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Secondary β-Hydrogen Isotope Effects in Ketal Formation Equilibria¹

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An n.m.r. technique was used to measure $K_{\rm H}/K_{\rm D}$ of ketal formation in methylene chloride solution for acetone and phenylacetone. For acetone, $K_{\rm H}/K_{\rm D} = 0.95$ per D for methyl ketal formation. Phenylacetone-1,1- d_2 , -3,3,3- d_3 , and -1,1,1,3,3- d_5 were examined for both dimethyl and ethylene ketal formation. For both ketals, $K_{\rm H}/K_{\rm D} = 0.91$ per D, for each ketone. Liquid scintillation counting was used to examine $K_{\rm H}/K_{\rm T}$ for ketal formation in methylene chloride. An extraordinarily large isotope effect was found for ethylene ketal formation in 1,3-diphenylacetone. Here $K_{\rm H}/K_{\rm T} = 0.67$ for one tritum atom. This isotope effect is too large to arise from hyperconjugative effects alone. It must have a substantial steric component.

VALERIE A. STOUTE et MITCHELL A. WINNIK, Can. J. Chem. 53, 3503 (1975).

On a utilisé une technique de r.m.n. pour mesurer le $K_{\rm H}/K_{\rm D}$ de la formation de cétals de l'acétone et de acétophénone en solution dans le chlorure de méthylène. Pour l'acétone, $K_{\rm H}/K_{\rm D} = 0.95$ par D pour la formation du cétal de méthyl. On a étudié les formations des diméthyl et éthylène cétals des phénylacétones $-1, 1-d_2, -3, 3, 3-d_3$ et $-1, 1, 1, 3, 3-d_3$. Pour les deux cétals on a trouvé un $K_{\rm H}/K_{\rm D} = 0.91$ par D pour chaque cétone. On a utilisé le comptage par scintillation liquide pour étudier le $K_{\rm H}/K_{\rm T}$ de la formation des cétals en solution dans le chlorure de méthylene. On a trouvé qu'il y a un effet isotopique très grand pour la formation de l'éthylène cétal de la diphényl-1,3 acétone. Dans ce cas, le $K_{\rm H}/K_{\rm T} = 0.67$ pour un atome de tritium. Cet effet isotopique est trop grand pour dériver uniquement d'effets d'hyperconjuguaison; il doit y avoir en plus une composante stérique.

[Traduit par le journal]

The wealth of secondary deuterium isotope data on the kinetics of nucleophilic addition to carbonyl compounds, (1) and hydrolysis of ketone adducts, (2) has not been accompanied by a similar effort to determine isotope effects on corresponding carbonyl addition equilibria (3). Equilibrium isotope effects serve as an important point of reference for kinetic isotope effects studies (3c). The latter are easier to carry out. Results can be obtained with greater precision,

and, for the most part, that has been where the attention has been focused.

In the course of our studies of isotope effects in the Baeyer-Villiger reaction, (4) it became necessary to model the isotope effect on the preequilibrium step. This meant determining an equilibrium isotope effect for an appropriate reaction involving nucleophilic addition to a ketone. Since we were concerned with an oxygen nucleophile, hemiketal or ketal formation seemed appropriate. In our original communication (4) we reported application of the method of Jones and Bender (3a) to obtain the isotope effect for hemiketal formation in phenyl-2-pro-

 $^{^{1}}$ The experimental results in this paper are taken from the Ph.D. Thesis of V.A.S.

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panone (phenylacetone). In this approach, the ketone, in methanol-dioxane, is treated with an acid catalyst and the equilibrium concentrations of all species are inferred from the decrease in carbonyl absorbance. This approach is unsatisfying, not only because of scatter in the data, and not only because the data unexpectedly required extrapolation of equilibrium constants to zero ketone concentration, but also because the spectroscopic technique does not guarantee that one is looking only at hemiketal formation.

Lamaty and co-workers have published extensive studies of kinetic isotope effects in the addition of nucleophiles to ketones (1c, 1d, 3). Among the nucleophiles studied is bisulfite (3b). Here secondary deuterium isotope effects on the kinetics of dissociation of the bisulfite addition complex were measured. $K_{\rm H}/K_{\rm D}$ has been measured in this system and $k_{\rm H}/k_{\rm D}$ for formation of the complex calculated from these data.

Isotope effects on equilibria of addition to aldehydes have recently been reported (3c). These isotope effects derive from substitution of deuterium for the aldehyde proton, and are properly referred to as α -isotope effects. Our concern is the perturbation of ketone-addition equilibrium constants by deuterium and tritium substitution at carbons adjacent to the carbonyl. These are called β -isotope effects. These β -isotope effects are related to β -isotope effects in solvolysis reactions (5, Chapt. 2, 6).

From the work of Lamaty and co-workers (3b) and of Bender and co-worker (3a) it is clear that nucleophilic addition to carbonyls gives rise to inverse β -deuterium isotope effects, $K_{\rm H}/K_{\rm D}$ < 1. The magnitude of these isotope effects (i.e. the degree to which $K_{\rm H}/K_{\rm D}$ differs from 1.0) is significantly greater than kinetic isotope effects for addition to carbonyls (1, 3c). Much more is known about the variation of $k_{\rm H}/k_{\rm D}$ with changes in ketone and nucleophile structure than about $K_{\rm H}/K_{\rm D}$. To understand kinetic isotope effects sufficiently to use them for inferring the position of the transition state along the reaction coordinate, corresponding values for $k_{\rm H}/k_{\rm D}$ and $K_{\rm H}/K_{\rm D}$ must be obtained. Lamaty has accomplished this for bisulfite additions to ketones (3b)

We have turned to an n.m.r. method to determine isotope effects in ketone-ketal equilibria in an unambiguous manner. What we wished to obtain was the ratio of equilibrium constants for reactions 1 and 2 under conditions in which hemiketal formation would be unimportant and the concentrations of all species at equilibrium could be monitored.

$$[1] \quad \text{RCH}_2\text{CCH}_2\text{R}' + 2\text{CH}_3\text{OH}$$

$$[1] \quad \text{RCH}_2\text{CCH}_2\text{R}' + 2\text{CH}_3\text{OH}$$

$$\overset{\text{CH}_3\text{O}}{\underset{\text{$\overset{K_H}{=}$}}{\overset{\text{CH}_2\text{CCH}_2\text{R}' + H_2\text{O}$}}$$

$$[2] \quad \text{RCX}_2\text{CCX}'_2\text{R}' + 2\text{CH}_3\text{OH} \rightleftharpoons$$

$$C\text{H}_3\text{O} \quad \text{OCH}_3$$

$$\text{RCX}_2\text{CCX}'_2\text{R}' + H_2\text{O}$$

$$X, X' = \text{H,D} \quad \text{R,R}' = \text{H,Ph}$$

We recognized (5, p. 97) that the equilibrium constant for reaction 3 was equal to the isotope effect on reactions 1 and 2, $K_3 = K_H/K_D$. The isotope effect could be obtained by mixing solutions of the deuterated ketone and undeuterated ketal, effecting equilibrium by addition of an acid catalyst, and observing all species by n.m.r.

CH₃O OCH₃ O

$$\begin{array}{c} & \parallel & K_3 \\ \hline \\ [3] & RCX_2CCX'_2R' + RCH_2CCH_2R' \rightleftharpoons \\ & O \\ & &$$

In this paper we report application of this method to determine $K_{\rm H}/K_{\rm D}$ for acetone dimethyl ketal formation, and for formation of both dimethyl and ethylene glycol ketals of three specifically-deuterated phenylacetones. A modified approach allowed us to measure $K_{\rm H}/K_{\rm T}$, by scintillation counting, for formation of the ethylene glycol ketal of tritiated dibenzyl ketone.

Results

Most reactions were carried out in dry methylene chloride solution. Reactions of acetone were also examined in 1,1,2,2-tetrachloroethane (sym-TCE). $BF_3 \cdot Et_2O$ was used as the acid catalyst. For the reactions discussed here, equilibrium was achieved in 2–10 h at room temperature (22 ± 1 °C), although reactions in some cases were examined up to 48 h after adding catalyst. The catalyst could be quenched by removing solvent and catalyst at reduced pressure. Monitoring the n.m.r. intermittently after several hours gave identical results. For tritiated

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dibenzyl ketone, the approach to equilibrium could not be followed by n.m.r. Instead, the reaction was examined at successive reaction times until $K_{\rm H}/K_{\rm D}$ became constant.

Proton-deuterium and proton-tritium exchange was a constant source of concern. The methylene position in phenyl acetone and dibenzyl ketone exchanges readily in base, more slowly in acid. Strict controls were run in which deuterated, partially deuterated, and tritiated ketones were exposed to the reaction conditions and then examined by n.m.r. and mass spectrometry. No exchange was detectable under these reaction conditions. In addition, all ketals were unchanged when exposed to the reaction conditions.

One technique was used to measure the isotope effects in the phenylacetone and acetone systems. In these series of experiments, the equilibrium isotope effect is given by Eq. 4.

$$[4] \quad \frac{K_{\rm H}}{K_{\rm D}} = K_3 = \frac{[\text{ketone} - d_x]_{\rm eq}[\text{ketal} - d_0]_{\rm eq}}{[\text{ketone} - d_0]_{\rm eq}[\text{ketal} - d_x]_{\rm eq}}$$

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(i) For phenylacetone, values of $K_{\rm H}/K_{\rm D}$ were determined both for dimethyl ketal formation and for ethylene ketal formation. These were obtained for each of the three deuterated species $PhCD_2COCH_3(d_2)$, $PhCH_2COCD_3(d_3)$, and Ph- $CD_2COCD_3(d_5)$. Mixtures of the deuterated ketones and undeuterated ketals were dissolved in dry methylene chloride. BF₃ · Et₂O in dry methylene chloride was added as a catalyst. The reaction was monitored by n.m.r. Once equilibrium was established, the solvent and catalyst were distilled off at room temperature. The relative concentrations of the deuterated and nondeuterated species were calculated from the n.m.r. spectrum and substituted into Eq. 4 to yield $K_{\rm H}/K_{\rm D}$.

[5] $PhCH_{2}COCH_{3} + PhCX_{2}CCX'_{3} \rightleftharpoons$ $CH_{3}O OCH_{3} \Leftrightarrow$ $CH_{3}O OCH_{3} + PhCX_{2}COX'_{3}$

6]
$$PhCH_2COCH_3 + PhCX_2CCX'_3 \rightleftharpoons$$

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 $PhCH_2CCH_3 + PhCX_2COCX'_3$

For the equilibrium mixtures in Eqs. 5 and 6 the equilibrium constants could be obtained by direct manipulation of the various n.m.r. intensities. The protons labelled by a, b, c, d, e and the phenyl hydrogens p in Eq. 5 all show discrete and resolved signals (see Table 1). The integrals for each signal were normalized by dividing the integral by the number of hydrogens contributing to the signal. These normalized values I_x were taken to be representative of the concentration of the species x in the mixture (Eqs. 7– 14). Eq. 16 gives the equilibrium isotope effect for both d_3 and for d_5 , while Eq. 17 allows $K_{\rm H}/K_{\rm D}$ to be obtained for d_2 and d_5 .

[7] Total [ketal]_{eq} $\propto I_e$

[8] [ketal
$$-d_0$$
]_{eq} $\propto I_c$ or I_d

[9] [ketal $-d_x$]_{eq} $\propto (I_e - I_c)$ or $(I_e - I_d)$

[10]
$$\frac{[\text{ketal} - d_0]_{eq}}{[\text{ketal} - d_x]_{eq}} = \frac{I_c}{I_e - I_c} \text{ or } \frac{I_d}{I_e - I_d}$$

[11] Total ([ketal]_{eq} + [ketone]_{eq})
$$\propto I_p$$

- [12] Total [ketone]_{eq} $\propto (I_p I_e)$
- [13] [ketone $-d_0$]_{eq} $\propto (I_a \text{ or } I_b)$
- [14] [ketone $-d_x$]_{eq} $\propto I_p (I_e + I_a)$ or $I_p - (I_e + I_b)$

 TABLE 1.
 Nuclear magnetic resonance shifts for the compounds in the ketal-ketone equilibrium mixtures

Compound	δ(p.p.m.) ^a
PhCH ₂ COCH ₃	a 3.55 b 2.00
СН₃О ОСн҃́₃ РhCH₂CCH₃	c 2.80 d 1.00 e 3.15
O Of $gPhCH2CCH3$	f 2.80 g 1.15 h 3.65
CH ₃ COCH ₃	i 2.10
CH ₃ O OCH ₃ CH ₃ CCH ₃	j 1.20 k 3.10

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$$[15] \quad \frac{[\text{ketone} - d_x]_{eq}}{[\text{ketone} - d_0]_{eq}} = \frac{I_p - (I_e + I_a)}{I_a}$$

or $\frac{I_p - (I_e + I_b)}{I_b}$
$$[16] \quad \left(\frac{K_H}{K_D}\right) = \left(\frac{I_p - (I_e + I_b)}{I_b}\right) \left(\frac{I_a}{I_e - I_a}\right)$$

for d_3 and d_5

$$[17] \quad \left(\frac{K_{\rm H}}{K_{\rm D}}\right) = \left(\frac{I_p - (I_e + I_a)}{I_a}\right) \left(\frac{I_c}{I_e - I_c}\right)$$
for d_2 and d_5

For the ethylene ketals in reaction 6, the

	CH ₃ O OCH ₃		
[18]	$CD_{3}COCD_{3} + CH_{3}CCH_{3}$	≑	
Initially:	[<i>a</i>] [<i>b</i>]		
At equilibrium:	$[a-x] \qquad [b-x]$,	

[19]
$$\frac{K_{\rm H}}{K_{\rm D}} = \frac{[a - x][b - x]}{[c + x][x]}$$

The relative ketal concentrations can be calculated (Eqs. 20-23) from the n.m.r. spectrum as before. Equation 23 can be solved for x and this value, along with the known concentrations [a], [b], [c], can be substituted into Eq. 19. The concentration [c] derives from a small and unavoidable amount of acetone in the freshly distilled 2,2-dimethoxypropane.

- [20] Total [ketal]_{eq} $\propto I_k$
- [21] [ketal $-d_0$]_{eq} $\propto I_j$

[22] [ketal
$$-d_x$$
]_{eq} $\propto (I_k - I_j)$

$$\begin{bmatrix} 23 \end{bmatrix} \quad \frac{[\text{ketal} - d_0]}{[\text{ketal} - d_x]} = \frac{[b - x]}{[x]} = \frac{I_j}{I_k - I_j}$$

(*iii*) The equilibrium with dibenzyl ketone could not be monitored by n.m.r. Furthermore, once equilibrium was achieved and the catalyst removed under vacuum, problems arose in attempts to separate and purify ketone and ketal. The most serious problem was that chromatography of the ketone on Florisil, alumina, or silica gel resulted in loss of radiolabel. Control experiments indicated that dibenzyl ketone could be methylene signals a overlapped part of the ketal signals h. We were able to correct for the appropriate intensity of h and obtain I_a by difference. The equilibrium constants for reaction 6 are described by equations identical to 16 and 17 with I_h substituted for I_e , and I_f and I_g substituted respectively for I_c and I_d .

(*ii*) A small modification of this method was necessary for calculation of $K_{\rm H}/K_{\rm D}$ for equilibria involving acetone. There is no way of obtaining, from the n.m.r. spectrum of the equilibrium mixture, the relative concentrations of the deuterated and non-deuterated acetone present. If the system is depicted by Eq. 18, $K_{\rm H}/K_{\rm D}$ is given by Eq. 19.

₹	CH ₃ O OCH CD ₃ CCD ₃ +	³ - CH ₃ COCH ₃	·
	0.	[c]	
,	[x]	[c + x]	

reduced to 1,3-diphenyl-2-propanol with lithium aluminum hydride in ether at -78 °C, without loss of molar activity, M.

[24]
$$PhCH_2^*CCH_2Ph + PhCH_2CCH_2Ph \Rightarrow$$

 $PhCH_2^*CCH_2Ph + PhCH_2CCH_2Ph \Rightarrow$
 $PhCH_2^*CCH_2Ph + PhCH_2CCH_2Ph$
[25] $\frac{K_H}{K} = \frac{M_{ketone}}{K}$

KΤ

M_{ketal}

The equilibrium mixture of ketone and ketal in ether was treated with lithium aluminum hydride at -78 °C. The product diphenylpropanol and unreacted ketal were chromatographed on activity II alumina using methanol-hexane as the eluting solvents. Radioactivities of the purified compounds were measured by scintillation counting. Absolute molar activities were not calculated. The a.e.s. (automatic external standardization) ratios of the ketal, ketone, and alcohol were found to be identical. Relative molar activities were obtained; $M_{\rm alcohol}$ was substituted for $M_{\rm ketone}$; and $K_{\rm H}/K_{\rm T}$ was obtained from Eq. 25.

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System	Ketone	Isotopic purity (%)	Ketal	$K_{\rm H}/K_{\rm D}{}^{a,b,c}$
1.	PhCD ₂ COCD ₃	96.8	PhCH ₂ C(OCH ₃) ₂ CH ₃	0.63 ± 0.02
2.	PhCD ₂ COCD ₃	96.8	PhCH ₂ CCH ₃	0.60 ± 0.02
3.	PhCD ₂ COCH ₃	85.6	PhCH ₂ C(OCH ₃) ₂ CH ₃	0.85 ± 0.03
	Ala ang ang ang ang ang ang ang ang ang an	· · · ·		. <u>.</u> ·
4.	PhCD ₂ COCH ₃	85.6	PhCH ₂ CCH ₃	0.82 ± 0.03
5.	PhCH ₂ COCD ₃	90.5	PhCH ₂ (OCH ₃) ₂ CH ₃	0.74 ± 0.05^{d}
6.	PhCH ₂ COCD ₃	90.5	PhCH ₂ CCH ₃	0.75±0.04
	• • •			
7.	PhCH ₂ *COCH ₂ Ph		PhCH ₂ CCH ₂ Ph	0.67±0.02 ^e
8.	CD ₃ COCD ₃	97.0	CH ₃ C(OCH ₃) ₂ CH ₃	0.72±0.05 0.70±0.03 ^r

TABLE 2 Equilibrium isotope effects

"All values of $K_{\rm H}/K_{\rm D}$ were calculated from the n.m.r. spectra of equilibrium mixtures. These values are the averages of five experiments.

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bin methylene chloride solution using $BF_3 \cdot Et_2O$ as the catalyst. Corrected to 100% isotopic abundance. Calculated from $(K_H/K_D)a_3 = (K_H/K_D)a_5/(K_H/K_D)a_2 = SYSTEM 1/SYSTEM 3.$ K_H/K_T , calculated from scintillation counting experiments. In sym-tetrachloroethane solvent using $BF_3 \cdot Et_2O$ as a catalyst.

The extraordinary magnitude of the isotope effect in reaction 24 suggested special care in examining the validity of our experimental method. Since $K_{\rm H}/K_{\rm T}$ is inverse, we were concerned that the number we obtained might be artificially too small. Two factors convince us that this is not the case. First, lithium aluminum hydride reduction of the ketone, followed by chromatography of the alcohol and distillation, gave diphenylpropanol with the same molar activity as that of the starting ketone. Second, the molar activity of the ketal plus that of the diphenylpropanol equalled that of the starting ketone. These controls demand that artifacts in $K_{\rm H}/K_{\rm T}$ be less than one percent.

Discussion

Calculated equilibrium isotope effects are presented in Table 2. In each case, the isotope effects are strongly inverse, $K_{\rm H}/K_{\rm D}$ < 1.0. Inverse β-deuterium isotope effects in carbonyl addition reactions are associated with decrease in the positive charge on the carbonyl carbon in rehybridization from sp^2 to sp^3 (3, 5, 6). The relationship between the magnitude of the β -deuterium isotope effect and the amount of positive charge at the adjacent carbon is well demonstrated by three examples taken from the literature. Protonation of acetophenone (7), (Eq. 26), occurs with a large isotope effect. Solvolysis of acetyl chloride (1e), (Eq. 27), in 10% and 20% aqueous acetone has a kinetic *B*-isotope effect in the opposite direction to that of the base catalysed hydrolysis of acetate esters (1e). The β isotope effect is a useful probe of charge development at an adjacent center. This makes it particularly useful for studies of solvolysis reactions (8). Other factors, however, are involved.



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[27]
$$CL_{3}CCI \rightarrow [CL_{3}C \equiv 0] \rightarrow CL_{3}CO_{2}H$$

10% H₂O-acetone $k_{H}/k_{D} = 1.62$
0 $-O$ OH
[28] $CL_{3}COC_{2}H_{5} + OH^{-} \rightarrow [CL_{3}COC_{2}H_{5}] \rightarrow$
 $k_{H}/k_{D} = 0.90$

Isotope effects arise from changes in zeropoint energies for C—H and C—D vibrational modes in going from reactants to the transition state $(k_{\rm H}/k_{\rm D})$ or products $(K_{\rm H}/K_{\rm D})$. These changes derive from changes in force constants for the respective modes, which in turn are determined by the shapes of the potential energy wells associated with the C—H bonds at which attention is focused (ref. 5, Chapt. 4 and p. 138). Steeper wells give rise to larger force constants, with greater separation of C—H and C—D zeropoint energies.

Isotopic substitution does not affect the shape of the electronic energy surface. The origin of secondary hydrogen isotope effects is purely vibrational. An explanation of the magnitude of isotope effects observed in an experiment must be couched in terms of the effect (steric, electronic) of the rest of the molecule on the C—H and C—D vibrations (ref. 5, Chapt. 4 and p. 138, and ref. 9).

V. J. Shiner has pointed out (ref. 5, p. 97) that there are two major contributors to β -isotope effects; the extent of nuclear attachment at the reactive carbon and the internal electronic distribution. The latter factor is sensitive to the dihedral angle between the β C—H or C—D bond and a p orbital at the electron deficient carbon. The charge induces a dipole into those adjacent C—H bonds with proper overlap. The C—H potential energy well is broadened, giving rise to weaker force constants, larger vibrational amplitudes, and decreased separation of C—H and C—D zero-point energies (ref. 5 Chapt. 4 and p. 138).

While the word 'hyperconjugation' is properly used to describe these dipole-induced dipole interactions, explanations which cite the greater polarizability of C—H bonds adjacent to a charge as the source of the β -isotope effect, focus on the wrong part of the potential energy surface. Hyperconjugation is a word commonly used. Keeping in mind its proper focus, we have found both the concept and the word convenient. In these terms, the major contributor to the inverse isotope effects presented in Table 2 is the loss of hyperconjugative delocalization when the ketones react to form ketals. The most compelling evidence for this point of view is the nearly identical isotope effects observed for both dimethyl ketal and ethylene glycol ketal formation from the three different deuterated phenyl-2propanones. Small changes in ketal structure apparently do not perturb the equilibrium isotope effects.

In the phenyl-2-propanones, the β -isotope effects are cumulative. For ethylene glycol ketal formation $K_{\rm H}/K_{\rm D}$ for $d_2 = 0.82$, $K_{\rm H}/K_{\rm D}$ for $d_3 = 0.75$, and their product (0.75)(0.82) = 0.615. This value compares favorably with the value 0.60 ± 0.02 measured for d_5 . Cumulative kinetic isotope effects were observed for these three ketones in their Baeyer-Villiger oxidation (4). Both results imply that PhCD₂— and CD₃— make the same contribution to the isotope effect in d_5 and in d_2 and d_3 , respectively.

From the tritium isotope effect $K_{\rm H}/K_{\rm T}$ for dibenzyl ketone, one can calculate from the Swain-Schaad equation, [29], (10) the corresponding isotope effect associated with a single deuterium. For dibenzyl ketone we calculate $K_{\rm H}/K_{\rm D} = 0.76$

[29]
$$\frac{K_{\rm H}}{K_{\rm D}} = \left[\frac{K_{\rm H}}{K_{\rm T}}\right]^{0.693}$$

The isotope effect for dimethyl ketal formation in acetone is significantly smaller than that for phenylacetone. On a per-deuterium basis, these differences become even more striking (see below).

In Table 3, our experimental results are presented in terms of the secondary β -isotope effect per deuterium. It is customary to present these results as $\Delta\Delta G/n$ values, where $\Delta\Delta G^0$ and $\Delta\Delta G^{\pm}$ are, respectively the change in standard free energy or activation free energy, in cal/mol, for substituting *n* hydrogens with deuteriums. Before commenting on the implications of the data, we ask the reader to note that small changes in $K_{\rm H}/K_{\rm D}$ per D lead to large changes in $\Delta\Delta G/n$, and that the $K_{\rm H}/K_{\rm D}$ values from which the $\Delta\Delta G^0/n$ values are calculated, for all examples in Table 3, are known only to about ± 0.01 .

One obvious and important conclusion from the data in Table 3 is that deuterium substitution at CH_2 and CH_3 in phenylacetone contributes equally to the observed isotope effect.

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STOUTE AND WINNIK: 6-HYDROGEN ISOTOPE EFFECTS

TABLE 3. Equilibrium and kinetic isotope effects on ketone-addition reactions

	Ketal	$\Delta\Delta G^{\circ}/n$		$\Delta\Delta G^{+}/n$			
Ketone	$K_{\rm H}/K_{\rm D}$ per D	Ketal	Hemiketal	Bisulfite	BH4 ^b	HSO ₃ ^{- a}	NH₂OH ^c
CH ₃ COCH ₃	0.95 ⁴ 0.94 ¹	32 ± 2 35 ± 4	26±5 [,]	26	3.6	9	8
PhCH ₂ COCH ₃	0.91 ^d 0.90 ^e	55 <u>+</u> 4 60 <u>+</u> 4	46 ± 10 ^g	28	÷ . • .	14	21
PhCH ₂ COCH ₃	0.92 ⁴ 0.91°	48 ± 10 55 ± 10	42±10 ^g		· .		
PhCH ₂ COCH ₃	0.90 ^d 0.91 ^e	60±13 55±11	47 ± 15 ^g	· . ·			and and a second se
Ph <i>CH</i> ₂COCH₂Ph	0.76*	160 ± 15	• •	a 17			34
Cyclopentanone			54 ^{,f}	58	•	33	25
1						1	

^aData from ref. 3b. ^bData from ref. 1c. ^cData from ref. 1d. ^dMethyl ketal formation.

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This result is somewhat surprising (3b). It is often found that β -isotope effects, per deuterium, are larger for methylene than for methyl (11). Note as an example the $\Delta \Delta G^0/n$ values for acetone and cyclopentanone hemiketal formation in Table 3, taken from experiments by Jones and Bender (3a). This empirical generalization does not yet have a sound theoretical basis. The observations probably reflect the effects of structural modification on either the C-H vibrational force constants or the preferred conformations of the molecule. The number of hydrogens adjacent to the reaction center, per se, may not be important.

A more difficult challenge is to understand how structural changes give rise to changes in $\Delta\Delta G^0/n$. For example $\Delta\Delta G^0/n$ nearly doubles for methyl ketal formation from 32 cal/mol in acetone to 55 cal/mol in phenylacetone. The same trend is seen in methyl hemiketal formation, with cyclopentanone having as large an effect as phenylacetone. Bisulfite addition is rather peculiar in that $\Delta\Delta G^0/n$ follows hemiketal formation for acetone and cyclopentanone, but is significantly smaller than for those reactions of phenylacetone (3b).

A complete normal coordinate analysis for proto- and deuteroketones, ketals, and bisulfite addition products is central to a complete understanding of these isotope effects. In its ab-

sence we can only speculate on the source of the isotope effects.

The larger isotope effect in cyclopentanone than acetone is probably related to the ketone conformations in solution. The most favorable



conformation of cyclopentanone is the halfchair form, which minimizes hydrogen eclipsing interactions (12). The pseudoaxial protons adjacent to the carbonyl overlap well with the ketone C=O p-orbital. Not only is this hyperconjugation lost on formation of a tetrahedral product, but there is significant increase in hydrogeneclipsing interactions. If these interactions narrow the energy well in those cross-sections of the potential energy surface describing the C-H bonds on the β carbon, the isotope effect will increase over that in acetone, almost irrespective of the reacting nucleophile.

In tetrahedral phenylacetone addition prod-

ucts, coupling of the carbon-nucleophile vibrational modes with the β C—H modes must be important. The bisulfite adduct, with its relatively long C-S bond, contributes less to the isotope effect than does the shorter C-O bond in the ketal and hemiketal. Similar trends appear in kinetic isotope effects determined by Lamaty (3b) (cf. Table 3). A significantly smaller kinetic isotope effect is observed in the addition of bisulfite to phenylacetone when compared to hydroxylamine. These differences are not apparent for the addition of those nucleophiles to acetone and cyclopentanone. Comparison of the kinetic and equilibrium isotope effects give some indication of what fraction of the carbonyl character is lost in the transition state for nucleophilic addition.

The β -isotope effect of extraordinary magnitude is that for ketal formation in dibenzyl ketone. It is our belief that such a large isotope effect must reflect a preferred conformation in the ketone giving rise to a strong hyperconjugative interaction between the ketone and the β-hydrogens. In addition, steric crowding in the tetrahedral product must seriously perturb its C-H bending or stretching modes.³ A comparison of phenylacetone and dibenzyl ketone is shown. Differences in ketone conformations and the energetics of ketal formation result primarily from phenyl-phenyl interactions in the latter. Space-filling molecular models suggest that the preferred conformation of dibenzyl ketone has a C-H bond parallel to the C=O π -bond. Phenylacetone has a slightly different geometry of lowest energy.





In phenylacetone, as in most α -CH₂ ketones, the preferred geometry has a CH bond eclipsing C=O. This allows a staggered geometry between α -substituents of the ketone. Phenyl-phenyl repulsion is rather severe in dibenzyl ketone. Increasing the dihedral angle between these staggered substituents increases the overlap between one C-H bond and the C=O π -bond. In no way does it appear possible for two C-H bonds simultaneously to achieve such overlap.

In the corresponding ketals, 1-3 steric interactions appear to dominate conformational preferences. These are difficult to assess. In conformation 4 there are obvious destabilizing steric interactions involving the hydrogens at which the isotope effect is probed. There is no doubt, however, that the ketal derived from dibenzyl ketone is significantly more crowded than that derived from phenylacetone. With the increase in isotope effects paralleling the increasing difficulty (primarily steric) in forming tetrahedral addition products from ketones, (13), it is likely that these steric factors are in part responsible for the size of the β -deuterium isotope effect.

Experimental

Acetone-d₆ was purchased from Merck, Sharp, and Dohme. Specifically deuterated phenyl-2-propanones were prepared and purified by methods we reported previously (14). Methylene chloride was distilled fresh from phosphorus pentoxide. Sym-tetrachloroethane was washed with concentrated sulfuric acid, followed by aqueous sodium carbonate. BF3 · Et2O was freshly distilled. Nuclear magnetic resonance spectra were run on a Varian T-60 spectrometer. Peak areas were determined by repetitive integration. The details of the n.m.r. method and typical correlation coefficients have been reported (15). Scintillation counting in toluene-Omnifluor was carried out in a Packard-Tri-Carb liquid scintillation spectrometer, model 3375. Counting data were recorded by teletype. Sample counts per minute normally had standard deviations of 0.1%. Those with deviations greater than 0.2 were discarded. An automatic external standardization (a.e.s.) feature allowed a.e.s. ratios to be measured. These give an indication of the counting efficiency of each sample.

1,3-Diphenyl-2-propanone-1-t

A solution of 32.5 g (0.15 mol) of 1,3-diphenyl-2-propanone (J. T. Baker, recrystallized from petroleum ether 30-60 °C) in 50 ml of pyridine was prepared. To this was added a mixture of 1.5 ml tritiated water (New England Nuclear Co., 1 mCi/ml) and 15 ml distilled deionized water. The reaction mixture was refluxed for 10 h. The pyridine and water were distilled off, and the ketone was twice recrystallized from petroleum ether, m.p. 33-34 °C. The sample activity was 2.1 \times 10° c.p.m./mol.

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2,2-Dibenzyl-1,3-dioxolan (Dibenzyl Ketone Ethylene Ketal)

Dibenzyl ketone (10.5 g, 0.050 mol) was refluxed with ethylene glycol (0.049 mol) in toluene using 0.5 g *p*toluenesulfonic acid as a catalyst. Water was removed via a Dean-Stark trap. After 5 h, the catalyst was quenched with powdered anhydrous potassium carbonate. After filtering, the solution was concentrated and then chromatographed on a column of activity II alumina. Hexane was used as the eluting solvent. Concentration of the hexane gave white crystals, m.p. 36-37 °C free of detectable traces of ketone. The overall yield was 88%.

2-Phenyl-2-methyl-1,3-dioxolan (Phenylacetone Ethylene Ketal)

An identical procedure gave the ketal as a liquid, which was distilled at 90 °C (pot temperature)/0.2 Torr through a 10 in. Vigreux column. The yield of product was 75%; however, it contained 5.5% phenylacetone by n.m.r. as the sole impurity. Further purification was unnecessary, as our analytical technique allowed us to monitor concentrations of all species at equilibrium.

1-Phenyl-2,2-dimethoxypropane (Phenylacetone Dimethyl Ketal)

Phenylacetone (2.08 g, 15.5 mmol) in 60 ml anhydrous methanol (distilled from magnesium) was treated with 10 ml 2,2-dimethoxypropane and 80 mg bis(*p*-nitrophenyl)phosphoric acid (Aldrich). After 15 min reflux, the acid was quenched with 10% aqueous sodium hydroxide. The solution was concentrated, taken up in hexane, washed with aqueous bicarbonate, dried with magnesium sulfate, and chromatographed on a 45 cm \times 1 cm Florisil column. Benzene (10%) in hexane was used as the eluant. The dimethyl ketal was collected as a colorless oil, rechromatographed on Florisil and distilled at 60°C (pot)/ 0.4 Torr. It was stored in a desiccator. The overall yield, 0.3 g, was poor, 11%, but the n.m.r. showed it to be free of ketone.

2,2-Dimethoxypropane (Aldrich) was fractionally distilled (82-83 °C) through a 10 in. Vigreux column. The compound decomposed in the g.l.c. on both DEGS and Carbowax columns. An n.m.r. analysis of the fraction used indicated that it contained 7.2% acetone. There was no detectable trace of methanol or other impurities in the n.m.r. spectrum. A suitable correction for this acetone impurity was applied to the calculation of isotope effects (see text).

Ketone-Ketal Equilibria

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In general, the catalytic solution of $BF_3 \cdot Et_2O$ (freshly distilled) in dry methylene chloride or *sym*-tetrachloroethane was prepared and a 0–5 ml aliquot of this was added to a pre-weighed mixture of the labelled ketone and unlabelled ketal.

(i) Acetone—Acetone- d_6 (150 mg, 2.58 mmol) and 2,2dimethoxypropane (210 mg, 2.0 mmol) were mixed together in 0.5 ml of solvent containing BF₃ Et₂O (0.05 mmol). In separate experiments methylene chloride or *sym*-tetrachloroethane was used as the solvent. The reaction was monitored by n.m.r. and spectra, recorded between 2–15 h after the addition of catalyst, were used to calculate values for $K_{\rm H}/K_{\rm D}$.

(ii) Phenylacetone-Mixtures of the ketone (0.75 mmol)

and the ketal (0.60 mmol) were stirred together in methylene chloride using $BF_3 \cdot Et_2O$ (0.05 mmol). The three deuterated species $PhCD_2COCD_3$, $PhCD_2COCH_3$, and $PhCH_2COCD_3$ were all examined in this way Mixtures of the d_5 and of the d_2 compounds with 2,2-dimethoxy phenylpropane and with phenylacetone ethylene ketal were studied. The d_3 species was equilibrated only with phenylacetone ethylene ketal. The solutions were concentrated at reduced pressure to remove solvent and catalyst. The n.m.r. spectra of these mixtures, recorded between 10–48 h after contact with the catalyst, were used to calculate values for K_H/K_D . (*iii*) Dibenzyl Ketone—Tritium labelled dibenzyl ke-

(iii) Dibenzyl Ketone—Tritium labelled dibenzyl ketone (0.75 mmol) and unlabelled dibenzyl ketone ethylene glycol ketal were dissolved in 0.5 ml dry methylene chloride, containing 0.010 mmol BF₃ \cdot Et₂O. The reaction mixture was stirred for 16 h. The methylene chloride and BF₃ \cdot Et₂O were removed at room temperature under reduced pressure. The solid residue was dissolved in 5 ml of dry ether and added dropwise to three molar equiv. of lithium aluminum hydride in 10 ml ether at -78 °C. The reactants were stirred ten minutes at -78 °C. The stirring was continued for 1 h as the contents of the reaction flask warmed to room temperature.

The reaction was quenched by slowly adding a saturated aqueous solution of sodium sulfate until a white powdery precipitate formed. After filtering, the ether solution was washed with 5 ml water followed by an equal volume of saturated sodium chloride solution. The concentrate was applied to a small (3 in. $\times \frac{1}{2}$ in.) column of activity II alumina. The ketal came off the column in hexane, whereas addition of methanol to the hexane was necessary to recover the 1,3-diphenyl-2-propanol. The ketal was crystallized, and the alcohol was molecularly distilled at 110 °C (pot)/0.2 Torr. Radioactivities of each were measured by scintillation counting.

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- (a) V. F. RAAEN, T. K. DUNHAM, D. D. THOMPSON, and C. J. COLLINS. J. AM. Chem. Soc. 85, 3497 (1963);
 (b) M. CHEREST, H. FELKIN, and C. FRAJERMAN. Tetrahedron Lett. 379 (1971); (c) P. GENESTE and G. LAMATY. Tetrahedron Lett., 4633 (1965); Bull. Soc. Chim. (Fr.), 669 (1968); (d) P. GENESTE, G. LAMATY, and J. P. ROQUE. Tetrahedron, 27, 5561 (1971); (e) M. L. BENDER and M. S. FENG. J. Am. Chem. Soc. 82, 6318 (1960).
- (a) V. J. SHINER, JR. and S. CROSS. J. Am. Chem. Soc. 79, 3599 (1957); (b) H. G. BULL, K. KOEHLER, T. C. PLETCHER, J. J. ORTIZ, and E. H. CORDES. J. Am. Chem. Soc. 93, 3002 (1971); (c) J. ARCHILA, H. BULL, C. LAGENAUR, and E. H. CORDES. J. Org. Chem. 36, 1345 (1971); (d) F. GUINOT and G. LAMATY. Tetrahedron Lett. 2569 (1972).
- (a) J. M. JONES and M. C. BENDER. J. Am. Chem. Soc. 82, 6322 (1960); (b) P. GENESTE, G. LAMATY, and J. P. ROQUE. Tetrahedron, 27, 5539 (1971); (c) L. DO AMARAL, H. G. BULL, and E. H. CORDES. J. Am. Chem. Soc. 94, 7579 (1972).

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- 4. M. A. WINNIK, V. A. STOUTE, and P. FITZGERALD. J. Am. Chem. Soc. 96, 1977 (1974).
- 5. C. J. COLLINS and M. S. BOWMAN. (Editors) Isotope effects in chemical reactions. Van Nostrand Reinhold, New York. 1970.
- S. E. SCHEPPELE. Chem. Rev. 72, 511 (1972); E. R. 6. THORNTON. Annu. Rev. Phys. Chem. 17, 349 (1966); E. A. HALEVI. Prog. Phys. Org. Chem. 1, 109 (1966); C. J. COLLINS. Adv. Phys. Org. Chem. 2, 1 (1964); L. MELANDER. Isotope effects on reaction rates. Ronald Press, New York. 1960. 7. E. M. ARNETT, T. COHEN, A. A. BOTHER-BY, and R.
- D. BUSHICK. Chem. Ind. (London) 473 (1961).
- 8 V. J. SHINER, JR. and W. DOWD. J. Am. Chem. Soc.
- 93, 1029 (1971), and references therein. 9. W. P. JENCKS. Catalysis in chemistry and enzymol-
- ogy. McGraw-Hill, New York. 1969. pp. 253 ff.

- 10. C. G. SWAIN, E. C. STIVERS, J. F. REUWER, JR., and L. J. SCHAAD. J. Am. Chem. Soc. 80, 5885 (1958).
- 11. V. J. SHINER, JR., B. L. MURR, and G. HEINEMANN. J. Am. Chem. Soc. 85, 2413 (1963); V. J. SHINER, JR. J. Am. Chem. Soc. 83, 240 (1961).
- 12. E. L. ELIEL. Stereochemistry of carbon compounds, McGraw-Hill, New York. 1962. pp. 250 ff.
- O. H. WHEELER. J. Am. Chem. Soc. 79, 4191 (1957); J. 13. W. BAKER. Tetrahedron, 5, 135 (1959); D. P. EVANS and J. R. YOUNG. J. Chem. Soc. 1310 (1954).
- 14. M. A. WINNIK. Synth. Commun. 3, 299 (1973).
- 15. M. A. WINNIK and V. A. STOUTE. Can. J. Chem. 51, 2788 (1973).
- V. A. STOUTE. Ph.D. Thesis, University of Toronto, 16. Toronto, Ontario. 1975.

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