Steric Origin of Some Secondary Isotope Effects of Deuterium[1a]

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The differential method (ref. 6) for determining isotope effects has now been extended to the acid-catalyzed reactions with 2,4-dinitrophenylhydrazine at 0° of several other carbon-14 labeled ketones. All carbonyl-labeled ketones investigated exhibited isotope effects (k^*/k) very close to 0.95. For the reaction of aceto-phenone-1-phenyl-C^{14}, $k^*/k = 1.0038 \pm 0.0003$. By using carbon-14 as a tracer for either hydrogen or deuterium, the differential method was also employed for determining isotope effects due to deuterium. The results for deuterium are discussed in terms of Jencks' mechanism (ref. 10) for carbonyl reactions and are explained on steric grounds.

Shiner,[2] Streitwieser,[3] Bartell,[4] and Halevi[5] have discussed possible origins of secondary isotope effects of deuterium and tritium. There appears to be general agreement[2,3] that hyperconjugation, induction, and steric properties can contribute, although the relative importance of each does not seem to have been established.[4,5] We now report our studies of secondary isotope effects of deuterium and also, incidentally, of carbon-14, in which we believe the hyperconjugative and inductive contributions have been minimized, thus allowing an evaluation of the magnitude of steric isotope effects caused by substitution of deuterium for hydrogen. The reactions studied were the formation, at 0°, of the 2,4-dinitrophenylhydrazones of various isotope position isomers of acetophenone, phenyl t-butyl ketone, and propiophenone. The deuterium-containing ketones whose isotope effects were determined with respect to the undeuterated species are shown in structures I–IV. The method used (the differential method) has been previously employed in

$$\text{CH}_3$$
$$|$$
PhCOCD₃   PhCOC—CD₃   PhCOCD₂CH₃   PhCOCH₂CD₃
$$|$$
$$\text{CD}_3$$

I   II   III   IV
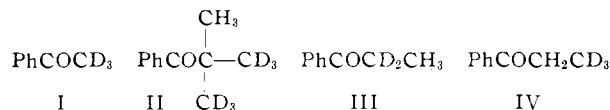
the establishment of an isotope effect (k^*/k) of 1.0085 ± 0.0004 in the formation of the 2,4-dinitrophenyl-hydrazone of acetophenone-β-C^{14}.[6] In determining the rate acceleration or deceleration caused by substitution of deuterium for hydrogen, known mixtures of deuterated and undeuterated species were prepared, one of which was always labeled with carbon-14, and the rate of change of carbon-14 content as a function of fraction of reaction was determined. The method requires that the isotope effects caused by the carbon-14 itself be known and these are determined in separate experiments. All reactants for study were purified on a preparation vapor-phase chromatograph.[7] The carbon-14-labeled materials were synthesized by standard methods.[8]

The data for each run were fitted to eq. 1 by means of a nonlinear least-squares code.[9] All experimental

$$A = A_0 (k^*/k)(1 - f)^{(k^*/k - 1)} \qquad (1)$$

A = molar radioactivity of each small sample at fraction f of reaction
A_0 = molar radioactivity of reactant at $f = 0$
k^*/k = ratio of specific rate constants for reaction of labeled and unlabeled molecules, respectively.

results are given in Table I. In order to obtain the isotope effect values (k_D/k_H) due only to the substituton of deuterium for hydrogen appropriate ratios from the third column of Table I were used. Thus, the isotope effect in the derivatization of trideuterioacetophenone

TABLE I

EXPERIMENTALLY DETERMINED VALUES OF THE ISOTOPE EFFECT IN CONVERSION OF KETONES TO THEIR 2,4-DINITROPHENYL-HYDRAZONES

Run	Mixture	k^*/k[a]
1	PhCOCH₃*[b]	0.949 ± 0.002
2	PhCOCH₃*[b,c]	1.0085 ± .0004
3	PhCOCH₃*[b]	1.0038 ± .0003
4	PhCOCD₃*[b]	0.941 ± .001
5	PhCOCH₃/PhCOCD₃	.847 ± .003
6	PhCOCH₃/PhCOCD₃*	.915 ± .002
7	PhCOC*—CH₃[b] (CH₃)	.951 ± .001
8	PhCO*C—CH₃[b] (CH₃) (CH₃*)	1.0041 ± .0007[d] 1.0020 ± .0009[d] 1.0027 ± .0005[d]
9	PhCOC—CD₃:PhCOC—CH₃ (CD₃)(CH₃)	1.046 ± .0015
10	PhCOCH₂CH₃*[b]	0.943 ± .002
11	PhCOCD₂CH₃*[b]	0.943 ± .004
12	PhCOCD₂CH₃/PhCOCH₂CH₃*	1.060 ± .001
13	PhCOCH₂CD₃*[e]/PhCOCH₂CH₃	0.9952 ± .0006

[a] Ratio of specific rate constants for carbon-14-labeled (k^*) and unlabeled (k) species. These values are corrected for mole fraction of each species present. All reactions were carried out under conditions of proved irreversibility. [b] Only carbon-14-labeled and unlabeled species present. [c] Data of ref. 6. [d] Significance doubtful. [e] The insignificant contribution of the terminal carbon-14 has been neglected.

(1) (a) This paper is based upon work performed at Oak Ridge National Laboratory, which is operated by Union Carbide Corporation for the Atomic Energy Commission; (b) Oak Ridge Institute of Nuclear Studies Research Participant from Sweet Briar College in Sweet Briar, Va., October, 1960–April, 1961.

(2) V. J. Shiner, Tetrahedron, 5, 243 (1959); V. J. Shiner, et al., Ann. N. Y. Acad. Sci., 84, 583 (1960).

(3) A. Streitwieser, Jr., ibid., 84, 576 (1960).

(4) L. S. Bartell, Tetrahedron Letters, 13 (1960); J. Am. Chem. Soc., 83, 3567 (1961).

(5) E. A. Halevi, et al., J. Chem. Soc., 630 (1960), 394, 1967, 1974 (1959); Tetrahedron, 1, 174 (1957).

(6) V. F. Raaen, A. K. Tsiomis, and C. J. Collins, J. Am. Chem. Soc., 82, 5502 (1960).

(7) A Burrell Kromo-Tog Model K-1, fitted with a 0.5-in. column packed with Apiezon-L supported on Kromat-F-13, was used.

(8) See the Experimental section for details.

(9) We are indebted to Dr. M. H. Lietzke of this Laboratory for writing the code for use with the IBM 7090 computer. Equation 1 is the exponential form of the equation derived by A. M. Downes, Australian J. Sci. Research, 5A,

521 (1952). See also C. J. Collins and M. H. Lietzke, J. Am. Chem. Soc., 81, 5379 (1959). A least-squares fit to Downes' linear equation gave identical results with those reported in Table I. The error (σ) in k^*/k was obtained as

$$\sigma = \sqrt{\Sigma r^2/(n - 2)b_{11}}$$

Σr^2 = sum of squares of the residuals of fit
n = number of data points
b_{11} = 1,1-element of the matrix $(X^T X)^{-1}$, where X = the matrix of the partial derivatives with respect to the parameters
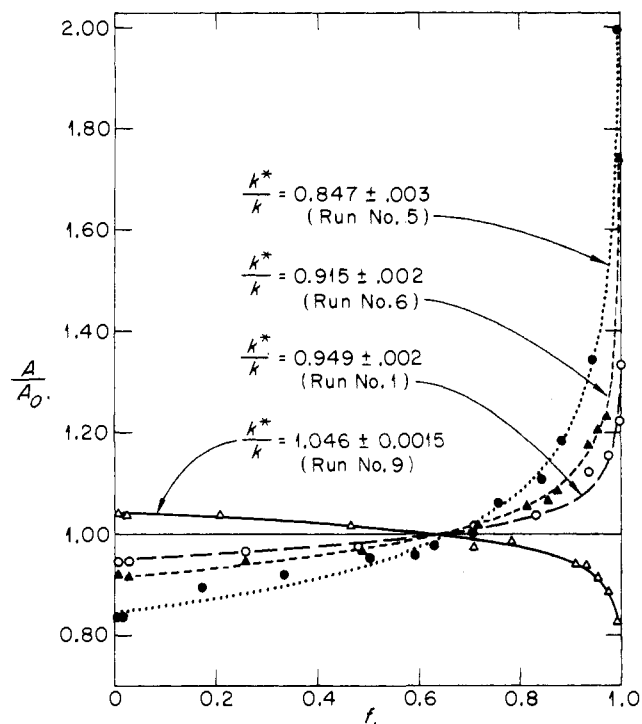
Fig. 1.—Differential plots for runs 1, 5, 6, and 9.

can be calculated by two completely separate and independent methods, the results being identical within $\pm 2\times$ the estimated error

$$\left(\frac{k_D}{k_H}\right)_1 = \frac{0.949 \pm 0.002}{0.847 \pm 0.003} = 1.119 \pm 0.005 \text{ (from runs 1 and 5,}$$
Table I)

$$= \frac{1.0085 \pm 0.0004}{0.915 \pm 0.002} = 1.104 \pm 0.002 \text{ (from runs 2 and 6'}$$
Table I)

The deuterium isotope effects (k_D/k_H) calculated from Table I are listed in Table II. The data for runs 1, 5, 6, and 9 are plotted in Fig. 1, and the data for runs 3 and 13 are given in Fig. 2. These plots are typical and demonstrate the value of the differential method. Figure 2 illustrates that even the very small isotope effects reported in Table I are meaningful.

TABLE II

Summary of k_D/k_H Isotope Effects in the Conversion of
Ketones I–IV to their 2,4-Dinitrophenylhydrazones

No.	Compound	k_D/k_H	Reference run (Table I)
1	PhCOCD₃ (I)	1.119 ± 0.005	1 and 5
2	PhCOCD₃ (I) CH₃	$1.104 \pm .002$	2 and 6
3	PhCOC—CD₃ (II) CD₃	$1.046 \pm .0015$	9
4	PhCOCD₂CH₃ (III)	$1.124 \pm .005$	10, 11, and 12
5	PhCOCH₂CD₃ (IV)	$0.9952 \pm .0006$	13

Given in Chart I is a scheme outlining some reactions which are probable during formation of the 2,4-dinitrophenylhydrazone of acetophenone.[10] In addition to these reactions, base attack on the free ketone and the repression of base concentration by hydrogen ion must also be considered.[10] From our data it is not possible to state with certainty which of these reactions is rate-determining under the conditions employed. The following facts, however, allow some empirical conclusions to be drawn. First, competitive experi-
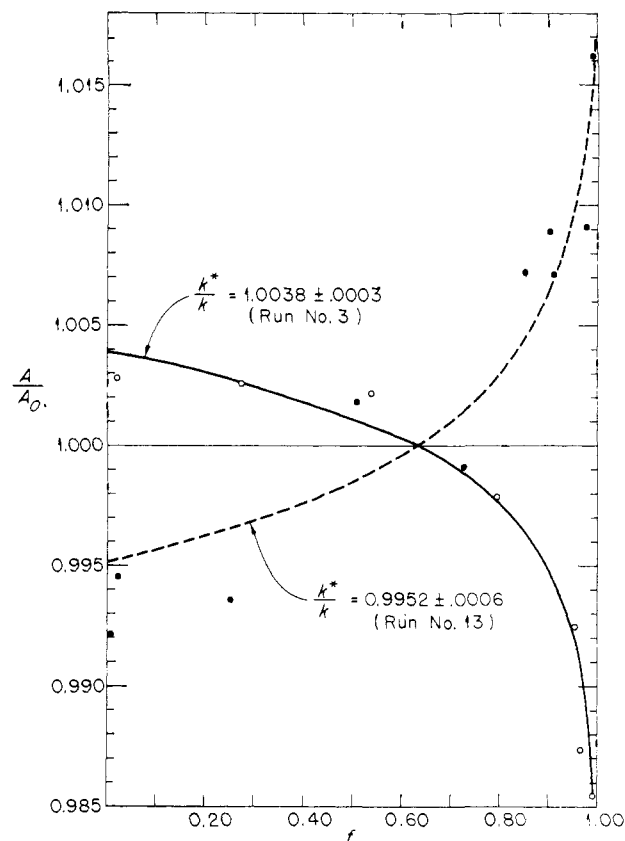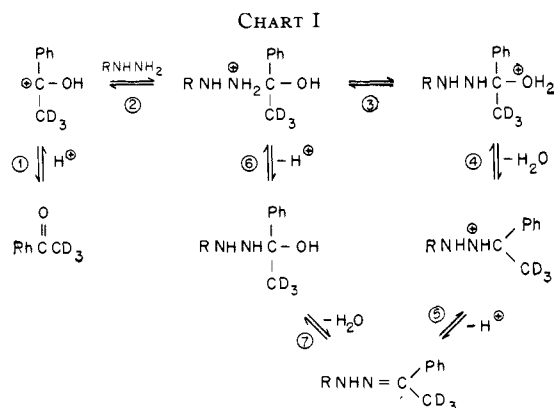
(10) W. P. Jencks, et al., J. Am. Chem. Soc., 81, 475 (1959); 82, 1773, 1778 (1960)

Fig. 2.—Differential plots for runs 3 and 13.

ments demonstrated that acetophenone forms its 2,4-dinitrophenylhydrazone about 20% more rapidly than m-nitroacetophenone, and at about one-half to one-third the rate at which p-methoxyacetophenone undergoes reaction. Secondly, it was also demonstrated that acetophenone reacts approximately two times faster than propiophenone and about forty times faster than phenyl t-butyl ketone. It thus seems an inescapable conclusion that steric factors are more important during these reactions than electron-donating or electron-withdrawing substituent effects. Thirdly, substitution of deuterium for hydrogen is said to favor inductive electron release[2,4,5] and to hinder hyperconjugative electron release.[2,3] Since both I and II react faster than their undeuterated partners, and since hydrogen hyperconjugation should be unimportant during the reaction of II, it appears that hydrogen hyperconjugation cannot be involved during reaction of I, provided we assume that the same factor is responsible, in both compounds, for the acceleration of rate. Finally, it is difficult to reconcile the result for compound IV with the other data of Table II on the basis of hyperconjugative or inductive effects. It is, of course, possible that severe structural changes can alter the mechanism by changing the rate-determining step, and this point needs further investigation. It has not yet been established also, whether there must be just one underlying cause for the isotope effects reported in runs 1–4 of Table II.

If we assume, however, that the isotope effects given in Table II have a common cause, and further that there is no change in mechanism with the structural changes in the reactants, then all of the results of Table II can be accommodated if the rate-determining step in these reactions is the attack by base on the conjugate acid of the ketone (step 2, Chart I). The increased rate owing to deuterium substitution (compounds I, II, and III) is then explained as a result of decreased steric

CHART I

Fig. 3.—Differential plot for determining rate differences between phenyl 2-propyl ketone-C¹⁴ and phenyl 2-propyl-2-d ketone.

crowding in the transition state for step 2. The lack of rate acceleration exhibited by ω-trideuteriopropiophenone (IV) could be a conformational effect, since there is no possible conformation which can be assumed by II in which a methyl group does not interfere with the entering group, whereas compound IV can assume two conformations which interfere no more than acetophenone itself.

We are unable to explain at this time the two, small, secondary isotope effects of carbon-14 (runs 2 and 3, Table I).

One further point is worthy of mention. A common procedure in determining isotope effects by the method of competing reactions involves the accumulation of the first 3 to 6% of reaction product, followed by a comparison of the isotopic content of the accumulated product with that of initial reactant.[11] We have noticed during several experiments that the first few per cent of reaction product often exhibit quite anomalous isotopic contents when compared with isotopic contents of small aliquots removed at intervals during the entire course of the reaction. One typical example is given in Fig. 3. These data indicate the possibility of serious error in the evaluation and interpretation of isotope effects which have been determined solely on the basis of the isotopic content of the initial fraction of reaction product. These errors are often quite duplicable even with reactants which have been prepared and purified separately,[12] and can be misleading not only with respect to the magnitude but also can indicate an incorrect *direction* of the isotope effect.

Experimental

Materials.—Ketones I and III were prepared through the base-catalyzed exchange between the parent ketones and D_2O. Ketone II (also labeled with carbon-14) was prepared from hexadeuterioacetone through reaction with methyl-C¹⁴-magnesium iodide to hexadeuterio-*tert*-butyl-(*methyl*-C¹⁴) alcohol, which was converted to the chloride. The *tert*-butyl chloride was diluted (11:1) with unlabeled *tert*-butyl chloride, and thence converted to the Grignard reagent whose reaction with benzo-

(11) See, for example, C. G. Swain and E. R. Thornton, *J. Org. Chem.*, **26**, 4808 (1961).

(12) Prof. J. F. Eastham of the University of Tennessee informs us that he has observed the same phenomenon during the application of the differential method to an evaluation of the S³²/S³⁵ isotope effect in the reaction of sulfur-35-labeled thiophenoxide ion with 2,4-dinitrochlorobenzene to yield phenyl dinitrophenyl thioether.
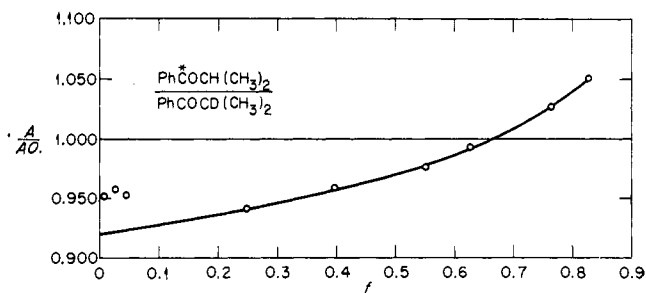
nitrile and the subsequent hydrolysis yielded II. Hexadeuterioacetone was prepared by the base-catalyzed exchange with D_2O. Ketone IV was obtained through the sequence: malonic acid (D_2O exchange) → malonic-d_4 acid → CD_2CO_2D (LiAlH₄) → CD_3CH_2OH → CD_3CH_2I (Grignard, CO_2, $SOCl_2$) → CD_3CH_2-$COCl$ → CD_3CH_2COPh. The deuterium contents of I and III were verified by means of n.m.r. spectra (less than 0.2% protium in the α-position) that of I was also confirmed by infrared spectra. The deuterium contents of II and IV were not measured directly, but those of appropriate precursors were determined from n.m.r. and infrared spectra. The possibility of loss of deuterium during unverified syntheses was ruled out by subsidiary experiments in which tritium was used as a tracer.

General Procedure.—A weighed quantity (usually 0.025 mole) of ketone was dissolved in 75 ml. of 95% ethyl alcohol in an Erlenmeyer flask. The solution was cooled to 0° in an ice bath before the addition of 2,4-dinitrophenylhydrazine reagent. The latter was prepared by adding sufficient 95% ethyl alcohol to 4.96 g. of 2,4-dinitrophenylhydrazine, 15 ml. of sulfuric acid, and 15 ml. of water to make 250.0 ml. of 0.1 N reagent. A 5-ml. aliquot of the reagent (sufficient for 2% reaction) was then added to the cooled, vigorously stirred (magnetically) ketone. Reaction was usually complete in a few minutes. The precipitate was then collected on a filter and was washed with a small amount of cold methanol. The combined filtrates were cooled to 0° before another 5-ml. aliquot of reagent was added. After three such isolations of products, a 50-ml. aliquot of reagent was cooled and added to the ketone. The precipitate was collected, and another 5-ml. aliquot of reagent was added alternating small and large amounts of reagent until about 90% reaction had occurred. Then 5-ml. aliquots were added until the reaction was complete. The dried precipitates were weighed to determine over-all yield, which varied from 95 to 99%.

Products from the large aliquot additions were discarded; the other fractions were recrystallized four times from chloroform–ethyl alcohol. Compounds were burned in a Pregl microcombustion apparatus similar to that described by Tolbert.[13] The labeled carbon dioxide was swept into an ion chamber for measurement on an electrometer.

Competitive Reactions.—The relative reaction rates of m-nitroacetophenone and p-methoxyacetophenone were determined by dissolving a mixture of these ketones in ethanol and adding an amount of 2,4-dinitrophenylhydrazone reagent insufficient to react with all of either ketone. The yield of each product was then determined by isotope-dilution analysis.

The relative reaction rates of acetophenone and propiophenone and of propiophenone and *tert*-butyl phenyl ketone were determined by adding sufficient 2,4-dinitrophenylhydrazine reagent to permit 50% reaction. Relative product yields were then determined by gas–liquid chromatography of the unreacted ketone fractions.

(13) B. M. Tolbert, Univ. Calif. Radiation Lab. Rept., U.C.R.L.-3499 (Aug., 1956).