

REDUCTION OF SUBSTITUTED BENZOPHENONES WITH SODIUM HYDROBORATES*

J. MINDL and M. VEČEŘA

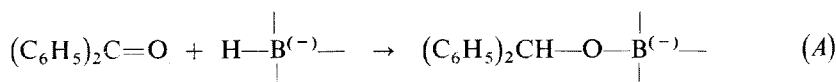
*Department of Organic Chemistry,
Institute of Chemical Technology, 532 10 Pardubice*

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The reduction rate of benzophenone with sodium tetrahydroborate depends on the used solvent and decreases in the series: methanolic 0.1M-NaOH, tert-butyl alcohol, isopropyl alcohol. Reduction of benzophenone with NaBH₄ resp. NaBD₄ in methanolic 0.1M-NaOH shows inverted primary isotopic effect ($k_H/k_D = 0.95$), whereas the reduction with NaBH(OCH₃)₃ resp. NaBD(OCH₃)₃ in tetrahydrofuran shows the expected value of this effects ($k_H/k_D = 4.15$). It has been found that triethoxyhydroborat in tetrahydrofuran solution is decomposed by disproportionation only slightly. The reduction rate depends on the type and concentration of the non-disproportionated reagent and increases in the series NaBH(OCH₃)₃, NaBH(OC₂H₅)₃, NaBH(OC(CH₃)₃)₃, the ratio being 1 : 10³ : 10⁵. The obvious sensitivity to the character of medium and substitution supports the presumption that the reductions with hydroborates proceed *via* the intermediate having tetrahedral arrangement at the carbonyl carbon atom. The substituent effects and their cumulation from the both aromatic rings are discussed.

In spite of the reduction of carbonyl compounds with complex hydroborates being a current laboratory procedure¹, the number of reports dealing with kinetics of this reaction is small (see ref.² and the references involved therein), especially so in the cases using benzophenone as the model³⁻⁶.

In our previous reports⁷ we dealt predominantly with the S_N1 substitutions at the aliphatic carbon atom of diphenylmethane compounds. A simple kinetic measurement of reduction of benzophenones with hydroborates makes it possible to study the addition reactions in this system, too. The aim of this work was to contribute to elucidation of the reduction mechanism of benzophenones with sodium tetrahydroborate in methanol and with trialkoxyhydroborates in tetrahydrofuran (Scheme (A)) and use the kinetic results for discussion of cumulative substituents effects on the reaction centre.



* Part VII in the series Reactivity of Compounds of Diphenylmethane Series; Part VI: This Journal 38, 3496 (1973).

EXPERIMENTAL

Reagents

Methanol (for UV spectroscopy) was dried with barium oxide, and, after 24 h standing with sodium tetrahydroborate (1% by wt.), it was distilled. Isopropyl alcohol and tert-butyl alcohol were dried in similar way. Tetrahydrofurane was dried by 10 h shaking with solid potassium hydroxide, about 4 h boiling with sodium trimethoxyhydroborate (5% by wt.) and distillation. Sodium tetrahydroborate was recrystallized from diethylene glycol dimethyl ether. Sodium tetradeuterioborate (D purity 98%) was prepared in the Institute of Inorganic Chemistry, Czechoslovak Academy of Sciences, Prague. Sodium trimethoxyhydro- resp.- deuterioborates were prepared by reaction of sodium deuteride (D purity 97%) with an excess of trimethoxyborane according to Schlesinger⁸. Similarly, sodium triethoxyhydroborate was synthesized by reaction of triethoxyborane with an excess of sodium hydride in tetrahydrofurane at 120°C in a sealed ampoule 8 h. This last procedure was used for preparation of sodium tritert-butoxyhydroborate from tritert-butoxyborane. The benzophenones were synthesized by the known procedure⁷.

Analytical Methods

The content of active hydrogen in the hydroborates and their solutions was measured by iodate⁹ and argentometric¹⁰ methods. Results of the both analytic methods were, in all cases, identical within experimental error. Identity of the starting alkoxyhydroborates or products obtained from their solutions in tetrahydrofurane after evaporation of the solvent was checked by powder X-ray analysis using an X-ray diffractograph JDX-8S JEOL. IR spectra were measured with a Spectromom 2000 apparatus (Budapest), and mass spectra were measured with a MS 902 AEI Mass Spectrometer.

Reduction of Benzophenone with Alkoxyhydroborates

A. Solution of 1 g tritert-butoxyhydroborate in 10 ml tetrahydrofurane was injected from a syringe into a solution of 0.2 g benzophenone in 5 ml tetrahydrofurane at 25°C with stirring. After 3 seconds 50 ml 1% hydrochloric solution was added. After distilling off tetrahydrofurane and cooling, the product was filtered, washed with 10 ml water and dried. The benzhydrol was crystallized from light petroleum, and its identity was checked by its melting point (67.5–68.0°C) and mixed melting point.

B. 1.3 g sodium trimethoxydeuterioborate in 10 ml tetrahydrofurane was mixed with solution of 2.5 g sodium tritert-butoxyhydroborate in 20 ml tetrahydrofurane at 25°C with stirring. After 3 minutes the mixture was treated with a solution of 0.2 g benzophenone in 5 ml tetrahydrofurane, and, after 1 minute, 50 ml 1% aqueous hydrochloric acid was added thereto. The benzhydrol was isolated and identified as in the above case.

Kinetic Measurements

Solutions of sodium hydroborates were prepared immediately before each kinetic run (except for those having shorter half-lives than 15 s) by shaking the corresponding reagent amount in the solvent and separating possible undissolved portion with a centrifuge. Solutions of benzophenones ($1 \cdot 10^{-2}$ M to $2 \cdot 10^{-4}$ M) and those of the respective sodium hydroborates ($2 \cdot 10^{-1}$ to $2 \cdot 10^{-2}$ M) were mixed in tempered cells at 25°C, the volume ratio being 1 : 1. The reaction rates of the first order (excess of hydroborates) were measured by the method of Bowden and

Hardy⁵. From the found values of the rate constants (k_1) and the known hydroborate concentrations it was possible to determine the rate constants of the bimolecular reaction $k = k_1/4b$ and $k = k_1/b$ for the reductions with sodium tetrahydro(deuterio)borate and trialkoxyhydroborate, respectively. The final extinctions of the reaction mixtures were read at a time greater than 10 half-lives; the optical densities were followed spectrophotometrically with a Specord UV VIS (Zeiss, Jena) and a Unicam SP 800 B apparatus in the UV region 250 to 310 nm. The reductions having the half-lives shorter than 15 s were measured with a stopped-flow spectrophotometer Durrum-Gibson Model D-110. The respective reaction half-lives were read from the kinetic curve on the screen of the apparatus.

RESULTS AND DISCUSSION

Sodium tetrahydroborate was sufficiently stable in all the solvents used. Its decomposition in methanol was suppressed by addition of sodium hydroxide (Davis and Gottbrath¹¹ used sodium methoxide for the same purpose). In methanolic 0.1M-NaOH the tetrahydroborate is relatively stable, its decomposition being less than 2% in the slowest reactions measured with the benzophenones (its concentration decreases by 10%, 25%, 50% and 64.2% after 60, 230, 650 and 915 minutes, respectively). The samples of sodium triethoxyhydroborate prepared without and with the presence of tetrahydrofuran were analyzed by powder X-ray analysis. Fig. 1 gives the both results along with that obtained for sodium tetrahydroborate. From comparison of the spectra it follows that sodium triethoxyhydroborate was decomposed only slightly in tetrahydrofuran. Sodium trimethoxyhydroborate undergoes disproportionation in tetrahydrofuran¹².

From the comparison of the rate constants given in Table I it follows that the reduction of benzophenones with sodium tetrahydroborate in methanolic 0.1M-NaOH

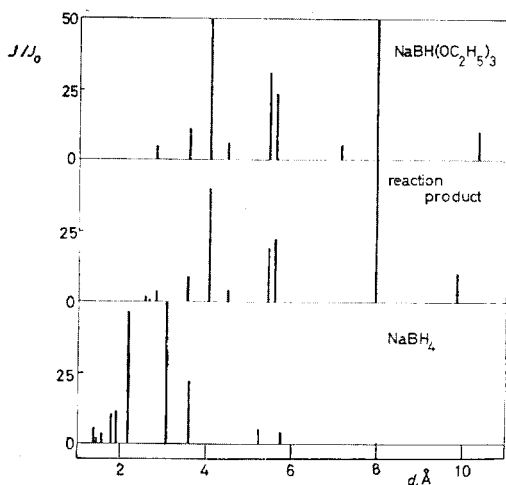


FIG. 1
Comparison of Powder X-rays Diffractograms of $\text{NaBH}(\text{OC}_2\text{H}_5)_3$ and NaBH_4
The reaction product of sodium triethoxyhydroborate with tetrahydrofuran is given in the middle.

proceeds more slowly than that with sodium tetradeuterioborate ($k_H/k_D = 0.95$ and 0.94 for benzophenone and 3-bromobenzophenone, respectively). The inverted isotopic effect was observed with other systems¹³ inclusive of hydrolysis of sodium tetrahydro(deuterio)borates and was ascribed to the secondary isotopic effect of the other three deuterium (hydrogen) atoms which are not involved in the rate-determining reaction step¹⁴. This explanation is supported also by the finding that the primary isotopic effect found in the reduction of 3-bromobenzophenone with trimethoxyhydro(deuterio)borate ($k_H/k_D = 4.15$) approaches the theoretical value 5.3 calculated for the B—H bond splitting¹⁴.

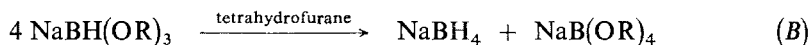
From Table I it follows that the reduction of benzophenone with trialkoxyborates depends on the type of the alkoxy group bound to boron, increasing in the series

TABLE I
Rate Constants k ($\text{l}\cdot\text{mol}^{-1}\text{s}^{-1}$) of Reactions of Substituted Benzophenones with Sodium Tetrahydroborate in Methanolic 0.1 M-NaOH at 25°C

| No | Substituent | 10^2k | No | Substituent | 10^2k |
|----|----------------------------------|----------------------|----|---|-------------------|
| 1 | H | 5.01 | 20 | 3-F | 30.2 |
| 2 | H | 5.26 ^a | 21 | 3-I | 36.8 |
| 3 | H | 0.837 ^b | 22 | 3-Br | 45.0 |
| 4 | H | 0.181 ^{c,d} | 23 | 3-Br | 48.0 ^a |
| 5 | H | 0.439 ^e | 24 | 3-Br | 1.21 ^c |
| 6 | H | 1.28 ^f | 25 | 3-Br | 3.01 ^e |
| 7 | H | 963 ^g | 26 | 3-Br | 9.63 ^f |
| 8 | H | 25 700 ^h | 27 | 3-Br | 2.32 ⁱ |
| 9 | 4-OCH ₃ | 1.49 | 28 | 3-Cl | 45.9 |
| 10 | 3-NH ₂ | 2.44 | 29 | 3-CN | 127 |
| 11 | 4-CH ₃ | 2.66 | 30 | 3-NO ₂ | 198 |
| 12 | 3-CH ₃ | 3.57 | 31 | 4-NO ₂ | 153 |
| 13 | 4-OC ₆ H ₅ | 4.85 | 32 | 4-CH ₃ , 4'-OCH ₃ | 0.91 |
| 14 | 3-OCH ₃ | 6.34 | 33 | 3-Br, 4'-OCH ₃ | 7.50 |
| 15 | 4-CO ₂ | 5.59 | 34 | 3-NO ₂ , 4'-OCH ₃ | 24.1 |
| 16 | 3-OC ₆ H ₅ | 8.21 | 35 | 4-NO ₂ , 4'-OCH ₃ | 34.4 |
| 17 | 4-F | 8.50 | 36 | 3,3'-Br ₂ | 154 |
| 18 | 4-Cl | 14.9 | 37 | 3,5-Br ₂ | 330 |
| 19 | 4-Br | 18.7 | 38 | 4-Cl, 4-NO ₂ | 630 |

^a Reduction with sodium tetradeuterioborate; ^b at 0°C ; ^c in isopropyl alcohol; ^d the authors⁵ give the value $0.158 \cdot 10^{-2} \text{l}\cdot\text{mol}^{-1}\text{s}^{-1}$; ^e in tert-butyl alcohol; ^f reduction with sodium trimethoxyhydroborate in tetrahydrofuran; ^g reduction with sodium triethoxyhydroborate in tetrahydrofuran; ^h reduction with sodium tritert-butoxyhydroborate in tetrahydrofuran; ⁱ reduction with sodium trimethoxydeuterioborate in tetrahydrofuran.

$\text{NaBH}(\text{OCH}_3)_3 < \text{NaBH}(\text{OC}_2\text{H}_5)_3 < \text{NaBH}(\text{OC}(\text{CH}_3)_3)_3$. Trimethoxyhydroborate undergoes disproportionation on dissolution in tetrahydrofuran, giving a mixture of sodium tetrahydroborate and tetramethoxyborate^{12,15}. However, the marked sensitivity to the isotopic effects supports the presumption that the decomposition of sodium trimethoxyhydroborate is only partial, and that the non-decomposed trimethoxyhydroborate reacts with benzophenone. As it was impossible to determine the accurate concentration of trimethoxyhydroborate in the reaction mixture, it was also impossible to determine the real reaction rate of this compound with benzophenone. High reactivity of tritert-butoxy- and triisopropoxyhydroborates (as compared with that of sodium tetrahydroborate) was predicted earlier^{15,16}. The rate constant found by us for the reaction of sodium tritert-butoxyhydroborate with benzophenone, $k = 257 \text{ l mol}^{-1} \text{ s}^{-1}$, confirms this prediction. The authors¹⁵ mention the easy disproportionation of sodium triethoxyhydroborate. Our observations, experiments with the powder X-ray analysis, and the high value of the reaction rate constant $k = 9.63 \text{ l mol}^{-1} \text{ s}^{-1}$ suggest that disproportionation (Scheme (B)) of this compound is very slight, its extent resembling more that of tritert-butoxyhydroborate than that of trimethoxyhydroborate in tetrahydrofuran. If the reduction of benzophenone

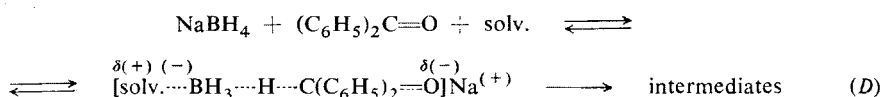


is carried out with a mixture $\text{NaBD}(\text{OCH}_3)_3 + \text{NaBH}(\text{OC}(\text{CH}_3)_3)_3$, no deuterium is incorporated in the product. Therefrom it follows that no exchange hydrogen-deuterium occurs between the both reagents, and sodium tritert-butoxyhydroborate is the reducing agent. Disproportionation of trimethoxyhydroborate into dihydrodimethoxyborate, trihydromethoxyborate, tetrahydroborate, and tetramethoxyborate¹⁷ complicates the identification of the proper reagent. We have found that sodium tetrahydroborate does not take part in the reduction of benzophenone (it is known that NaBH_4 in organic solvents does not reduce even the more reactive substrates as *e.g.* acetone¹⁸). Sodium trihydromethoxyborate obviously does not take part in the reduction, too, as it was found that this reagent is still less reactive than sodium tetrahydroborate². The found lower isotopic effect 4.2 (for trimethoxyhydroborate it was calculated 5.3) (ref.¹⁴) does not exclude the possibility that sodium dimethoxydihydroborate is the reducing agent besides sodium trimethoxyhydroborate (secondary isotopic effect of hydrogen).

Mechanism of Reduction of Benzophenones with Sodium Hydroborates

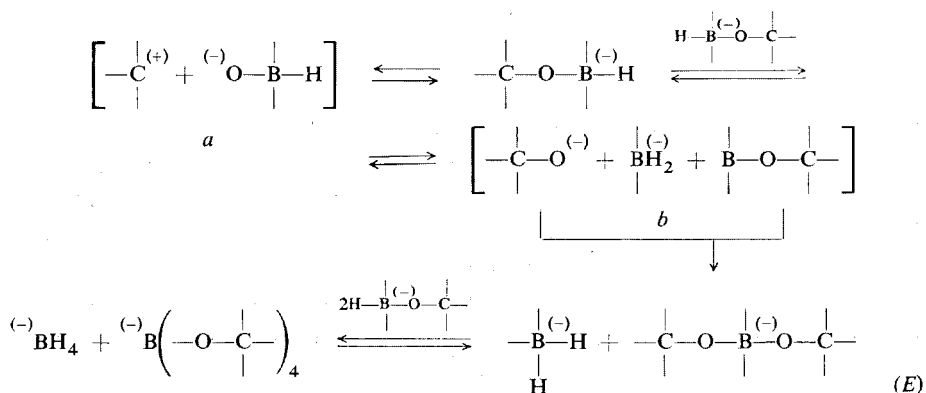
Table I gives the dependence of benzophenone reduction with sodium tetrahydroborate on the solvent used. In methanolic 0.1M-NaOH the rate is greater than in isopropyl alcohol by the factor of about 25. That is why we suppose that solvent

$\Delta S^\ddagger = -115.2 \text{ J K}^{-1} \text{ mol}^{-1}$ is common for simple bimolecular reactions and close to the data given by Brown⁴ for reduction of benzophenone with sodium tetrahydroborate in isopropyl alcohol ($\Delta S^\ddagger = -116.0 \text{ J K}^{-1} \text{ mol}^{-1}$). Besides that the sensitivity of the reaction to the substituent effects is substantially greater ($\rho = 2.26$) than that in the reduction of benzophenone with aluminium hydride ($\rho = 0.89$) or aluminium sesqui(2-methoxyethoxy)hydride ($\rho = 0.34$), where the mechanism is preferred involving a similar tetracentric complex with the character of ionic pair^{20,21}. The reaction going through the complex (a) agrees best with the found effects of medium and substituents. The overall reaction course representing the solvent effects is given in Scheme D (ref.³), where the formation of the complex is rate-limiting, and the



role of solvent consists in lowering of the activation energy of the hydrid-transfer by electron donation⁴ (E^\ddagger of the reaction of benzophenone with NaBH_4 in methanolic 0.1M-NaOH is 48.4 kJ mol^{-1} , Brown⁴ gives the value $E^\ddagger = 56.9 \text{ kJ mol}^{-1}$ for a similar reaction in isopropyl alcohol).

Reactions of trialkoxyhydroborates differ substantially both in the reaction rates (Table I) and in the extent of disproportionation of the reagent^{12,15}. The differences cannot be explained by sterical effects of the alkyl groups, rather they are due to electronic effects. We presume that, before the reaction with the carbonyl compound, the bonds C—O or O—B in the reagent are polarized or split (Scheme (E)). The relatively high stability of tert-butyl cation prefers the C—O bond splitting with formation of reactive ionic pair (Scheme (E), variant a) able to reduce benzophenones.

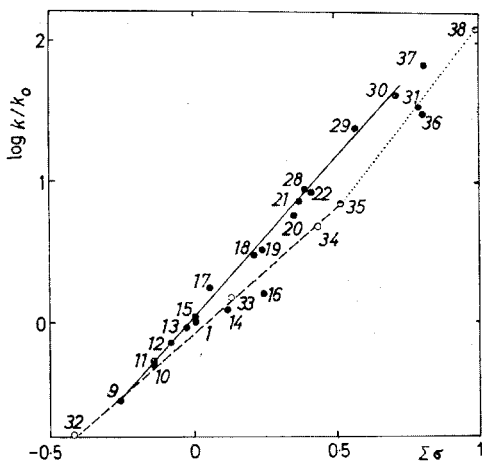


Disproportionation of $\text{NaBH}(\text{OCH}_3)_3$ proceeds probably in a series of bimolecular intermolecular reactions of the reagent according to the variant (b), Scheme (E). Similar changes in the site of splitting due to different alkyl groups were observed in hydrolyses of carboxylic acid esters²² (B_{Ac} , B_{Al}), Fig. 2 represents the correlation of the rate constants of the reactions of mono- and disubstituted benzophenones with sodium tetrahydroborate in methanolic 0.1M-NaOH at 25°C with the σ constants. Application of the normal Hammett σ constants²³ for 16 monosubstituted derivatives gave the reaction constant $\rho = 2.26$ which is somewhat lower than that found⁵ for reduction of acetophenones in isopropyl alcohol ($\rho = 3.06$). The lowering of sensitivity to the substituent effects is explained by deviation of the plane of one benzene ring (with respect to carbonyl) due to introduction of the second benzene ring. 4-Nitrobenzophenone deviates from the correlation (Fig. 2) and was not involved in calculation of the reaction constant. The deviations are explained by a change in coplanarity of the both nuclei due to the electronegative nitro group. We presume that, in contrast to the non-substituted benzophenone, the angle between the planes of the non-substituted benzene ring and carbonyl group is smaller in 4-nitrobenzophenone, which makes the +M effect of the non-substituted phenyl group on the reaction centre more important in the ground state, whereby the reactivity of the carbonyl group is decreased. This presumption is supported by similar electronic action of 4'-substituents as well as by further 4-nitrobenzophenones which exhibit a similar deviation and lie on a common line of the dependence $(\log k)/\sum\sigma$ different from that of the rest of the series.

4-Methoxy group, being an electron donor, increases the electron density between carbonyl carbon atom and aromatic nucleus whereby the angle between the planes

FIG. 2
The Hammett Correlation of Relative Rate Constants of Reduction of Benzophenones with Sodium Tetrahydroborate in Methanolic 0.1M-NaOH at 25°C

Full line connects the monosubstituted benzophenones (●), the dotted line connects the disubstituted benzophenones with constant 4'-NO₂ substituent (⊙), the dashed line connects the disubstituted benzophenones with constant 4'-OCH₃ substituent (○). For numbers of the benzophenones see Table I.



of this nucleus and carbonyl group is decreased. Sterical strain due to this effect causes a greater deviation of the other nucleus from the plane of the reaction centre and thus decreases the possibility of transmission of electronic effects from the other nucleus to the reaction centre. In accord with that the reaction constant of the reduction of 4-methoxy-4'(or 3')-substituted benzophenones is decreased to the value $\rho = 1.80$ (Fig. 1). Value of the coefficient $\iota_{4,4'}$, representing the measure of mutual harmony of electronic effects and non-additive action of two substituents was calculated for reduction of benzophenones, $\iota_{4,4'} = 0.2$. The value is smaller than those found for the protonation equilibria of benzhydrols⁷ and solvolyses of benzhydrol chlorides^{24,25}, where the carbonium ion is formed in the rate-limiting step ($\iota_{4,4'} = 0.4$). Further studies of cumulation of the electronic effects from the positions 3 and 5 could not be evaluated, because the chosen models (3-nitro-5-substituted benzophenones) quickly react with hydroborates to give coloured Meisenheimer complexes which are further reduced and decomposed to esters of boric acid. Similar complexes were identified also in reaction of hydroborates with trinitrobenzene²⁶. 3-Methoxy- and 3-phenoxybenzophenones were not involved in the correlation analysis; they are reduced more slowly than they should according to the respective σ constants. So far we have no explanation for this behaviour.

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