.0107	9.3	.0412	.0084	6.4
.0558	.0154	9.7	.0570	.0132	7.8
.0785	.0230	10.5	.0795	.0202	8.6
.0900	.0280	11.1	(.0824)	(.0212)	(8.9)
			.0846	.0226	9.2

The dissociation constant of the hemiketal, *K*, increases with increasing equilibrium ketone concentration. Possibly the change in equilibrium constant with ketone concentration is a consequence of changing activity coefficients. Attempts to define an equilibrium constant in terms other than a one-to-one adduct of ketone and methanol resulted in a wider range of constants. Partial condensation of the ketone could also explain the variation in equilibrium constants. Figure 1 shows this relationship in graphical form, with the least squares

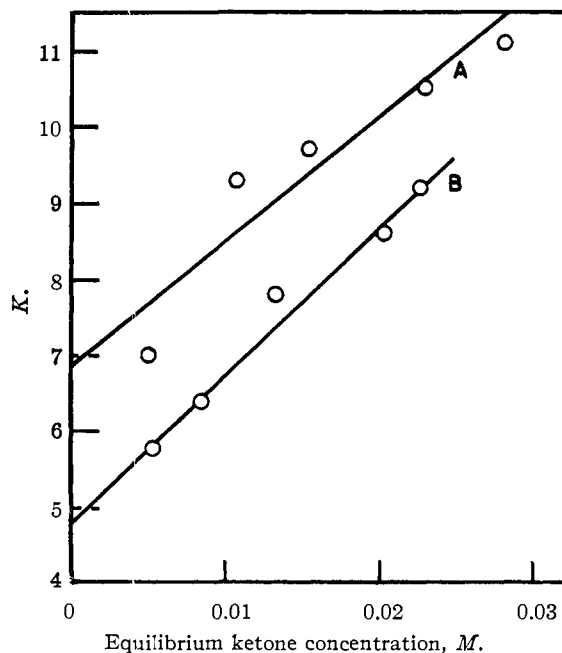


Fig. 1.—Dissociation constants of hemiketals of cyclopentanone (A) and cyclopentanone-2,2,5,5-*d*₄ (B) in methanol.

lines for the normal and deuterated ketones. At each concentration, the deuterium hemiketal is less dissociated than the hydrogen compound, and the

(7) O. H. Wheeler, THIS JOURNAL, 79, 4191 (1957)

concentration dependence is approximately the same for each ketone. (The lines are roughly parallel.) Extrapolating to infinite dilution, it is found that $K_H = 6.89 \pm 0.29$ for cyclopentanone and $K_D = 4.78 \pm 0.25$ for cyclopentanone-2,2,5,5- d_4 . Therefore, $K_H/K_D = 1.44 \pm 0.09$.

Discussion

In the introduction, the nature of the secondary deuterium isotope effects predicted by the hyperconjugation hypothesis was described, and it is apparent that the results of the current investigation agree with the predictions made there. The change in free energy per deuterium atom⁸ for the acetone hemiketal equilibrium is 26 cal./mole and for the cyclopentanone hemiketal equilibrium is 55 cal./mole while the change in free energy of activation per deuterium atom for the related hydrolysis of ethyl acetate is 21 cal./mole. A further comparison of these results can be made with the secondary deuterium isotope effects in the rate constants of the "spontaneous" hydration of acetaldehyde and acetaldehyde-2,2,2- d_3 .⁹ In this reaction it was found that $k_H/k_D = 0.94$ at 0° which corresponds to a change in free energy of activation per deuterium atom of 12 cal./mole. Although the direct comparison of these results is not strictly valid because of the fact that equilibrium data are being compared with rate data and because of solvent changes in the equilibrium data, one noteworthy conclusion can be drawn from these data: the effect per deuterium atom is larger in a methylene group (of cyclopentanone) than in a methyl group (of acetone) in agreement with data on the solvolysis of tertiary chlorides.⁴

One might conclude from these results that hyperconjugation stabilizes molecules in the ground state, a view that has been attacked on the basis that π -orbital repulsion should prevent delocalization of electrons.¹⁰ In a carbonyl compound the π -electrons of the carbonyl group prevent migration of electrons from the β -carbon-hydrogen bond to form a partial carbon-carbon double bond. In valence bond terms this argument means that the contribution of polar structures of the type

H^+
—C=C—O⁻

to the resonance hybrid should be very small. On the other hand, the observed lowering of the carbonyl stretching frequency on going from the gas phase to solution¹¹ suggests that the carbonyl bond is more polar in solution. However the additional frequency lowering by β -deuterium¹² is contrary to what one would expect if the frequency lowering reflected greater hyperconjugation.

While the deuterium isotope effect in the basic hydrolysis of ethyl acetate- d_3 superficially appears to fit in with the hyperconjugation picture, the isotope effect found in the basic hydrolysis of methyl

p-methyl-*t*-benzoate ($k_H/k_T = 1.05$) does not.¹³ Presumably the reaction mechanism of these two hydrolytic processes are identical to one another and one would expect a similar result, at least qualitatively. The fact that the two results do differ qualitatively can be rationalized on the basis that the isotope effect is dependent on two factors: (1) greater electron release for the heavier hydrogen isotope by the inductive effect and (2) smaller electron release for the heavier hydrogen isotope by means of resonance, particularly by the hyperconjugative mechanism.¹³ The use of two opposing factors does in general dodge the issue quite nicely, but it is difficult to explain why the inductive effect is not operative in the ethyl acetate- d_3 hydrolysis since the relatively small distance involved in the transmission of an inductive effect there should facilitate its effectiveness with respect to a hyperconjugative effect. It should be noted further that the use of the inductive effect to explain the secondary deuterium isotope effect has been attacked on theoretical grounds.¹⁴

A further difficulty with the hyperconjugation hypothesis is the lack of secondary isotope effects in various aromatic electrophilic substitutions involving toluene- α, α, α - d_3 . In these reactions including aromatic hydrogen exchange¹⁵ and bromination¹⁶ one would expect very considerable hyperconjugative stabilization of the electron-deficient intermediate and, therefore, large secondary isotope effects. In fact, negligibly small kinetic isotope effects have been found in these reactions, which places considerable strain on the hyperconjugation hypothesis of secondary isotope effects and makes it advisable to look at other possible interpretations of the secondary isotope effect.

Recently Bartell¹⁷ has attributed secondary isotope effects to non-bonded repulsions, a theory in accord with Robertson, *et al.*'s,¹⁸ explanation of the inverse isotope effect observed on γ -substitution in *n*-propyl compounds. These authors, however, retain the orbital overlap explanation of the β -effect. Like the α -H bonding theory of Kreevoy and Eyring¹⁹ these theories predict steric requirements for a β -deuterium isotope effect. Shiner²⁰ has recently given a convincing demonstration of such steric requirements in a solvolysis reaction.

The changes in equilibrium constants and rate constants on isotopic substitution depend on the fundamental vibrational frequencies of the molecule in a manner first developed by Bigeleisen.²¹ Starting with the usual relationship between equilibrium constant and free energy, one can write the following equation relating the effect of deuterium

(13) E. M. Hodnett, R. D. Taylor, J.-V. Torino and R. E. Lewis, *ibid.*, **81**, 4528 (1959).

(14) R. E. Weston, Jr., *Tetrahedron*, **6**, 31 (1959).

(15) A. J. Kresge and D. P. N. Satchell, *Tetrahedron Letters*, **13**, 20 (1959).

(16) C. G. Swain, T. E. C. Knee and A. J. Kresge, *THIS JOURNAL*, **79**, 505 (1957).

(17) L. S. Bartell, *Tetrahedron Letters*, **6**, 13 (1960).

(18) K. T. Lefek, J. A., Llewellyn and R. E. Robertson, *Chemistry & Industry*, 588 (1960).

(19) M. M. Kreevoy and H. Eyring, *THIS JOURNAL*, **79**, 5121 (1957).

(20) V. J. Shiner, *ibid.*, **82**, 2655 (1960).

(21) J. Bigeleisen, *J. Chem. Phys.*, **17**, 675 (1949); **15**, 261 (1947).

(8) E. S. Lewis and G. M. Coppinger, *THIS JOURNAL*, **76**, 4495 (1954).

(9) Y. Pocker, *Proc. Chem. Soc.*, 17 (1960).

(10) M. J. S. Dewar and M. N. Schmeising, *Tetrahedron*, **5**, 166 (1959).

(11) L. J. Bellamy, "The Infrared-red Spectra of Complex Molecules," J. Wiley and Sons, Inc., New York, N. Y., 1958, 2nd ed., Chap. 23.

(12) R. N. Jones and A. R. H. Cole, *THIS JOURNAL*, **74**, 5648, 5662 (1952).

substitution on an equilibrium process

$$\ln K_H/K_D = [(F_H^r - F_D^r) - (F_H^p - F_D^p)]/RT \quad (2)$$

where $F^{r,p}$ are the standard free energies of reactants and products, respectively, and the subscripts H and D refer to hydrogen and deuterium containing molecules. Since the minimum of the potential energy curves of isotopically substituted molecules are the same, one may let $\Delta F^{r,p}$ be the energy measured from the minima of the potential energy curves of reactants and products.

$$\ln K_H/K_D = [(\Delta F_H^r - \Delta F_D^r) - (\Delta F_H^p - \Delta F_D^p)]/RT \quad (3)$$

Bigeleisen²¹ has shown that

$$-(\Delta F_H - \Delta F_D)/RT = \sum [-1/2\Delta\mu + \ln(1 + \Delta\mu/\mu) + \ln(1 - e^{-\mu})/(1 - e^{-(\mu + \Delta\mu)})] + \ln s/s' \quad (4)$$

where the summation is over all the fundamental vibration frequencies; $\mu = hc\omega/kT$ where ω is the vibrational frequency in cm.^{-1} ; $\Delta\mu = (\mu_H - \mu_D)$ is the shift on isotopic substitution; and s, s' are symmetry numbers. Equation 4 may be substituted in eq. 3 for both reactants and products giving $\ln K_H/K_D$ in terms of the fundamental vibrational frequencies of reactants and products. It can be seen that the symmetry terms will cancel, and the expression can be further simplified by making the following approximations: (1) $e^{-\mu} = 0$ for frequencies over 1000 cm.^{-1} and (2) for most carbon-hydrogen and carbon-deuterium vibrations, $\mu_H/\mu_D = 1.35$. Substituting these values and the values of the universal constants and the experimental temperature, 25° into the combined eq. 3 and 4, we can obtain an expression for the effect of deuterium substitution on the equilibrium constant solely in terms of carbon-hydrogen and carbon-deuterium vibrations

$$\log K_H/K_D = \pm 0.000995 \sum (\omega^r - \omega^p) \quad (5)$$

where the summation is over all the carbon-hydrogen vibrations of reactant and product.

The carbon-carbon, carbon-oxygen, oxygen-hydrogen and skeletal frequency shifts on deuterium substitution can be expected to be small compared with carbon-hydrogen shifts. If $\Delta\mu/\mu$ is substituted for $\ln(1 + \Delta\mu/\mu)$, one obtains

$$-\ln K_H/K_D = \sum (-1/2\Delta\mu^r + \Delta\mu^r/\mu^r) - \sum (-1/2\Delta\mu^p + \Delta\mu^p/\mu^p) \quad (6)$$

For such frequencies $\Delta\mu/\mu$ terms will be much smaller than $\Delta\mu$ terms and the former can therefore be neglected. Then upon substitution of the various constants as before, we can get an expression for the effect of deuterium substitution on the equilibrium constant in terms of vibrations other than carbon-hydrogen and carbon-deuterium bonds

$$\log K_H/K_D = 0.00552 (\sum \Delta\omega^r - \sum \Delta\omega^p) \quad (7)$$

where the summation is over all the fundamental frequencies of reactant and product except the carbon-hydrogen frequencies.

Equations 5 and 7 can be used to calculate the frequency shifts that would correspond to the observed isotope effect on the equilibrium constant on deuterium substitution. Such calculations are shown in Table III. Also shown in Table III is a calculation for the frequency shift corresponding to the observed isotope effect on a rate constant, which

involves the additional assumption that the transmission coefficients are equal and that the reduced mass term equals one.

TABLE III
FREQUENCY SHIFTS CORRESPONDING TO SOME SECONDARY DEUTERIUM ISOTOPE EFFECTS

Substance	K_H/K_D	Frequency shift based on C-H, C-D shifts only (eq. 5), cm.^{-1}	Frequency shift based on other shifts only (eq. 7), cm.^{-1}
Acetone	1.29	110	20
Cyclopentanone	1.44	175	30
Ethyl acetate	0.90	38	7

If carbon-hydrogen frequency shifts are to explain the isotope effect, the direction of the isotope effect requires that there be a fall in carbon-hydrogen frequencies in going from the tetrahedral hemiketal and hydrolysis transition state to the ketone and acetate (eq. 5). If frequency shifts other than the carbon-hydrogen ones are to explain the isotope effect, the direction of the isotope effect requires that the decrease in frequency on deuteration be greater in the tetrahedral molecule than in the trigonal ketone and acetate (eq. 7).

Quantitative agreement between the observed frequency shifts and the figures in Table III can only be expected when the approximations made in the derivation are valid, and further when the frequencies are measured under the same solvent conditions as the experiment. Qualitatively the frequency shifts calculated according to eq. 7 are what one would expect from a mass effect on the vibrational frequencies. Increase in mass generally lowers vibrational frequencies, and apart from carbon-hydrogen frequencies, the vibrational frequencies of single bonds are more susceptible to substituent mass changes than are those of terminal double bonds.¹¹ For example, the carbonyl stretching frequency is known to be relatively insensitive to changes in mass,²² in contrast to the skeletal frequencies which are quite sensitive to changes in mass. Moreover the tetrahedral addition compounds have one more mass-sensitive carbon-oxygen bond than the carbonyl compounds; none of the isotopic shift in this bond will be balanced out by a corresponding shift in the carbonyl compound. These considerations lead to the qualitative conclusion that the decrease in frequency on deuteration will indeed be greater in the tetrahedral molecule than in the trigonal ketone or acetate.

A detailed examination of the vibrational frequencies of the ketones acetone and cyclopentanone and the alcohols 2-propanol, 2-methyl-2-propanol and cyclopentanol (serving as models of the hemiketals) reveals some interesting facts. The carbon-hydrogen frequencies of acetone, ethyl acetate and cyclopentanone are indeed different from the corresponding frequencies of isopropyl alcohol, *t*-butyl alcohol and cyclopentanol.^{6,11,23} Stretching frequencies of carbon-hydrogen bonds in methyl groups are higher in carbonyl compounds than in alcohols, and the bending frequencies are lower. These shifts are of about the same magnitude (20 to

(22) J. O. Halford, *J. Chem. Phys.*, **24**, 830 (1956).

(23) M. Magat, "Tables Annuelles de Constantes et Donnees Numeriques No. 15, Effect Raman," Hermann and Co., Paris, 1937, Sec. 26, p. 35.

30 cm.⁻¹) and might cancel each other, so that the observed isotope effect must arise elsewhere. The stretching frequencies of carbon-hydrogen bonds in methylene groups are the same in cyclopentanone and cyclopentanol, but the bending frequencies are about 1410 cm.⁻¹ in the ketone and 1438 cm.⁻¹ in the alcohol. The net frequency shift of $4 \times 28 = 112$ cm.⁻¹ is enough to account for 70% of the observed isotope effect.

The comparison of relative frequencies of normal and deuterated compounds is possible in a few cases, among them acetone.²³ One of the striking observations is that the skeletal vibrations in acetone change markedly on deuterium substitution. Below 1000 cm.⁻¹, for example, frequencies at 906, 788, 530, 488 and 391 cm.⁻¹, ascribed to CH₃ rocking, C-C stretching, C-C=O bending (2) and C-C-C bending²⁴ are replaced by frequencies

(24) R. E. Pennington and K. A. Kobe, *THIS JOURNAL*, **79**, 300 (1957).

at 894, 700, 483, 413 and 335 cm.⁻¹. The skeletal vibrations in the hemiketal would be expected to change even more, from the arguments given above, but in the absence of definite information on the vibrational assignments for normal and deuterated alcohol, it is not possible to make quantitative calculations relating frequencies and the isotope effect.

In conclusion it may be said that it has been possible to make semi-quantitative correlations of the isotope effect in reactions of carbonyl compounds with the frequency changes in reactants and products, caused by isotopic substitution. A quantitative treatment of these frequency shifts is not possible at the present time, but qualitatively they seem to be directly attributable to the effect of changes in mass. Consequently, it appears that the observed secondary deuterium isotope effects in carbonyl compounds may be considered solely in terms of mass effects on vibrational frequencies.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE UNIVERSITY, AMES, IOWA]

Alkylation of Carbon-Metallic Compounds with Trialkyl Phosphates

BY HENRY GILMAN AND BERNARD J. GAJ

RECEIVED FEBRUARY 8, 1960

The reactions of several sterically hindered Grignard reagents and organolithium compounds with trialkyl phosphate esters were studied. These reactions were found to proceed *via* nucleophilic displacements from carbon (alkylation), in contrast to earlier work with less hindered organometallic compounds which attack the ester at phosphorus. Some of the factors which may determine the position of attack in these reactions are discussed.

Recently we reported the reactions of trialkyl^{1,2} and triaryl³ phosphate esters with triphenylsilyllithium in tetrahydrofuran. The alkyl esters were found to react in a 1:1 mole ratio with this silylmetallic compound *via* nucleophilic displacements of oxygen from carbon, giving alkyltriphenylsilanes in high yields.² The use of three equivalents of triphenylsilyllithium and forced conditions in reactions with tri-*n*-butyl phosphate, however, gave only *ca.* 50% of the alkylation product, *n*-butyltriphenylsilane.² These reactions also afforded varying amounts of hexaphenyldisilane, hexaphenyldisiloxane, 4-triphenylsilylbutanol and triphenylsilanol. A mechanism involving a nucleophilic displacement of oxygen from phosphorus followed by a cleavage of the silicon-phosphorus bond was proposed to account for the formation of the disilane and the triphenylsilanol isolated.²

The reactions of triaryl phosphates with triphenylsilyllithium, likewise, were found to proceed *via* displacements from phosphorus. Here also, hexaphenyldisilane and triphenylsilanol were the major silicon-containing products of reaction. The phenol derived from the ester used was also found to be among the products of reaction.

Previously, esters of this type having the P-O-R linkage had only been observed to undergo attack at the central phosphorus atom when treated with either Grignard reagents or organolithium com-

pounds.⁴ Esters of other inorganic acids, except sulfates and sulfonates, also react with organometallic compounds *via* attack at the central element.^{4b,c,5} The use of alkyl sulfates and sulfonates as alkylating agents for R-M compounds, on the other hand, is well known, and extensive use has been made of this reaction to prepare alkyl derivatives from Grignard reagents.⁵

Other nucleophiles besides Grignard reagents have been observed to show specificity as to the position of attack on phosphorus esters. For example, lithium chloride in ethoxyethanol solution reacts with tribenzyl phosphate to give benzyl chloride, nucleophilic attack by chloride ion having occurred on carbon.⁶ Hydroxide ion, on the other hand, has been shown to react with alkyl phosphates and phosphonates *via* displacements from

(1) M. V. George, B. J. Gaj and H. Gilman, *J. Org. Chem.*, **24**, 624 (1959).

(2) H. Gilman and B. J. Gaj, *ibid.*, in press.

(3) H. Gilman and B. J. Gaj, *ibid.*, in press.

(4) See, for example (a) A. Michaelis and F. Wegner, *Ber.*, **48**, 316 (1915); (b) H. Gilman and C. C. Vernon, *THIS JOURNAL*, **48**, 1063 (1926); (c) H. Gilman and J. Robinson, *Rec. trav. chim.*, **48**, 328 (1929); (d) G. M. Kosolapoff, *THIS JOURNAL*, **72**, 5508 (1950); (e) A. Burger and N. D. Dawson, *J. Org. Chem.*, **16**, 1250 (1951); (f) G. M. Kosolapoff and R. M. Watson, *THIS JOURNAL*, **73**, 4101 (1951); (g) P. W. Morgan and B. C. Herr, *ibid.*, **74**, 4526 (1952); (h) R. H. Williams and L. A. Hamilton, *ibid.*, **74**, 5418 (1952); (i) N. D. Dawson and A. Burger, *J. Org. Chem.*, **18**, 207 (1953); (j) M. H. Maguire and G. Shaw, *J. Chem. Soc.*, 2039 (1955); (k) R. H. Williams and L. A. Hamilton, *THIS JOURNAL*, **77**, 3411 (1955); (l) R. C. Miller, J. S. Bradley and L. A. Hamilton, *ibid.*, **78**, 5299 (1956); (m) R. C. Miller, C. D. Miller, Wm. Rogers, Jr., and L. A. Hamilton, *ibid.*, **79**, 424 (1957); (n) B. B. Hunt and B. C. Saunders, *J. Chem. Soc.*, 2413 (1957); (o) J. L. Willans, *Chemistry & Industry*, 235 (1957); (p) M. Janczewski, *Roczniki Chem.*, **33**, 185 (1959).

(5) See M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954.

(6) V. M. Clark and A. R. Todd, *J. Chem. Soc.*, 2030 (1950).