CHEMICAL EFFECTS OF STERIC STRAINS—XIII[*]

KINETICS OF THE REACTION OF
SODIUM BOROHYDRIDE WITH CARBONYL GROUPS—
A CONVENIENT TOOL FOR INVESTIGATING THE
REACTIVITIES OF ALDEHYDES AND KETONES

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Abstract—The reactions of sodium borohydride in isopropyl alcohol with acetone, acetophenone, benzophenone and benzaldehyde show simple second order kinetics, first order in the concentration of borohydride, and first order in the carbonyl component. Benzaldehyde reacts far faster than any of the ketones, corresponding to the greater reactivity of aldehydic carbonyl groups toward attack by nucleophilic reagents. The decrease in rate, acetone > acetophenone and benzophenone, is attributed to the resonance and steric contributions of the aromatic rings. The reaction of sodium borohydride with carbonyl compounds promises to provide a valuable tool for investigating the effect of structure on the reactivity of aldehydes and ketones.

NUMEROUS attempts have been made to examine the effects of structure upon the reactivity of aldehydes and ketones by determining the rates of reactions of these compounds with reagents such as hydroxylamine,[1] phenylhydrazine,[2] and semi-carbazide.[3] However, the mechanism of these reactions appears to involve a number of stages and it is not always clear that the same step is rate-determining.[4] A reaction with a kinetically simple rate-determining stage should be quite valuable in facilitating the study of structural effects.

The discovery of sodium borohydride[5] made available a convenient reagent which rapidly reduces carbonyl compounds in suitable solvents.[6] It was demonstrated by Garrett and Lyttle that the reduction of 3α-hydroxy-11α-acetoxypregnan-20-one by sodium borohydride was second order.[7] Relatively rough kinetic studies have indicated that this reaction holds promise for the investigation of structural effects.[8,9] Accordingly a detailed study of the kinetics of the reaction of sodium borohydride

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‡ Post-doctorate research assistant, 1954-1956, on Contract DA–33–008–ORD–992 supported by the Office of Ordnance Research, U.S. Army.
1 E. Barrett and A. Lapworth J. Chem. Soc. 93, 85 (1908).
2 G. H. Stempel, Jr. and G. S. Schaffel J. Amer. Chem. Soc. 66, 1158 (1944).
3 J. B. Conant and P. D. Bartlett Ibid. 54, 228 (1932); F. P. Price, Jr. and L. P. Hammett Ibid. 63, 2387 (1941)
4 L. P. Hammett Physical Organic Chemistry p. 331. McGraw-Hill, New York (1940).
5 H. I. Schlesinger, H. C. Brown, H. R. Hockstra, and L. R. Rapp J. Amer. Chem. Soc. 75, 199 (1953).
6 S. W. Chaikin, and W. G. Brown Ibid. 71, 122 (1949).
7 E. R. Garrett and D. A. Lyttle Ibid. 75, 6051 (1953).
8 E. H. Jensen A Study on Sodium Borohydride NYT Nordisk Forlag Arnold Busck, Copenhagen (1954).
9 H. C. Brown, E. J. Mead, and B. C. Subba Rao J. Amer. Chem. Soc. 77, 6209 (1955).

with acetone, acetophenone, benzophenone and benzaldehyde was undertaken to test this possibility.

Sodium borohydride has been utilized as a reducing agent primarily in water or methanol solution. It reacts with these solvents, complicating the kinetic study.[7,8] However, it is moderately soluble in *iso*propyl alcohol and exhibits no measurable reaction with this solvent over extended periods of time.[9] Accordingly, *iso*propyl alcohol was selected as the reaction medium.

RESULTS

Solutions of acetone in *iso*propyl alcohol were mixed with solutions of sodium borohydride in the same solvent at 0°. At appropriate intervals of time aliquots were removed and titrated for residual borohydride by the potassium iodate method.[10]

Four moles of ketone react for each mole of borohydride.

$$(CH_3)_2CO + NaBH_4 \rightarrow Na[(CH_3)_2CHO]_4B$$
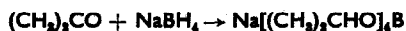
It was shown in each kinetic run that the overall rates could be expressed by the equation

$$\frac{dx}{dt} = k_2 (a - 4x)(b - x)$$

where a is the initial molar concentration of ketone, b is the initial molar concentration of sodium borohydride, and x is the amount of sodium borohydride which has reacted at time t. Plots of the quantity $\dfrac{2 \cdot 303}{a - 4b} \log \dfrac{b(a - 4x)}{a(b - x)}$ against the time t gave straight lines which passed through the origin. (Fig. 1.)
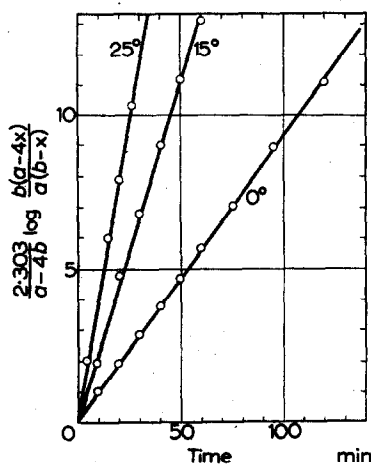

FIG. 1. Second order plots for the reaction of acetone with sodium borohydride in *iso*propyl alcohol at 0°.

The concentration of acetone was varied from 0·0400M to 0·320M and the concentration of borohydride from 0·00970M to 0·0305M without noticeable change in the rate constants, $15 \cdot 1 \times 10^{-4}$ 1 mole^{-1} sec^{-1}. (This compares with the value 13×10^{-4} 1 mole^{-1} sec^{-1} observed in a preliminary study of this reaction.[9]) Rate

[9] D. A. Lyttle, E. H. Jensen, and W. A. Struck   *Anal. Chem.* **24**, 1843 (1952).
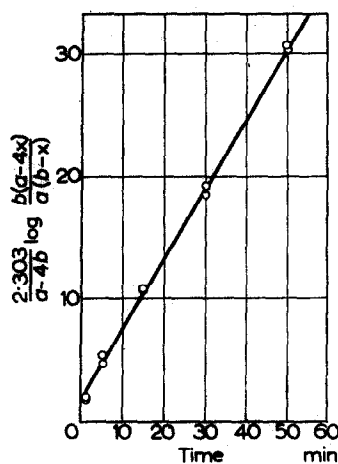
FIG. 2. Temperature dependence of the second order rate constants for the reaction of sodium borohydride with acetone.

TABLE 1. SECOND ORDER CONSTANTS FOR THE REACTION OF SODIUM BOROHYDRIDE WITH CARBONYL COMPOUNDS IN isoPROPYL ALCOHOL

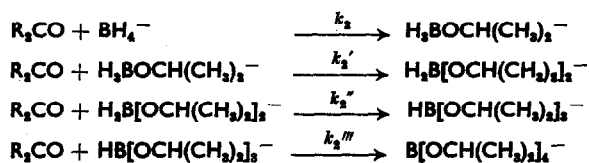| Compound	Temp., °C	Initial conc. of compound	Initial conc. of NaBH$_4$	$k_2 \times 10^4$ l. mole^{-1} sec^{-1}
Acetone	0·00 ± 0·01	0·0400	0·0201	15·3
		0·0800	0·0201	15·2
		0·160	0·0204	15·0
		0·320	0·0204	15·0
		0·160	0·0305	15·1
		0·160	0·0159	15·1
			0·00970	15·0
			Mean value	15·1
	15·00 ± 0·02	0·160	0·0175	36·1
	25·00 ± 0·02	0·160	0·0187	63·0
	35·00 ± 0·02	0·160	0·0182	105
Acetophenone	0·00 ± 0·01	0·160	0·0170	2·05
	25·00 ± 0·02	0·0803	0·0182	14·0
		0·161	0·0185	13·7
			Mean value	13·9
	35·15 ± 0·02	0·161	0·0155	26·2
Benzophenone	0·00 ± 0·01	0·0800	0·0213	1·87
	25·00 ± 0·02	0·0400	0·0223	15·8
		0·0800	0·0197	15·9
		0·160	0·0195	15·4
		0·320	0·0172	15·8
		0·160	0·0102	15·9
		0·160	0·0280	15·8
			Mean value	15·8
	35·00 ± 0·02	0·160	0·0193	33·9
Benzaldehyde	−35·3 ± 0·1	0·0416	0·00905	94
	−21·1 ± 0·1	0·0502	0·00848	242
	− 8·7 ± 0·1	0·0390	0·00789	502

constants were also determined at 15·0, 25·0 and 35·0°. The data yielded an excellent log k_2 vs. $1/T$ plot (Fig. 2). The results are summarized in Table 1.

The reactions of sodium borohydride with acetophenone and benzophenone also exhibit second order kinetics, with the rate constants considerably smaller than that observed in the case of acetone. In the case of benzaldehyde the reaction proved to be so fast that it was necessary to utilize both highly dilute solutions and lower temperatures in order to slow the reaction down sufficiently to permit the satisfactory determination of the rate constants.

The results are reported in Table 1.

DISCUSSION

The reaction of acetone with sodium borohydride must involve four successive stages.

$$R_2CO + BH_4^- \xrightarrow{k_2} H_3BOCH(CH_3)_2^-$$

$$R_2CO + H_3BOCH(CH_3)_2^- \xrightarrow{k_2'} H_2B[OCH(CH_3)_2]_2^-$$

$$R_2CO + H_2B[OCH(CH_3)_2]_2^- \xrightarrow{k_2''} HB[OCH(CH_3)_2]_3^-$$

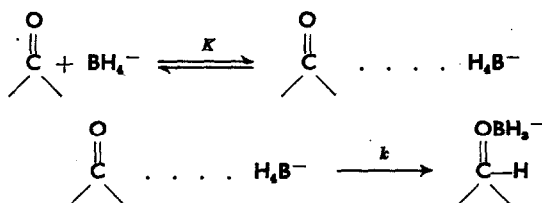$$R_2CO + HB[OCH(CH_3)_2]_3^- \xrightarrow{k_2'''} B[OCH(CH_3)_2]_4^-$$

In this case, with isopropyl alcohol as the solvent, interchange of the alkoxy groups on boron with the solvent should not alter the intermediates involved.[9]

The observed kinetics are consistent with a slow rate-determining reaction for the first stage, with successive stages being considerably faster.[4] This postulate has been confirmed by the preparation of the intermediate, sodium tri-isopropoxyboro-hydride, NaHB[OCH(CH₃)₂]₃, and the demonstration that its reaction with acetone is indeed much faster than the reaction of the ketone with sodium borohydride itself.[11]

The observed rate constants may either represent the rate of the direct reaction of borohydride ion with the carbonyl group,

$$\underset{\diagup\diagdown}{\overset{O}{\underset{\|}{C}}} + BH_4^- \xrightarrow{k_2} \underset{\diagup\diagdown}{\overset{OBH_3^-}{\underset{|}{C}}}{-}H$$
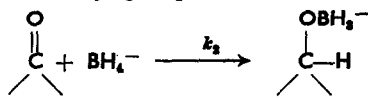
or it may represent the product of an equilibrium constant for the association of borohydride ion and the aldehyde or ketone, and the rate constant for the subsequent transfer of a hydride ion to the carbonyl group ($k_2 = Kk$).

$$\underset{\diagup\diagdown}{\overset{O}{\underset{\|}{C}}} + BH_4^- \overset{K}{\rightleftharpoons} \underset{\diagup\diagdown}{\overset{O}{\underset{\|}{C}}} \ldots \ldots H_4B^-$$

$$\underset{\diagup\diagdown}{\overset{O}{\underset{\|}{C}}} \ldots \ldots H_4B^- \xrightarrow{k} \underset{\diagup\diagdown}{\overset{OBH_3^-}{\underset{\|}{C}}}{-}H$$

A choice between these possibilities does not appear possible at this time. However, irrespective of this difficulty, the structural effects observed with the four carbonyl compounds here examined do appear to be simply related to the structure of the molecules.

[11] H. C. Brown, E. J. Mead, and C. J. Shoaf   J. Amer. Chem. Soc. **78**, 3613 (1956).

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For convenience in following the discussion, the rate constants at 0°, the relative rates and derived data are summarized in Table 2.

TABLE 2. KINETIC DATA FOR THE REACTION OF SODIUM
BOROHYDRIDE WITH SELECTED CARBONYL COMPOUNDS IN
*iso*PROPYL ALCOHOL

Compound	$k_2 \times 10^4$ (0°) 1. mole^{-1} sec^{-1}	Rel. rate (0°)	$E_{act.}$ kcal/mole	$\log A$	$\Delta H^{\ddagger}$ kcal/mole	$\Delta S^{\ddagger}$ e.u.
Acetone	15·1	1·00	9·3	4·59	8·8	−39·1
Acetophenone	2·05	0·136	12·2	6·10	11·7	−32·4
Benzaldehyde	820[a]	53·3	8·0	5·27	7·8	−34·8
Benzophenone	1·87	0·124	13·6	7·18	13·1	−27·7

[a] Calculated from data at lower temperatures.

The decrease in rate from acetone to acetophenone and benzophenone is in accord with the greater steric requirements of the phenyl groups and their ability to conjugate with the carbonyl groups and reduce their sensitivity to attack by nucleophilic reagents.

Similarly, the marked difference in the rates for acetophenone and benzaldehyde is in accord with the postulated difference in the inductive and steric effects of the methyl group as compared to the hydrogen atom.

The enthalpy of activation increases by 2·9 kcal/mole from acetone to acetophenone, and increases a further 1·4 kcal/mole to benzophenone. The reactive benzaldehyde molecule exhibits a sharp drop in this quantity.

The entropies of activation are also interesting. The value of −39·1 e.u. for acetone is of the order of magnitude to be expected for a bimolecular reaction. The introduction of a single phenyl group in acetophenone and benzaldehyde results in a somewhat smaller decrease in entropy of activation, while the two phenyl groups in benzophenone result in a further decrease.

These observations can be rationalized in terms of the proposed interpretation of the reaction. In the initial state, resonance interactions between the phenyl group and the carbonyl group should favor a coplanar configuration for the molecule.

On the other hand, in the transition state, the partial transfer of a hydride ion from the borohydride group to the carbon atom of the carbonyl group should reduce the possibilities for such resonance interactions and greatly modify the geometry of the organic moiety
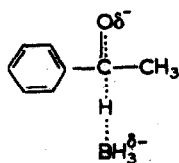
In other words, the restriction to free rotation caused by resonance interactions of one or two phenyl groups with the carbonyl group should largely disappear in the transition state. Thus the difference in entropies of activation for the reactions must largely reflect the differences in the entropies of the carbonyl derivatives.

The simple kinetics and large structural effects observed in this study appear highly promising for the objectives of the present investigation. The results encouraged the application of the reaction to the examination of structural effects in a number of related derivatives with structural features of importance to current theoretical problems. An examination of the reaction of sodium borohydride with cyclic ketones is reported in the following publication.

EXPERIMENTAL

Materials. Sodium borohydride was carefully purified by recrystallization from diglyme.[9] The product was analysed for active hydrogen by the iodate method, for sodium by titration (as sodium hydroxide) with standard acid and for boron by titration (as boric acid) with sodium hydroxide in the presence of mannitol. The analysis indicated the composition $Na_{1\cdot000}$ $B_{1\cdot000}$ $H_{4\cdot000}$ with a purity of 99·9 per cent based upon the weight of samples taken.

*Iso*propyl alcohol was dried over Drierite and distilled through a packed column, b.p. 81·6–81·7° at 743 mm, n_D^{20} 1·3772.

Benzophenone was recrystallized from ethanol. It exhibited m.p. 48·1°. The remaining carbonyl derivatives were dried over Drierite and distilled through a packed column. Fractions of constant boiling point and refractive index were utilized. The products exhibited the following properties: acetone, b.p. 55·9–56·0° at 743 mm, n_D^{20} 1·3589; acetophenone, b.p. 82·7–82·8° at 12 mm, n_D^{20} 1·5342; benzaldehyde, b.p. 62·0–62·1° at 10 mm, distilled and handled under nitrogen.

Rate measurements. Standardized solutions of sodium borohydride and of the carbonyl component in *iso*propyl alcohol were prepared. A known volume of the sodium borohydride solution (75 or 100 ml) was placed in a reaction flask with a long narrow neck, immersed in the constant temperature bath. A known volume of the ketone solution, at reaction temperature, was added to the borohydride solution with vigorous mixing. At intervals 10 ml portions of the reaction mixture were withdrawn, added to a large excess of 0·1 N potassium iodate solution (25 or 50 ml) containing 2 g of potassium iodide, followed by 10 ml of 5 N sulfuric acid. The liberated iodine was titrated with 0·1 N sodium thiosulfate.

As previously mentioned, plots of $\dfrac{2\cdot303}{a - 4b} \log \dfrac{b(a - 4x)}{a(b - x)}$ against time gave straight lines passing through the origin for acetone (Fig. 1) and the other ketones. However, in the case of benzaldehyde, the reaction proved to be so fast that this procedure yielded erratic results. The procedure was therefore modified.

A small thin glass bulb containing 5·00 ml of benzaldehyde solution was placed in a large test tube and 10 ml of the sodium borohydride solution was added. The tube was brought to reaction temperature and the reaction initiated by crushing the bulb and vigorously shaking the tube and its contents in the constant temperature bath. After a suitable reaction time (30 sec for the first measurement), potassium iodate-potassium iodide solution, and then sulfuric acid were added directly to the

test tube and the entire solution titrated for iodine as in the usual procedure. Approximately 10 individual measurements were made for each determination of the rate constant. Typical data are shown in Fig. 3.
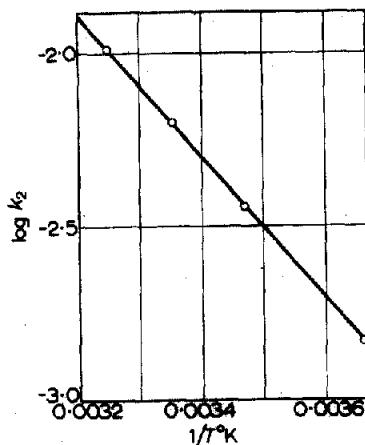

FIG. 3. Second order plots for the reaction of benzaldehyde with sodium borohydride in *iso*propyl alcohol at −35·3°.

Usually the second order plots passed through the origin (Fig. 1). However, in the case of benzaldehyde and other carbonyl compounds which react very rapidly, small intercepts are observed (Fig. 3). The reaction of sodium borohydride with carbonyl derivatives proceeds considerably faster in water than in *iso*propyl alcohol (observations of Dr. K. Ichikawa). In the analytical procedure the sample is added to potassium iodate-potassium iodide solution and the reaction is halted by adding sulfuric acid. There is a short interval of time, approximately 30 sec, between the mixing of the sample and the iodate solution and the destruction of the borohydride by the iodine liberated by the sulfuric acid. It is believed that the intercept arises from a small amount of reaction between the borohydride and the carbonyl component in this brief interval.