[CONTRIBUTION FROM THE RICHARD B. WETHERILL LABORATORY OF PURDUE UNIVERSITY, LAFAYETTE, IND.]

The Rates of Reaction of Sodium Borohydride with Some Representative Ketones[1]

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The rates of reaction of sodium borohydride with representative ketones in isopropyl alcohol have been determined at several temperatures, yielding values for the relative rates at 0°, and for the enthalpies and entropies of activation. The relative rates decrease from acetone (1.00), to diethyl ketone (0.101) to di-*n*-propyl ketone (0.0291). Further lengthening of the chain has little effect: di-*n*-butyl ketone (0.0403) and di-*n*-hexyl ketone (0.0300). Branching of the alkyl groups also results in a rate reduction: acetone (1.00), methyl ethyl ketone (0.417), methyl isopropyl ketone (0.195), methyl *t*-butyl ketone (0.0815). The presence of two branched alkyl groups decreases the rate considerably beyond that estimated from the effect of a single branched group: acetone (1.00), diethyl ketone (0.101), diisopropyl ketone (0.00551), di-*t*-butyl ketone (0.000191). The marked decrease accompanying the introduction of two bulky groups is attributed to steric effects. A modest decrease is observed with chain branching in the phenyl alkyl ketones, with a sudden large increase in the phenyl *t*-butyl derivative: acetophenone (0.136), phenyl ethyl ketone (0.0756); phenyl isopropyl ketone (0.0709); phenyl isobutyl ketone (0.0111), phenyl *t*-butyl ketone (2.47). The effect of the *t*-butyl group is attributed to its large steric requirements which force the acyl group from its preferred configuration, coplanar with the aromatic ring, causing a reduction in the resonance interactions and permitting the phenyl group to exert its normal -I inductive effect. The data are compared with the rates of solvolysis of the related tosylates to test the proposal that the ketones may be taken as reasonable models for carbonium ions of related structures.

The reaction of sodium borohydride with aldehydes and ketones in isopropyl alcohol solution exhibits simple second-order kinetics, first order in borohydride and first order in the carbonyl derivative[3] (1) Consequently, the reaction appears to

$$\text{rate} = k_2[\text{RCOR}'][\text{NaBH}_4] \qquad (1)$$

involve a kinetically simple rate-determining stage.

In the past a number of reactions have been utilized in studies of the effects of structure on the reactivity of aldehydes and ketones. These include the reaction of these compounds with hydroxylamine,[4] phenylhydrazine[5] and semicarbazide.[6] However, the available evidence indicates that the mechanism of these reactions involves a number of stages, and it is not always clear that the same step is rate-determining.[7] This difficulty has handicapped the exploration of the influence of structure on carbonyl group reactivity.

The observation that the borohydride reaction appears to be simple kinetically[3,8] suggested that it might provide a means of circumventing these difficulties. Accordingly, we undertook an extensive study of the influence of structure on the reaction of carbonyl derivatives toward sodium borohydride. The results of a study of the effect of ring size on the reactivity of the cyclic ketones was published earlier.[9] In the present paper we report on the effects of alkyl group branching on the reactivity of acetone and acetophenone derivatives.

Results

Standard solutions of sodium borohydride and the appropriate ketone in isopropyl alcohol were brought to temperature and rapidly mixed. Aliquots were removed and analyzed for residual borohydride. The reactions were generally run at two different initial ketone concentrations. In all cases the reactions followed second-order kinetics with satisfactory agreement (within 2%) between the rate constants calculated for the determinations at the two concentrations.

The rate constants were measured at three temperatures, generally 0, 25 and 35°. However, in some cases, where the reaction proved to be quite slow, such as with diisopropyl ketone and di-*t*-butyl ketone, it proved necessary to utilize a higher range, calculating the 0° value from the data at higher temperatures.

The results are summarized in Table I.

Discussion

The Aliphatic Ketones.—In the case of the purely aliphatic ketones, the entropy of activation proves to be remarkably constant, −41 ± 2 e.u. Consequently, in these derivatives the changes in rate are primarily the result of changes in the enthalpy of activation. The observed values range from a low of 8.8 kcal./mole for acetone to a high of 13.5 kcal./mole for di-*t*-butyl ketone.

A marked decrease in rate is observed in proceeding from acetone, with relative rate at 0° of 1.00, to diethyl ketone, with a relative rate of 0.101. There is a further decrease observed with di-*n*-propyl ketone, with relative rate 0.0291, but further lengthening of the alkyl group has relatively little effect, as shown by di-*n*-butyl ketone and di-*n*-hexyl ketone with relative rates of 0.0403 and 0.0300, respectively.

Chain-branching results in a decrease in rate, as indicated by the series: acetone, 1.00; methyl ethyl ketone, 0.417; methyl isopropyl ketone, 0.195; methyl *t*-butyl ketone, 0.0815. Moreover, the introduction of two branched groups results in a very sharp decrease in rate: acetone, 1.00; diethyl ketone, 0.101; diisopropyl ketone, 0.00551; di-*t*-butyl ketone, 0.000191.

It is generally accepted that the inductive contributions of alkyl substituents will increase with the increasing bulk of the substituent: methyl <

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[1] Chemical Effects of Steric Strains. XV.

[2] Post-doctorate research associate on Contract DA-33-008-ORD-992, supported by the Office of Ordnance Research, U. S. Army.

[3] H. C. Brown, O. H. Wheeler and K. Ichikawa, *Tetrahedron*, **1**, 214 (1957).

[4] E. Barrett and A. Lapworth, *J. Chem. Soc.*, **93**, 85 (1908).

[5] G. H. Stempel, Jr., and G. S. Schaffel, *J. Am. Chem. Soc.*, **66**, 1158 (1944).

[6] J. B. Conant and P. D. Bartlett, *ibid.*, **54**, 2881 (1932); F. P. Price, Jr., and L. P. Hammett, *ibid.*, **63**, 2387 (1941).

[7] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 331.

[8] E. R. Garrett and D. A. Lyttle, *J. Am. Chem. Soc.*, **75**, 6051 (1953).

[9] H. C. Brown and K. Ichikawa, *Tetrahedron*, **1**, 221 (1957).

TABLE I

RATE CONSTANTS AND DERIVED DATA FOR THE REACTION OF SODIUM BOROHYDRIDE WITH REPRESENTATIVE KETONES IN ISOPROPYL ALCOHOL SOLUTION

Ketone	Rate constant, $k_2 \times 10^4$, l. mole^{-1} sec.$^{-1}$				Rel. rate at 0°	E_{act}, kcal./mole	log A	$\Delta H^{\ddagger}$, kcal./mole	$\Delta S^{\ddagger}$, e.u.
	0.0°	25.0°	35°	45.0°					
Acetone[a]	15.1	63.0	105		1.00	9.3	4.59	8.8	−39.1
Diethyl	1.52	7.40	13.0		0.101	10.3	4.49	9.7	−40.4
Di-*n*-propyl	0.439	2.10	4.03		.0291	10.6	4.14	10.0	−43.6
Di-*n*-butyl	0.608	2.84	5.01		.0403	10.1	3.83	9.5	−42.9
Di-*n*-hexyl[b]	(0.454)[c]	2.67	5.05	9.00	.0300	11.5	4.87	10.8	−38.8
Methyl ethyl	6.26	27.9	50.0		.417	9.9	4.72	9.4	−38.9
Methyl isopropyl	2.94	14.7	25.1		.195	10.4	4.74	9.8	−38.8
Methyl *t*-butyl	1.23	5.74	10.2		.0815	10.1	4.14	9.5	−41.5
Diisopropyl	(0.0832)[c]	0.549	1.03	1.99	.00551	12.1	4.64	11.6	−39.3
Di-*t*-butyl	(0.00288)[c]	(0.192)[d]	0.0493	0.0954	.000191	13.8	4.47	13.5	−39.2
Phenyl methyl[a]	2.05	14.0	26.3		.136	12.2	6.10	11.7	−32.4
Phenyl ethyl	1.14	7.83	15.8		.0756	12.6	6.10	12.0	−32.4
Phenyl isopropyl	1.07	6.62	12.4		.0709	11.8	5.48	11.3	−35.4
Phenyl isobutyl	0.167	1.14	2.46		.0111	12.9	5.54	12.3	−34.8
Phenyl *t*-butyl	37.3	131	223		2.47	8.5	4.37	8.1	−40.1

[a] From ref. 3. [b] From ref. 9. [c] Calculated from data at higher temperatures. [d] At 55.0°.

ethyl < isopropyl < *t*-butyl.[10] Consequently, we must consider the possibility that the observed decreases are primarily due to the increased inductive effects of the more bulky alkyl substituents.

If the observed effects were indeed due to this factor alone, we should expect the rates of the dialkyl ketones, R_2CO, to be calculable from the relative rate factors, k_{RCOMe}/k_{Me_2CO}, obtained from the monoalkyl methyl ketones. Thus methyl ethyl ketone reacts with sodium borohydride at a rate 0.417 that of acetone. Consequently, the effect of the two ethyl groups in diethyl ketone should be given by the result, $k_{Me_2CO} \times (0.417)^2$.

The results of this treatment are summarized in Table II.

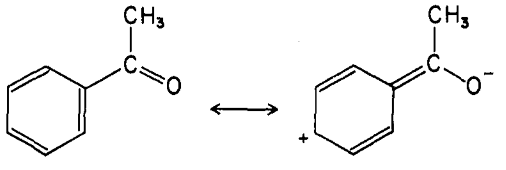
TABLE II

OBSERVED AND CALCULATED RELATIVE RATES OF THE DIALKYL KETONES AT 0°

Methyl ketone $RCOCH_3$	Relative rate	Ketone R_2CO	Relative rate		Ratio calcd./obsd.
			Calcd.	Obsd.	
Methyl	1.00	Dimethyl		1.00	
Ethyl	0.417	Diethyl	0.178	0.101	1.8
Isopropyl	.195	Diisopropyl	.0380	.00551	6.9
t-Butyl	.0815	Di-*t*-butyl	.00664	.000191	35

It is apparent that the observed rates are all smaller than the calculated values, and the discrepancy between the calculated and observed values increases from ethyl to isopropyl to *t*-butyl. The data clearly show that it is not possible to account for the marked decreases observed in the reaction of the dialkyl ketones with sodium borohydride by the inductive effects of the alkyl groups. In order to account for the observed rates, it appears necessary to call upon the large steric requirements of these substituents and their effect upon the stability of the transition state composed of the ketone and borohydride moieties.[3]

The decrease in rate in the monoalkyl methyl ketones is also consistent with the presence of a steric influence. However, since both the inductive factor and the steric factor should operate in the same direction, it does not appear possible to attempt a breakdown into the relative magnitudes of the contributions of these two factors to the observed rates.[11]



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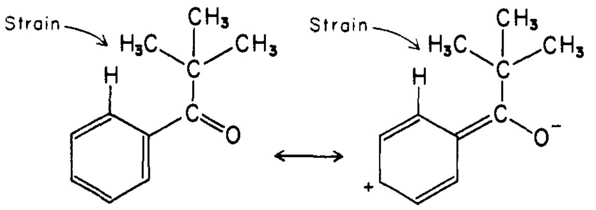

II

The Aromatic Ketones.—It had been previously observed that the presence of the phenyl group in benzaldehyde and acetophenone brought about an increase in the entropy of activation from −39.1 e.u. for acetone to values in the range of −32.4 to −34.8 for the phenyl derivatives.[3] The present data for phenyl ethyl, phenyl isopropyl and phenyl isobutyl ketone exhibit the same influence of the phenyl group (Table I). Only phenyl *t*-butyl ketone is anomalous, with an entropy of activation in the range of the aliphatic ketones, −40.1 e.u.

The increase in the entropy of activation for benzaldehyde and acetophenone had previously

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(10) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953.

(11) R. W. Taft, Jr., has proposed polar substituent constants, σ^*, for alkyl groups and these might be utilized in an attempt to analyze the data for monoalkyl methyl ketones into their steric and polar components. However, it is not certain at the present time that these constants are true estimates only of the polar contributions of alkyl groups and do not incorporate a steric contribution within themselves. R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," edited by M. S. Newman, John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 586–629.

been rationalized in terms of the coplanar configuration of these molecules, resulting from resonance interactions between the carbonyl group and the aromatic ring, and the effect of this configuration on the transition state for the borohydride reaction.[3] In phenyl *t*-butyl ketone there are strong arguments for believing that the bulky alkyl group prevents the realization of a similar coplanar configuration.[12]

The unusually high reactivity of phenyl *t*-butyl ketone in this borohydride reaction points to the same conclusion.

Acetophenone reacts at a considerably slower rate (0.136) than acetone. The −I inductive effect of the phenyl group should bring about a significant rate increase. However, resonance interactions between the phenyl ring and the carbonyl group will increase the electron density on the carbonyl group and diminish its reactivity toward borohydride (I).

The decreases in rate observed in proceeding from acetophenone (0.136) to phenyl ethyl ketone (0.0756), to phenyl isopropyl ketone (0.0709), and to phenyl isobutyl ketone (0.0111) are presumably the net result of the increased inductive effects of these substituents and their increased steric requirements.

On this basis, one might have expected a further rate decrease with phenyl *t*-butyl ketone. However, there is observed instead a sharp increase in reactivity—to a value of the relative rate of 2.47. Thus phenyl *t*-butyl ketone is actually even more reactive toward sodium borohydride than the parent molecule, acetone.

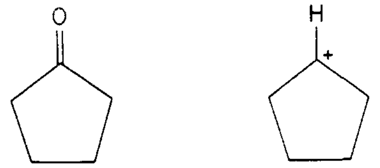
The high rate must arise from the effect of the *t*-butyl group in forcing the carbonyl group out of the coplanar configuration most favorable for resonance interactions[12] (II). The inhibition of resonance is evidently sufficiently important that the normal −I inductive effect of the phenyl can operate and bring about the observed increase in reactivity, even though this requires overcoming both the steric and polar contributions of the *t*-butyl group.

This steric inhibition of resonance must also be a factor in the simpler phenyl alkyl ketones examined. It presumably accounts for the relatively small decreases in rate observed in the replacement of the methyl group in acetophenone (0.136) with an ethyl (0.0756) and an isopropyl (0.0709) group. The observed decreases accompanying similar structural changes are much larger in the aliphatic derivatives (Table II).

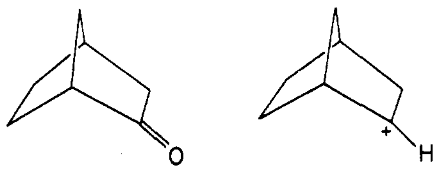
Summing up, the observed changes in reactivity in the phenyl alkyl ketones are the net effect of the polar and steric contributions of the alkyl substituents. The steric effect appears to operate in two ways. In addition to the simple bulk effect of the substituent, which increases the energy of the transition state, as observed in the aliphatic derivatives, the alkyl group also influences the reactivity by altering the resonance interactions of the carbonyl group with the aromatic ring. The ability of the ethyl, isopropyl and isobutyl groups to bring about such inhibition of resonance is relatively small, presumably because these groups can minimize the steric interactions with the *ortho* hydrogen by rotating.[13] On the other hand, the *t*-butyl group possesses essentially spherical symmetry and mere rotation of the alkyl group fails to reduce the steric interactions significantly. Only rotation of the entire acyl group about the aryl–carbonyl bond is capable of reducing the steric compression, but this is then accomplished at the cost of the resonance contributions of the aromatic ring.

Ketones as Models for Carbonium Ions.—The influence of structure on the rates of solvolysis of alkyl halides and arylsulfonates has been of major theoretical interest for many years.[14] A number of strained derivatives exhibit enhanced rates of solvolysis. In some cases the enhanced rates have been attributed to the driving force associated with relief of steric strain in the ionization step.[15] In other cases, it has been suggested that the enhanced rates are primarily the result of the formation of unusually stable "non-classical" ions.[16] A rigorous test of the relative importance of these factors in various systems has been rendered difficult by the transient nature of these carbonium ions and the consequent difficulty of making direct observations of the effect of structural changes on these intermediates

As a possible route out of this difficulty, it was suggested that ketones might provide reasonably satisfactory models for carbonium ions of related structures[9] (III–V).



III



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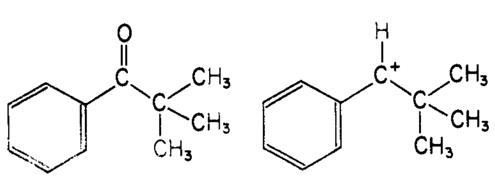

V

On this basis, a structural change which facilitates the ionization of a tosylate, with a change in coördination from four to three, should have the opposite effect on the rate of reaction of sodium borohydride with the corresponding ketone, with a change in coördination from three to four. For example, similar inverse effects of this kind are noted in comparing the first-order rate constants

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[12] G. D. Hedden and W. G. Brown, *J. Am. Chem. Soc.*, **75**, 3744 (1953).

[13] H. C. Brown, *J. Chem. Education*, **36**, 424 (1959).

[14] A. Streitwieser, Jr., *Chem. Revs.*, **56**, 571 (1956).

[15] H. C. Brown, *J. Chem. Soc.*, 1248 (1956).

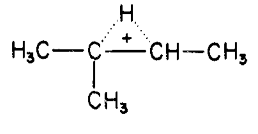
[16] S. Winstein, *Bull. soc. chim. France*, **18**, 55 (1951).

for the acetolysis at 70° of the cycloalkyl tosylates ($k_1 \times 10^5$ sec.$^{-1}$) with the second-order rate constants for the reaction of sodium borohydride at 0° ($k_2 \times 10^4$ l. mole^{-1} sec.$^{-1}$) with the corresponding ketones.[9]

C_5H_9OTs	32.2	C_5H_8O	7.01
$C_6H_{11}OTs$	2.37	$C_6H_{10}O$	161
$C_7H_{13}OTs$	60.0	$C_7H_{12}O$	1.02
$C_8H_{15}OTs$	452	$C_8H_{14}O$	0.078
$C_9H_{17}OTs$	408	$C_9H_{16}O$	0.032
$C_{10}H_{19}OTs$	891	$C_{10}H_{18}O$	0.0132

The observation that the slowness of the reaction of borohydride with cyclodecanone corresponds closely to the observed very fast rate of solvolysis of cyclodecyl tosylate was considered to argue against a non-classical structure for the cyclodecyl ion as a significant factor in the enhanced solvolysis of cyclodecyl tosylate.

In the present study, the rates of reaction decrease in the order: MeCOMe > EtCOMe > *i*-PrCOMe > *t*-BuCOMe. According to our original postulate, the inverse order of solvolysis of the tosylates should be observed if no new factor were involved: MeCH(OTs)Me < EtCH(OTs)Me < *i*-PrCH(OTs)Me < *t*-BuCH(OTs)Me. In actual fact, these arylsulfonates do not exhibit a regular increase in reactivity.[17] The results indicate either that the acetolysis of the isopropyl methyl derivative is enhanced by some factor not present in the ketone reaction, or that the *t*-butyl compound is slowed down.



$$H_3C-\underset{\underset{CH_3}{|}}{C}\overset{\overset{H}{+}}{-}CH-CH_3$$

VI

Winstein and his co-workers have advanced reasonable arguments that the solvolysis of the isopropylmethylcarbinyl brosylate is enhanced by participation of the tertiary hydrogen.[17,18] Such participation makes possible the distribution of the charge between both the secondary and tertiary carbon atoms and thereby stabilizes the transition state VI.

The very slow rate of reduction of di-*t*-butyl ketone predicts a very fast rate of solvolysis for the tosylate of di-*t*-butylcarbinol. We attempted to test this prediction, but were unable to synthesize the desired arylsulfonate ester.[19] However, it has been reported that the related derivative, di-*t*-butylcarbinyl chloride, does exhibit unusually high reactivity.[20]

We were likewise unable to synthesize the tosylates of the arylmethylcarbinols to test the correlation between their rates of solvolyses and those predicted from the borohydride results.[19] However, the tosylate of phenyl-*t*-butylcarbinol has been synthesized.[21] It was noted that the rate of solvolysis was unusually slow for a benzylic derivative. This result was also attributed to hindered resonance in the non-coplanar carbonium ion V.[21] Consequently, the slow rate of solvolysis of phenyl-*t*-butylcarbinyl tosylate is in qualitative agreement with the very fast rate of reaction of phenyl *t*-butyl ketone observed in the present study.

We are extending this approach, based on the rates of reaction of borohydrides with ketones, to explore further the factors influencing the stability of carbonium ions.

Experimental Part

Materials.—The purification of isopropyl alcohol and sodium borohydride have been described earlier.[3] Most of the ketones were commercial products, purified by distillation in an efficient column before use. Diisopropyl ketone was prepared by the chromic acid oxidation of diisopropylcarbinol. Di-*t*-butyl ketone was prepared from sodium, *t*-butyl chloride and methyl pivalate.[22] Di-*n*-hexyl ketone was prepared from the reaction of *n*-hexylcadmium halide (from *n*-hexylmagnesium bromide and cadmium chloride) on heptoyl chloride. Phenyl *t*-butyl ketone was synthesized by the reaction of phenylmagnesium bromide on pivaloyl chloride.[23]

Physical properties of the products utilized for the kinetic studies are summarized in Table III.

TABLE III

PHYSICAL PROPERTIES OF KETONES

Ketone	B.p. °C.	B.p. Mm.	$n^{20}D$
Diethyl	101.0	749	1.3918
Di-*n*-propyl	143.5	739	1.4061
Di-*n*-butyl	73.5–74.0	14	1.4190
Di-*n*-hexyl	124–125	8	32.5–33.0[b]
Methyl ethyl	78.8–78.9	738	1.3786
Methyl isopropyl	93.2	734	1.3873
Methyl *t*-butyl	106–106.5	740	1.3969
Diisopropyl	123.0–124.0	738	1.3999
Di-*t*-butyl	151–153	745	1.4190
Phenyl ethyl	141–142	78	1.5272
Phenyl isopropyl	103–104	14	1.5182
Phenyl isobutyl	115–115.5	14	1.5118
Phenyl *t*-butyl[a]	99–99.5	12	1.5102

[a] Purified *via* the semicarbazone; m.p. 157–158.5°. [b] M.p.

Kinetic Measurements.—The experimental procedure was identical with that described previously.[3] The temperatures were controlled to within ±0.02°. In most cases two kinetic measurements were made at two different initial concentrations of the ketone, such as 0.01727 *M* sodium borohydride, and 0.08213 *M* and 0.1610 *M* diethylketone. The two rate constants agreed to within 2%, usually to within 1%. The mean values are reported in Table I.

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[17] S. Winstein and H. Marshall, *J. Am. Chem. Soc.*, **74**, 1120 (1952), report for the relative rates of acetolysis of the brosylates at 25°: MeCH(OBs)Me, 1.00; EtCH(OBs)Me, 2.3; *i*-PrCH(OBs)Me, 6.0; *t*-BuCH(OBs)Me, 2.9.

[18] S. Winstein and J. Takahashi, *Tetrahedron*, **2**, 316 (1958).

[19] Unpublished research with Dr. G. Goldman.

[20] F. Brown, T. D. Davies, I. Dostrovsky, O. J. Evans and E. D. Hughes, *Nature*, **167**, 987 (1951).

[21] S. Winstein and B. K. Morse, *J. Am. Chem. Soc.*, **74**, 1133 (1952). These authors report that in 80% aqueous alcohol at 50°, the methyl derivative, phenylmethylcarbinyl chloride, solvolyzes at a rate 490-fold greater than the *t*-butyl derivative, phenyl-*t*-butylcarbinyl chloride.

[22] P. D. Bartlett and A. Schneider, *ibid.*, **67**, 141 (1945).

[23] J. H. Ford, C. D. Thompson and C. S. Marvel, *ibid.*, **57**, 2619 (1935).