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THE REDUCTION OF SUBSTITUTED ACETOPHENONES BY SODIUM BOROHYDRIDE

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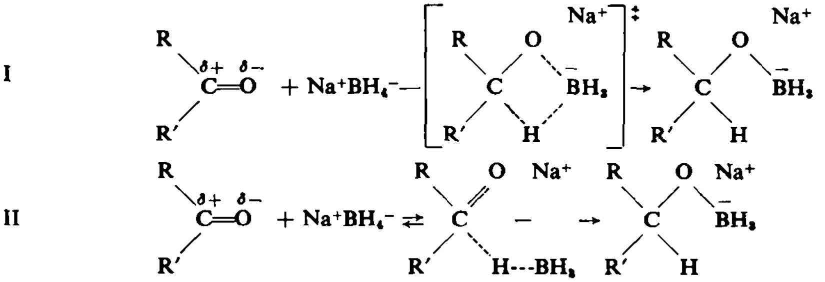
Abstract—The rates of reaction of sodium borohydride in isopropyl alcohol with acetophenone and nine *meta*- and *para*-substituted acetophenones at 30·0° have been measured. Hammett reaction constant ρ was found to be 3·06 and this agrees with the proposed mechanism. This result is compared with the results of other workers for the reduction of fluorenones. The separation of polar and steric effects in the reduction of arylaliphatic and aliphatic ketones by a Taft equation was attempted and the implications of the successful results are discussed.

INTRODUCTION

The mechanism and rates of reaction of a number of ketones and aldehydes with sodium borohydride in isopropyl alcohol have been investigated by Brown *et al.*[1-4] The reaction was considered to proceed with a rate-determining transfer of the first hydrogen atom of the borohydride ion to the carbonyl carbon. The two possible postulated pathways are shown below. These ion-pair reactions could proceed by the direct reaction pathway (I) or by the initial formation of a complex, followed by internal hydride transfer (II). This position is analogous to the one found earlier for the $B_{AC}2$ mechanism for ester hydrolysis.[5]



Previous investigations of polar substituent effects in this reaction have been made only on the fluorenone systems.[6,7] The application of the Hammett equation[8] (i) was

$$\log(k/k_0) = \rho\sigma \qquad \text{(i)}$$

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

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

[3] H. C. Brown and K. Ichikawa, *J. Amer. Chem. Soc.* **83**, 4372 (1961).

[4] H. C. Brown, R. Bernheimer and K. J. Morgan, *J. Amer. Chem. Soc.* **87**, 1280 (1965).

[5] M. L. Bender, *Chem. Revs.* **60**, 60 (1960).

[6] G. G. Smith and R. P. Bayer, *Tetrahedron* **18**, 323 (1962).

[7] J. A. Parry and K. D. Warren, *J. Chem. Soc.* 4049 (1965).

[8] H. H. Jaffé, *Chem. Rev.* **53**, 191 (1953).

complicated because of the possibility of transmission of the polar effect through the interannular link. The present study was undertaken to attempt to measure the reaction constant for a more ideal system, the substituted acetophenones, and to use this information to further interpret the existing data. The choice of acetophenones as a model system appears to be valid. In the reactant state the acetyl group will be co-planar with the aromatic ring, as in the fluorenone system. Benzophenones, however, exhibit considerable steric interactions between the aromatic rings and this results in twisting to give partial de-conjugation of the aromatic rings and the carbonyl group.

EXPERIMENTAL AND RESULTS

Materials. Isopropyl alcohol was dried by standing over $NaBH_4$ for 24 hr and heating under reflux for 2 hr. It was fractionally distilled and had b.p. 81–82°/750 mm (lit.[9] b.p. 82.4°/760 mm). $NaBH_4$ (reagent grade B.D.H.) was used and this was found to give the same results as samples recrystallized from diglyme.

The ketones were all available commercially and were recrystallized or redistilled under reduced pressure. Their physical properties were then found to agree well with the literature values.

Rate measurements. Sodium borohydride–isopropyl alcohol solutions were prepared by adding excess $NaBH_4$ to the isopropyl alcohol and, after standing, with intermittent shaking for 3 to 4 hr, filtering. The solutions were standardized by a modification of the iodate method of Lyttle *et al.*[10]. Aqueous 0·25N KIO_3 (40 ml), and 2M NaOHaq (5 ml) were mixed and 10 ml of the $NaBH_4$–isopropyl alcohol solution was added with careful swirling to ensure thorough mixing. After standing for 3 to 5 min, KI (2 g) was added, followed immediately by 2·5M H_2SO_4 (10 ml) and water (200 ml). The excess iodate was then titrated with 0·25N $Na_2S_2O_3$.

The rate of reaction was determined spectrophotometrically at 30·0° using a Unicam S.P. 500 spectrophotometer. The method used was similar to that previously employed successfully for the reaction of carboxylic acids with diazodiphenylmethane.[11] Solutions of the ketone (approximately 0·0001 to 0·003M) and $NaBH_4$ (0·03 to 0·08M) in isopropyl alcohol were stored in the thermostatic bath at 30·0 (±0·05)°. A 25 ml sample of the ketone solution was then added to the reaction flask immersed in the thermostatic bath and fitted with a rapid sampling device. The borohydride solution (25 ml) was then added and the timing was commenced on half addition. After thorough mixing, samples were taken at intervals and the optical density, in 1 cm silica cells, measured at the previously determined wavelength for the ketone (Table 1).

Under these conditions of excess borohydride, the reaction was first order in ketone alone. The apparent first-order rate coefficients k_1 were determined by the expression:

$$k_1 = \ln [a/(a - 4x)]/t$$

where a was the initial ketone concentration and $(a - 4x)$ was the concentration of ketone at time t (see also Brown *et al.*[1]). Thus the first-order rate coefficients are calculated from the slope of the linear relation between the logarithm of the optical density of the unreacted ketone and time. The second-order rate coefficients k were then obtained from the known standard borohydride concentration b as $k = k_1/4b$. The reaction was followed for about 2 half-lives of the ketone. An "infinity" (after about 10 half-lives of the ketone) optical density reading was taken. The ketone absorption obeyed the Beer-Lambert law. The reaction products also absorbed at wavelengths less than 260 mμ The method was easily adjusted[12] by using the optical density at zero time and "infinity" for ketones

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[9] A. Weissberger. *Techniques of Organic Chemistry* (2nd Edition) Vol. VII. Interscience, New York (1955).

[10] D. A. Lyttle, E. H. Jensen and W. A. Struck, *Analyt. Chem.* **24**, 1843 (1952).

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TABLE 1. REACTION OF SUBSTITUTED ACETOPHENONES WITH SODIUM BOROHYDRIDE IN ISOPROPYL ALCOHOL AT 30·0°

Substituent	λ Max (mμ)	10^4k (l. mole^{-1} sec^{-1})
p-Me	250·5	3·76
m-Me	286	9·58
H	278	15·7*
p-OMe	271	20·4
p-F	244	28·0
p-Cl	251	95·0
p-Br	255	115
m-F	291	152
m-Cl	288·5	174
m-Br	289	208
(Benzophenone	335	21·0*)

The rate coefficients k(l. mole^{-1} sec^{-1}) were reproducible to ±3% or better.

* Interpolated values (10^4k) from results of earlier workers[1] are 19·4 (acetophenone) and 23·3 (benzophenone).

which had absorption maxima at these wavelengths.† The reaction results in quantitative yields of 1-phenylethanols and has been used preparatively.[14]

The results are summarized in Table 1 and are the mean of at least two separate measurements. The rate coefficients for acetophenone and benzophenone were in reasonable agreement with those of previous workers.[1] The results of other workers[6,7] on the fluorenones are in less satisfactory mutual agreement.

DISCUSSION

Application of the Hammett equation

The Hammett Eq. (i) was applied to the rate coefficients in Table 1. The σ values recommended by McDaniel and Brown[15] were used and the correlation is shown in Fig. 1. The *para*-methoxy substituent was extremely poorly correlated and was excluded from the calculations, giving ρ equal to 3·06, shown in Table 2. A possible explanation of this behaviour would be the formation of a complex between the aryl alkyl ether and borohydride species, especially as there is a large excess of borohydride present. However, this does not seem very likely. The correlation is not improved by the use of the σ^n values for *para*-substituents[16] when ρ equals 3·13. The corresponding correlations have been made for the substituted fluorenones[6,7] and are also shown in Table 2. It seems very reasonable to consider the reaction constants at 25° and 30° directly comparable. The results of the correlations indicate that the transmission of polar effects in the fluorenone system, *in general*, was not enhanced in this reaction. Neither a significant σ- or π-electron transmission through the unsubstituted ring or an increased field effect appears to occur.

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† These ketones have no maxima in their C band absorption and it was necessary to use the B band absorption.[13]

[13] W. Forbes, W. A. Mueller, A. S. Ralph and J. F. Templeton, *Canad. J. Chem.* **35**, 1049 (1957).

[14] H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.* **77**, 3164 (1955).

[15] D. H. McDaniel and H. C. Brown, *J. Org. Chem.* **23**, 420 (1958).

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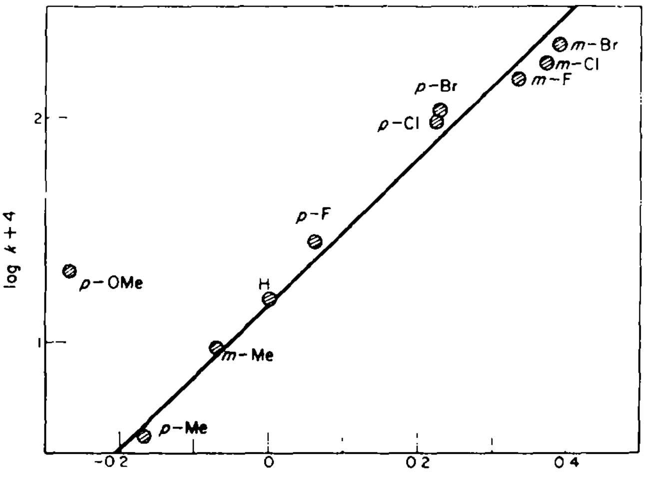
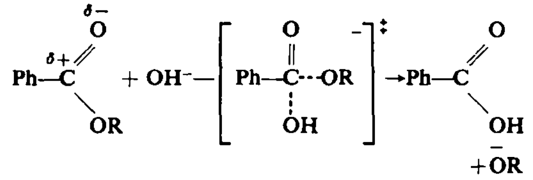


FIG. 1

The value of the reaction constant found re-confirms the character of the rate determining step as involving a nucleophilic attack resulting in a negatively charged transition state (see also previous workers[6,7]). This reaction constant is similar to that observed for alkaline ester hydrolysis, where the ρ values are found to be between 2·1 and 2·8 at 25° or 30° in various solvents. This expresses the stabilization by the polar effect of the substituent on the formation of the transition state, which approximates to the addition of a hydroxide ion to the alkyl benzoate (III).

III



Separation of polar and steric effects

Brown *et al.*[1–4] have postulated a dominant role for steric effects in the borohydride reduction of ketones where substituents are varied in the vicinity of the reaction site. These workers do however admit the likelihood of a polar contribution but doubt the

TABLE 2. HAMMETT ANALYSIS OF REDUCTION OF KETONES WITH SODIUM BOROHYDRIDE[a]

System	ρ	$-\log k_0$	r	n	Ref.
Acetophenones at 30°	[b] 3·058	2·806	0·990	9	This work
	[c] 3·131	2·844	0·989	9	This work
Fluorenones[d] at 25°	[b] 2·969	1·919	0·961	13	6
	[c] 3·185	1·834	0·951	13	6
Fluorenones[d] at 25°	[b] 3·111	2·170	0·970	14	7

[a] r is the correlation coefficient, n is the number of substituents studied

[b] Using σ values

[c] Using σ^n values

[d] Using *meta*-σ values for 2-substituents and *para*-σ values for 3-substituents.

possibility of a meaningful separation of the polar and steric effects.[3] The use of the borohydride reduction reaction as a model for solvolysis reactions[4] makes the estimate of the relative significance of the two effects important.

Taft[17] has suggested the use of the following equation (ii) to correlate reaction systems involving dependence on both polar and steric effects. The constants σ^* and E_s are the polar and steric substituent constants respectively;

$$\text{(ii)} \qquad \log (k/k_0) = \rho^*\sigma^* + \delta E_s$$

while ρ^* and δ are the polar and steric reaction constants respectively. The polar substituent constants appear to have a wide range of application. However, the steric effects must be of the same type as those involved in alkaline ester hydrolysis. The steric factors are those involved in forming the tetrahedral transition state for alkaline ester hydrolysis from a trigonal reactant state (see III). The formation of the transition state will be inhibited by an increase in steric interactions within the molecule and by the repulsive interaction between the entering nucleophile and the molecule itself.[18] The Taft relation (ii) has been used successfully to correlate basic ester reactions.[19–21]

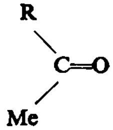
The data available for arylalkyl and alkyl methyl ketones are shown in Table 3, together with the polar and steric substituent constants for the varied group.[17,21] The correlation, which was very successful, is given below (iii). The success of the correlation

$$\text{(iii)} \qquad \log k = 0{\cdot}760\,\sigma^* + 0{\cdot}574\,E_s - 0{\cdot}045$$

$$\text{Correlation coefficient } r = 0{\cdot}998$$

$$\text{Standard deviation } s = 0{\cdot}036$$

TABLE 3. TAFT ANALYSIS OF REDUCTION OF KETONES



WITH SODIUM BOROHYDRIDE

Substituent R	log (k/k_0) at 50·0°.[3,4]	Subst. constants.[17,21] σ^*	E_s
CH_3	0·000	0·0	0·0
$PhCH_2$	0·190	0·215	−0·37
Ph_2CH	−0·712	0·405	−1·43
Ph_3C	−2·312	0·560	−4·68
$MeCH_2$	−0·270	−0·100	−0·07
Me_2CH	−0·590	−0·190	−0·47
Me_3C	−0·991	−0·300	−1·54
PhMeCH	−0·636	0·110	−1·19

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[17] R. W. Taft. In *Steric Effects in Organic Chemistry* (Edited by M. S. Newman) Chap. 13. J. Wiley, New York (1956).

[18] F. Becker, *Z. Naturforsch.* **16b**, 236 (1961).

[19] W. A. Pavelich and R. W. Taft, *J. Amer. Chem. Soc.* **79**, 4935 (1957).

[20a] C. K. Hancock, E. A. Meyers and B. J. Yager, *J. Amer. Chem. Soc.* **83**, 4211 (1961).

[b] C. K. Hancock and C. P. Falls, *Ibid.* **83**, 4214 (1961).

[c] C. K. Hancock, B. J. Yager, C. P. Falls and J. O. Schreck, *Ibid.* **85**, 1297 (1963).

[21] K. Bowden, N. B. Chapman and J. Shorter, *J. Chem. Soc.* 3370 (1964).

appears to indicate that the mechanistic comparison made previously is suitable and that the rate-determining step is as suggested. Steric effects of the same type as are found in alkaline ester hydrolysis must occur.

The E_s values include a polar contribution, i.e. $E_s = \rho^*\sigma^* + E_s^N$ where E_s^N is the true steric substituent constant.† The latter ρ^* value would be probably negative and comparatively small. This will *decrease* the values of ρ^* found by use of equation (ii). Thus, these values are not then directly comparable to those obtained by using the simple relation (iv), such as the ionization of carboxylic acids in water.

$$\log (k/k_0) = \rho^*\sigma^* \qquad \text{(iv)}$$

A selection of comparable ρ, ρ^* and δ values are shown in Table 4.

However, these latter considerations do not affect the general significance of the correlations using both σ^* and E_s.[22,23] The conclusions that can be made are, therefore, relative to the alkaline ester hydrolysis reaction. In the arylalkyl and alkyl system, the susceptibility of the borohydride reaction to polar effects is less than that of alkaline ester hydrolysis reaction. This is the converse of the position in the aromatic series. The inhibition of the reaction by the steric effect of the substituents is also less than that present in the ester reaction. The value of δ/ρ^* for the borohydride reaction (0·8) is however much greater than that for the alkaline ester hydrolysis (between 0·4 and 0·5). Steric effects therefore appear to have a dominant role in this reaction.

As can be seen from Table 4, the relation between ρ and ρ^* is very complex and only the consideration of model reaction systems[24] will elucidate the relation between these reaction constants.

Table 4. Comparison of Hammett and Taft reaction constants

Reaction	Hammett reaction constant ρ	Ref.	Taft reaction constants ρ^*	δ	Ref.
1. Ionization of acids in water at 25°	1·000	8	1·752	—	17,24
2. Esterification of acids with diazodiphenylmethane in ethanol at 30·0°	0·944	25	1·084	—	24
3. Alkaline hydrolysis of methyl esters in 80% v/v methanol–water at 60·0°	2·079	26	1·64	0·87	21
4. Methoxide-catalysed methanolysis of *l*-menthyl esters in methanol at 30·0°	2·65	27	2·70	1·30	19
5. Reduction of methyl ketones in isopropyl alcohol by sodium borohydride	3·058[a]	This Work	0·76[b]	0·57[b]	1,4 This Work

[a] at 30°. [b] at 50°.

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† The reaction used most often in defining E_s values was the acid-catalysed esterification of carboxylic acids in methanol. The ρ value for this reaction[18] is −0·521 at 25°.

[22] D. Farcasiu, *Sposobnost Organ. Soedin., Tartusk. Gos. Univ. Reaktsionnaya* **2**, 119 (1965).

[23] V. A. Palm, *Sposobnost Organ. Soedin., Tartusk. Gos. Univ. Reaktsionnaya* **2**, 123 (1965).

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