Kinetics of Reduction of Acetophenones by Alkali-metal Alkoxides, and the Mechanism of Reduction of Ketones by Borohydride

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The reduction of *p*-substituted acetophenones by lithium, sodium, and potassium isopropoxides gives Hammett reaction constants (ρ) of +1.45, +1.62, and +1.75, respectively. Comparison with data for reductions of acetophenones by borohydride supports the view that the transition state for reduction of ketones by borohydride is product-like. Stereochemical variations in the reduction of steroidal ketones by borohydrides are reinterpreted in terms of ' steric strain control ' as the principal contributing factor.

DIFFERING opinions on the detailed mechanism of reduction of ketones by complex hydrides have included preferences for both reactant-like and product-like transition states. Barton[1] first pointed out that unhindered cyclohexanones give mainly the more stable equatorial alcohols, and Dauben and his co-workers[2] developed the twin concepts of ' product development control ' for unhindered cyclohexanones, contrasting with ' steric approach control ' for hindered cyclohexanones. Despite the generally assumed implication of two distinct types of transition state, these ideas have been useful as a basis for interpreting the stereochemistry of reduction of steroidal and similar ketones. Dauben's proposals have been followed by numerous arguments based on experimental data and on theoretical considerations, in the quest for a satisfactory unified interpretation of the kinetic and stereochemical features of the reduction of ketones by hydride donors. Reviews[3] have coincided with or been followed by further significant papers. Chérest and Felkin,[4] criticising hypotheses which require two different types of transition states, proposed that torsional strains may affect the energy of a transition state which they considered to be reactant-like. Geneste, Lamaty, and Roque, however, interpreted kinetic data in favour of a product-like transition state.[5] Eliel and Senda[6] found little evidence for ' product development control ' from a study of the reduction of alkylcyclohexanones, but considered that their data supported the concept of ' steric approach control.' Cense[7] based a preference for a product-like transition state on the results of enthalpy measurements. Wigfield and Phelps,[8] extending earlier studies of deuterium isotope effects in the reduction of ketones (by $NaBD_4$ *vs.* $NaBH_4$), confirmed the reported *inverse* isotope effect, and showed that its magnitude is almost invariant with the degree of steric hindrance in the ketone, an observation considered to be incompatible with the idea of a variable transition state. After re-evaluating evidence prior to 1971, they defined ' approach control ' (omitting the word ' steric ') as referring to any (bimolecular) reaction with an early transition state, in contrast to ' product development control ' for a reaction where the transition state lies relatively late in the reaction. The same authors more recently reported 2-alkyl substituent effects on enthalpies of activation for the reduction of cyclohexanone derivatives by borohydride:[9] their findings seem rather more readily explained on the basis of a reactant-like transition state, but they preferred to remain undecided about the position of the transition state pending further studies. Calvet and Levisalles[10] have reported a study of 5α-substituent effects on the reductions of 3-oxo-steroids, which point to a product-like transition state.

Other recent contributions have been concerned with orbital distortion; the formally localised carbonyl π and π* orbitals were considered to be deformed by mixing with adjacent σ and σ* orbitals in cyclohexanone derivatives[11] or other ketones,[12] the effect being a preference for hydride approach from one side rather than from the other, so as to favour formation of the observed major products. Hyperconjugative interactions between C_α–C_β bonds and the carbonyl group, varying according to β-substitution, have also been proposed[13] as an important factor contributing to control of the stereochemistry of reduction of 3-oxo-steroids substituted at C-5.

The present work was undertaken essentially as a test of the validity of Geneste, Lamaty, and Roque's opinion[5] that Hammett reaction constants (ρ) for reductions by borohydride provide evidence of a product-like transition state. Large positive values of ρ (+2.81 and +3.06) for reduction of benzophenones by lithium borohydride,[14] and of acetophenones by sodium borohydride,[15] respectively, were taken to imply considerable transfer of electronic charge from the borohydride to the organic

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[1] D. H. R. Barton, *J. Chem. Soc.*, 1953, 1027.

[2] W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Amer. Chem. Soc.*, 1956, **78**, 2579.

[3] (*a*) O. H. Wheeler, in ' The Chemistry of the Carbonyl Group,' ed. S. Patai, Interscience, London, 1966, p. 541; (*b*) D. N. Kirk and M. P. Hartshorn, ' Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, p. 135; (*c*) D. M. S. Wheeler and M. M. Wheeler, in ' Organic Reactions in Steroid Chemistry,' ed. J. Fried and J. A. Edwards, van Nostrand–Reinhold, New York, 1972, vol. 1, p. 66.

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[6] E. L. Eliel and Y. Senda, *Tetrahedron*, 1970, **26**, 2411.

[7] J. M. Cense, *Tetrahedron Letters*, 1972, 2153.

[8] D. C. Wigfield and D. J. Phelps, *Canad. J. Chem.*, 1972, **50**, 388.

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[10] A. Calvet and J. Levisalles, *Tetrahedron Letters*, 1972, 2157.

[11] J. Klein, *Tetrahedron Letters*, 1973, 4307; *Tetrahedron*, 1974, **30**, 3349.

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[13] C. Agami, A. Kazakos, and J. Levisalles, *Tetrahedron Letters*, 1975, 2035.

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[15] K. Bowden and M. Hardy, *Tetrahedron*, 1966, **22**, 1169.

reactant, indicating a more product-like transition state than for attack by other nucleophiles (*e.g.* CN$^-$, SO$_3^{2-}$, or Grignard reagents), which gave smaller ρ values. Values of ρ in the range $+2.5$ to $+3.1$ have also been reported for the reductions of substituted fluorenones.[16]

The transition state for reduction of a carbonyl group by borohydride must be structurally unsymmetrical, since a hydride transfer from boron to carbon forms the core of the transition state, whatever may be the associated arrangement of cations and solvent molecules.

We reported in 1969 [17] that alkali-metal (particularly lithium) isopropoxides are efficient hydride transfer reagents for the reduction of ketones. Since hydride would be expected to transfer from carbon to carbon in a single step, the transition state should have *local* symmetry. Figure 1 gives schematic illustrations of two possible transition states, one ' bimolecular ' and cyclic [Figure 1(a)], the other ' termolecular ' [Figure 1(b)]. Although these diagrams are no doubt oversimplified, in failing to include solvent molecules or to take account of the likely oligomer state of the alkoxide,[18] they illustrate the essential symmetry of the $\overset{\delta-}{O}\text{⋯}C \cdots H \cdots C\text{⋯}\overset{\delta-}{O}$ component, which requires that the charge densities in the two C $\cdots$ H partial bonds should be equal, except insofar as they are modified by any differences between alkyl (or aryl) groups (Me, R^1, and R^2). Hydride transfer from alkoxides is reversible, unlike that from borohydrides.

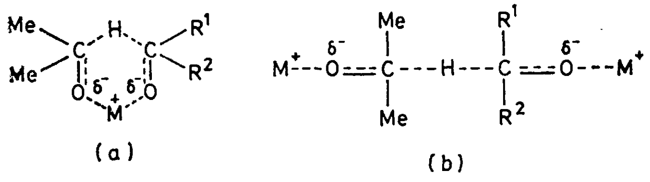
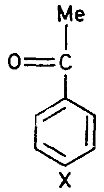


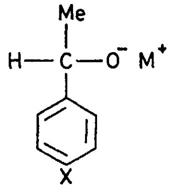
FIGURE 1 Possible transition states for the reduction of ketones by alkali-metal isopropoxides

Local symmetry in the transition state represented by Figure 1 implies that approximately half of the electronic charge has been transferred from reagent to reactant in the transition state. We therefore studied the kinetics of some reactions of this type, considering them as having a transition state approximately mid-way along the reaction co-ordinate, and thereby providing a reference point for the evaluation of the borohydride data for the same ketones in terms of either a relatively more reactant-like or a relatively more product-like transition state.

Present Investigation.—The ideal symmetrical reduction would have been of an acetophenone (1) by the corresponding 1-phenylethoxide (2). It would be necessary in practice to distinguish structurally between reagent and reactant molecules, and for Hammett analysis to employ substituted acetophenones. However, the mutual oxidation-reduction of a pair of compounds differing only in their *para*-substitution should not cause gross departure from the ideal of a symmetrical transition state. We therefore made an attempt to study the kinetics of reduction of a series of *p*-substituted acetophenones (1) by lithium 1-phenylethoxide (3). Lithium metal would not react smoothly with 1-phenylethanol, so a solution of lithium t-butoxide in toluene was treated with the stoicheiometric amount of 1-phenylethanol, and t-butyl alcohol was removed along with some toluene by distillation. This solution reduced acetophenones, but the resulting second-order rate constants were not at all reproducible.



(1) X = Me,H, F, or Cl



(2) M = Li, Na, or K; X = Me, H, F, or Cl
(3) M = Li, X = H

Attention was therefore turned to the use of alkali-metal isopropoxides in refluxing propan-2-ol, which gave satisfactory kinetic data for the reduction of acetophenones. Despite the departure from perfect symmetry in the gross structure of the transition state, the essential requirement of hydride transfer between two secondary carbon atoms is met by this system. Moreover the use of propan-2-ol as solvent, and inclusion of Na$^+$ among cations studied, ensured the closest possible identity with earlier kinetic studies of reductions of acetophenones by sodium borohydride.

The reductions of a series of acetophenones by lithium, sodium, and potassium isopropoxides followed first-order kinetics, for the concentration of isopropoxide remains essentially constant in propan-2-ol as solvent. Product mixtures were analysed by g.l.c. Slopes of first-order plots were calculated from experimental data by the method of least squares; correlation coefficients (r) were all better than 0.99. Second-order rate constants (k_2), obtained by taking account of the constant isopropoxide concentration, are listed in Table 1. Graphs of log k_2 against Hammett substituent constants (σ) were essentially linear, and gave the reaction constants (ρ) listed in Table 2.

TABLE 1

Second-order rate constants for the reductions of *p*-substituted acetophenones (0.05M) with alkali-metal isopropoxides (0.05M) in refluxing propan-2-ol (*ca.* 83 °C)

	k_2/l mol^{-1} min^{-1}		
p-Substituent	LiOPr	NaOPr^i	KOPr^i
Me	0.27	0.035 5	0.012
H	0.54	0.070 5	0.022
F	0.59	0.084	0.023
Cl	1.03	0.158	0.061

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[16] G. G. Smith and R. P. Bayer, *Tetrahedron*, 1962, **18**, 323; J. A. Parry and K. D. Warren, *J. Chem. Soc.*, 1965, 4049; K. D. Warren, and J. R. Yandle, *ibid.*, p. 5518; A. J. Harget, K. D. Warren, and J. R. Yandle, *J. Chem. Soc.* (*B*), 1968, 214.

[17] D. N. Kirk and A. Mudd, *J. Chem. Soc.* (*C*), 1969, 804.

[18] C. W. Kamienski and D. H. Lewis, *J. Org. Chem.*, 1965, **30**, 3498.

Discussion.—Values of ρ, averaging +1.6, are much smaller than the value of +3.06 reported for reduction of the same compounds with sodium borohydride, supporting the interpretation[5] of the latter result as evidence for a product-like transition state. Possible differences in metal-ion binding between the two reactions seem unlikely to be large enough to account for the large difference in ρ values, in view of the extent of similarities between reaction constituents. Variations in ρ with the cation are too small to be treated as significant, but there is a marked dependence of overall rates of reaction on the cation, the ratios of rates being *ca.* 25 : 3.2 : 1 for $Li^+ : Na^+ : K^+$. A similar trend was noted in our earlier work with isopropoxides.[17] This order corresponds to the respective abilities of the cations to polarise the carbonyl group, but other factors, such as the extents of solvation of the alkali-metal alkoxides, seem likely to be involved. Differences[19] in ion-pair dissociation constants ($RO^-Li^+ > RO^-Na^+ > RO^-K^+$) may also contribute, if the reductions are effected wholly or in part by free isopropoxide ions. Cation involvement is indicated, however, by the metal-dependence of axial : equatorial product ratios in reductions of cyclohexanones by isopropoxides.[17]

TABLE 2

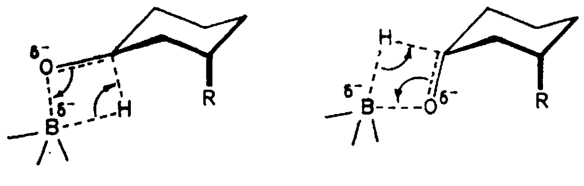
Hammett reaction constants (ρ) for reduction of *p*-substituted acetophenones with alkali-metal isopropoxides

Reagent	ρ [a]
$LiOPr^i$	$+1.45 \pm 0.12$
$NaOPr^i$	$+1.62 \pm 0.03$
$KOPr^i$	$+1.75 \pm 0.15$

[a] ρ Values with standard deviations.

Reduction of Ketones by Borohydride.—We believe that the weight of recent evidence, cited above and reinforced by our present results, strongly supports the view that borohydrides reduce ketones through a product-like transition state, in which both charge transfer from the reagent and rehybridisation at carbon are well advanced. We consider it necessary, however, to reinterpret some of the evidence previously cited in favour of an early or reactant-like transition state. The ' steric approach control ' concept,[2] generally considered to imply an early transition state, arose originally from the observed formation of the more strained *cis*- (axial) alcohols in the reductions of some hindered cyclohexanone analogues having a ' 3-axial ' substituent (*e.g.* 3,3,5-trimethylcyclohexanone[6] or 4-oxo- and 6-oxo-5α-steroids[3b]). These reactions, which are manifestly not under ' product development ' control, give products of attack from the less hindered side of the carbonyl group. Moreover Eliel and Senda[6] were unable to find any clear indications of product development control of reduction in their series of alkylated cyclohexanones. These authors pointed out, however, that the geometry of a cyclic four-atom transition state (Figure 2) would not permit either the $C \cdots H$ or the $C\overset{\cdots}{-}O$ bond to take up the truly axial direction which one of them must assume in the final product. The 1,3-diaxial interactions which destabilise compounds like *cis*-3,3,5-trimethylcyclohexanol, and 4β-hydroxy- or 6β-hydroxy-5α-steroids, need not be fully developed until after the transition state has been passed.

The term ' steric approach control ' is usually taken to imply an early transition state, but we believe the emphasis to have been wrongly placed on 'approach'. With Brown and Deck,[20] we prefer the term ' steric strain control ', referring to destabilisation of a transition state by steric congestion at whatever point the transition state may occur on the reaction co-ordinate. The state of compression which undoubtedly develops and increases as a borohydride approaches the hindered side of a carbonyl group may well contribute to a prohibitively high total free-energy of activation in a *late* transition state. The usual preference for reduction of a 3- (axial) alkylcyclohexanone analogue to give the axial (*cis*-) alcohol is compatible with a late transition state of the four-centre type (Figure 2); attack of the reagent from the ' axial ' direction would produce a highly congested transition state [Figure 2(a)], where compression between the incoming hydride and the ' 3-axial ' methyl group could be even greater than in the final product, as a consequence of the transition state geometry. The alternative attack of hydride from the ' equatorial ' direction would be relatively more favourable [Figure 2(b)], for the only opposing interaction here is ' 1,3-diaxial ' compression between the oxygen and the axial methyl group, but this would not be fully developed in a transition state with the geometry of Figure 2(b), where the oxygen atom is not truly axial.



(a) R = Me (b) R = Me
(c) R = H (d) R = H

FIGURE 2 Cyclic four-centre transition states for the reduction of cyclohexanones by borohydride

There remains the case of unhindered cyclohexanones, which are reduced to give mainly the more stable equatorial alcohols. The choice is between the transition states illustrated in Figure 2(c) (' axial ' attack) and in Figure 2(d) (' equatorial ' attack). The former mode of attack encounters only minimal compression between axial and quasi-axial hydrogens, whereas the latter introduces a little of the instability associated with compression of axial oxygen. This distinction alone may not be sufficient to account for the observed preference

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[19] J. Barthel, G. Schwitzgebel, and R. Wachter, *Z. phys. Chem. (Frankfurt)*, 1967, **55**, 33; we are grateful to a referee for bringing this paper to our attention.

[20] H. C. Brown and H. R. Deck, *J. Amer. Chem. Soc.*, 1965, **87**, 5620.

(*ca.* 80—90%) for formation of equatorial alcohols, but an additional requirement that the oxygen atom in Figure 2(d) should be solvated or closely associated with a solvated cation [14] would increase the total steric congestion in this transition state. A further possible explanation has recently been advanced by Wertz and Allinger,[21] who argue for a significant and hitherto unsuspected *gauche*-hydrogen interaction, and have illustrated its effect by reference to the preferential formation of equatorial alcohols from unhindered cyclohexanones, among other phenomena. An equatorial hydrogen atom is subject to four *gauche* H–H interactions, compared with only two such interactions for an axial hydrogen atom. It is proposed that the extra two H–H interactions destabilise equatorial H, and so favour an equatorial hydroxy-group, by *ca.* 0.9 kcal mol^{-1}, a value even larger than that corresponding to the observed conformational preference of the OH group. Other arguments are offered [21] to explain the discrepancy. The Wertz–Allinger hypothesis, if valid, introduces a ' steric strain ' contribution of the correct order of magnitude to explain the stereochemistry of reduction of unhindered cyclohexanones, and is fully compatible with a product-like transition state.

In summary, we propose that the transition state in borohydride reductions of ketones is always more product-like than reactant-like, and that the stereochemistry of the reduction is decided largely by the imbalance of the steric strain energies associated with attack on one face or the other of the carbonyl group.

Recent arguments [11-13] based upon unsymmetrical π orbitals or perturbed electron distribution in the intact carbonyl group seemingly would apply only to a reactant-like transition state, and will need re-evaluation to allow for advanced rehybridisation, with loss of much of the π character, if the transition state is always essentially product-like as we propose.

EXPERIMENTAL

Materials.—Acetophenone and *p*-substituted acetophenones were as supplied (Koch-Light). They were essentially pure ($\geqslant$99% by g.l.c.) with the exception of *p*-methylacetophenone (93%); the impurities, probably the *o*- and *m*-isomers, were not removed by fractional distillation, so allowance was made for their presence during weighings and calculations. Propan-2-ol was distilled from 2,4-dinitrophenylhydrazine and calcium hydride, then twice from lithium isopropoxide immediately before use; the final distillation was performed directly into the flask to be used for the reduction. Precise volumes of solvent were measured after completion of reactions. Metals were cut and weighed immediately before use.

Reduction of Acetophenones.—Propan-2-ol (*ca.* 530 ml), in a dry three-necked 1 l flask equipped with a reflux condenser (drying tube), a rubber septum, and a stopper, was treated with the required weight of lithium, sodium, or potassium metal to obtain a *ca.* 0.05M-solution. The mixture was heated under gentle reflux until a clear solution was obtained, then the weighed acetophenone, in a small wide-necked vial, was added through the side-arm, the mixture was swirled vigorously, and refluxing was allowed to continue.

Samples (*ca.* 2 ml) were withdrawn at intervals *via* the septum with a hypodermic syringe, and were quenched at once in a slight excess of 0.1M-hydrochloric acid. Each sample was extracted twice with ether (10 ml), and the combined extracts were washed with dilute sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and left in an open-necked vial at room temperature until the ether had evaporated.

A control experiment using an equimolar mixture of acetophenone and 1-phenylethanol showed that the extraction procedure was reliable, giving a ratio of 50 : 50 ($\pm$0.5%) after g.l.c. analysis.

Samples were analysed by g.l.c. Each acetophenone was completely resolved from its reduction product, and peaks were integrated automatically. Analysis of an equimolar mixture of acetophenone and 1-phenylethanol showed identical detector responses (f.i.d.).

Rate constants (Table 1) were calculated according to the normal second-order rate equation; each run gave a good linear plot when treated as first-order in ketone. Runs with lithium and potassium isopropoxides were duplicated: Table 1 records mean values of k_2. Table 2 lists Hammett reaction constants (ρ) with their standard deviations; consideration of possible accumulated errors in the sampling and analytical procedure suggests maximum probable errors in ρ of $\pm$0.2.

[6/070 *Received, 12th January,* 1976]

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[21] D. H. Wertz and N. L. Allinger, *Tetrahedron*, 1974, **30**, 1579.