On the Mechanism of Reduction of Benzophenones by Aluminium Hydride and Alkoxyaluminium Hydrides

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The rates of reduction of a group of *pp*′-disubstituted benzophenones by lithium tri-t-butoxyaluminium hydride have been determined together with the relative rates of reaction with aluminium hydride. The Hammett plots obtained show that the carbonyl group acquires carbanion character in the former reaction but that there is little charge separation in the latter; this is consistent with the cyclic transition state assumed for aluminium hydride reductions. Only a small proportion of the hydrogen atoms of aluminium hydride were available for the reduction of benzophenones. Alkoxyaluminium hydrides produced as intermediates in the reduction of benzophenones, or by exchange between aluminium hydride and alkoxides, reduce aliphatic ketones preferentially.

THE coincidence in the steric results of reduction of 3,3,5-trimethylcyclohexanone (dihydroisophorone) with lithium aluminium hydride–tri-t-butoxyaluminium, aluminium hydride–tri-t-butoxyaluminium, and lithium tri-t-butoxyaluminium hydride led us to consider[1] the possibility that a common hydride donor was effective in these three systems. Dissociation (1) and/or exchange (2) reactions could, for example, lead to di-t-butoxyaluminium hydride as a common component.

$$\left.\begin{array}{l} \mathrm{Li^+AlH_4^-} \rightleftharpoons \mathrm{Li^+ + AlH_3 + [H^-]} \\ \mathrm{Li^+Al^-(OBu^t)_3H} \rightleftharpoons \\ \qquad \mathrm{Li^+ + Al(OBu^t)_2H + Bu^tO^-} \end{array}\right\} \quad (1)$$

$$\mathrm{AlH_3 + 2Al(OBu^t)_3} \rightleftharpoons \mathrm{3Al(OBu^t)_2H} \quad (2)$$

We expected that a Hammett plot for the reduction of a group of aromatic aldehydes or ketones would reveal donation of hydride by an anion, when the slope (ρ) would be large and positive. In contrast, a neutral aluminohydride effective as a Lewis acid would give a negative ρ value, for the reaction would be accelerated by the interaction of electron-donating substituents with the electron-deficient carbonyl carbon atom as this became co-ordinated to aluminium in the transition state (*cf.* Figure 3). Lithium tri-t-butoxyaluminium hydride was available for a study of this kind and although dialkoxyaluminium hydrides are unobtainable, aluminium hydride itself provided a comparison. We selected a group of *pp*′-disubstituted benzophenones because the parent substance is the least reactive of all simple carbonyl compounds. Even so the initial rate of reduction of benzophenone by aluminium hydride was unmanageably fast at −75 °C and for this part of the work we had recourse to comparison by competitive reactions.

EXPERIMENTAL

Materials.—Tetrahydrofuran dried over sodium wire was twice distilled from lithium aluminium hydride and used immediately. Solutions of aluminium hydride (*ca.* 0·4M) in tetrahydrofuran were prepared by the procedure of Brown and Nung Min Yoon[2] and standardised by Felkin's procedure.[3] Lithium tri-t-butoxyaluminium hydride was obtained by the addition of t-butyl alcohol (3 equiv.) to lithium aluminium hydride (1 equiv.) in diethyl ether. The product[4] was filtered off, dried *in vacuo*, and dissolved

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[1] D. C. Ayres and R. Sawdaye, *Chem. Comm.*, 1966, 527.

[2] H. C. Brown and Nung Min Yoon, *J. Amer. Chem. Soc.*, 1966, **88**, 1464.

[3] See D. C. Ayres, D. N. Kirk, and R. Sawdaye, *J. Chem. Soc.* (*B*), 1970, 505.

[4] H. C. Brown and R. F. McFarlin, *J. Amer. Chem. Soc.*, 1956, **78**, 252; 1958, **80**, 5372.

in tetrahydrofuran (3 equiv.); it was characterised by collection of hydrogen during preparation and also by Felkin's procedure.

Tri-t-butoxyaluminium was prepared [5] from the alcohol and amalgamated aluminium and distilled *in vacuo* before use.

The *pp'*-disubstituted benzophenones were all commercial samples which were recrystallised from ethanol or aqueous ethanol and their m.p.s checked against literature values; [6] g.l.c. confirmed sample purity.

Preparation of pp'-*Disubstituted Diphenylmethanols.*—When this was attempted with *pp'*-dimethoxybenzophenone (0·60 g., 2·5 mmoles) in tetrahydrofuran (30 ml.) at 20 °C with an eightfold excess of lithium aluminium hydride (5 mmoles; 3 ml. of a 1·66M solution), *pp'*-dimethoxydiphenylmethane, m.p. 53° (lit.,[7] 52°) was obtained after quenching in ammonium chloride solution. This hydrogenolysis also occurred when the other substituted benzophenones were treated with lithium aluminium hydride; it was overcome by the following procedure: the ketone (2·5 mmoles) in tetrahydrofuran (25 ml.) was reduced by the addition of lithium tri-t-butoxyaluminium hydride (7·5 mmoles, 23·8 ml. of 0·315M) in tetrahydrofuran at 20 °C under nitrogen. After 12 hr. the product was quenched in saturated ammonium chloride solution, extracted into ether, and the dried evaporate crystallised from aqueous ethanol. It was found that diphenylmethanol and its derivatives underwent appreciable etherification if dilute mineral acids were used for the quenching. The reaction probably occurs in the ether layer before this is washed free from dissolved acid.

In the preparation of di-(*p*-methoxyphenyl)methanol, column chromatography on acid-washed alumina and elution with benzene–light petroleum (1 : 1, b.p. 60—80°) was needed to obtain a pure product, m.p. 72° (lit.,[6] 72°). Satisfactory m.p.s and i.r. spectra were obtained for the other alcohols which were all free from impurities (g.l.c.).

Conditions for the Determination of the Rates of Reduction of pp'-*Disubstituted Benzophenones by Lithium Tri-t-butoxyaluminium Hydride.*—A solution of the ketone (1 mmole) in tetrahydrofuran (350 ml.) at 0 °C was added to a solution of the hydride (10 equiv., 31·7 ml. of 0·315M) in tetrahydrofuran at 0 °C under nitrogen with vigorous stirring. Samples (*ca.* 15 ml.) were pipetted out at intervals and immediately quenched by addition to excess of ammonium chloride solution. Under these conditions the diphenylmethanol was the only product and the composition of a dry ($MgSO_4$) ether extract was determined (g.l.c.).

Competitive Reductions of Pairs of Benzophenones with Aluminium Hydride.—A solution of the ketones (0·25 mmole of each) in tetrahydrofuran (8 ml.) at 0° was added to a 50% deficit of aluminium hydride (0·5 mmole taking 1 H in 6 as available, see below) in tetrahydrofuran (2·8 ml. of 0·18M solution). After 2 hr. the mixture was quenched and worked up as above, and the ether layer sampled for g.l.c. The diphenylmethanols were the only products.

Reduction of 4-t-Butylcyclohexanone by Aluminium Hydride and Alkoxyaluminium Hydrides.—(a) When a smaller quantity of aluminium hydride (0·08 mmole taking all H as available) was used only a limited reduction of the diaryl ketones occurred, but there was considerable evolution of hydrogen on quenching. The capacity of the residue to reduce an aliphatic ketone was demonstrated by the addition of 4-t-butylcyclohexanone (0·125 mmole) in tetrahydrofuran at 20 °C to the residue from a duplicate experiment before quenching. G.l.c. showed that the cyclohexanone was reduced completely and by injection of a reference sample [8] the mixture of alcohols was characterised as 76% *trans* and 24% *cis*. A similar result was obtained when the cyclohexanone (0·125 mmole) was added to aluminium hydride (0·25 mmole) after its partial solvolysis by dry diphenylmethanol (0·25 mmole).

(b) Under similar conditions to those in (a) the cyclohexanone was reduced by pure aluminium hydride (10 equiv.) in tetrahydrofuran to a mixture containing *trans*-4-t-butylcyclohexanol (84%) and the *cis*-epimer (16%).

(c) When a solution of a substituted benzophenone (0·5 mmole) in tetrahydrofuran (50 ml.) was added to a mixture of aluminium hydride (5 mmoles) and tri-t-butoxyaluminium (5 mmoles redistilled), reduction was incomplete. G.l.c. showed that benzophenone was reduced to the extent of 37%; the dimethyl and dimethoxy-derivatives were unaffected. Addition of 4-t-butylcyclohexanone to the residue from the latter experiment, before quenching, led to complete reduction to a mixture containing 73% of the *trans*-cyclohexanol.

Gas Chromatography Procedures.—A Perkin-Elmer F11 instrument was used. The stationary phase was QF-1 (fluoroalkylmethyl polysiloxanes, W. G. Pye, Ltd.) suspended on Chromosorb W (80—100 mesh, Perkin-Elmer Ltd.). When greater resolution was needed the trimethylsilyl ethers of alcohols were prepared as before.[3] The working conditions are summarised in Table 1 where the column efficiencies (n) were calculated from the relation [9] $n = (5{\cdot}54/L)(t_r/W_h)^2$, L being the column length (cm.), W_h the peak-width at half-height (cm.), and t_r the retention time (measured in cm.). The degree of resolution $R = \Delta t_r/W_m$ where W_m is the mean of the base-widths (cm.). The response factors (m) were determined from the linear plots of g.l.c. peak area ratios to weight ratios for six alcohol–ketone mixtures in the range 5—60% of alcohol and are given in Table 1.

4-t-Butylcyclohexanols were separated on a 12 ft. column loaded with QF-1 (8%) on Chromosorb W (80—100 mesh) at 140 °C with a N_2 pressure of 10 lb. in.$^{-2}$. The *cis*-isomer had $t_r = 5{\cdot}3$ and its epimer $t_r = 6{\cdot}6$ min. ($n = 152$; $R = 2{\cdot}14$).

RESULTS AND DISCUSSION

Reductions with Lithium Tri-t-butoxyaluminium Hydride.—The kinetics of reduction of several cyclohexanones by this hydride have been recorded and the reactions shown to be of the first order in ketone, and in the hydride.[10] Our findings showed that under varying reagent concentrations there was an acceptable fit with an overall second-order relation. Only the

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[5] W. Wayne and H. Adkins, *Org. Synth.*, Coll. Vol. **3**, 1955, p. 48.

[6] J. P. Picard and C. W. Keerns, *Canad. J. Res.*, 1950, **28***B*, 56.

[7] L. H. Conover and D. S. Tarbell, *J. Amer. Chem. Soc.*, 1950, **72**, 3586.

[8] J. C. Richer, *J. Org. Chem.*, 1965, **30**, 324.

[9] L. S. Ettre and A. Zlatkis, 'The Practice of Gas Chromatography,' Interscience, New York, 1967, p. 156.

[10] J. Klein, E. Dunkelblum, E. L. Eliel, and Y. Senda, *Tetrahedron Letters*, 1968, 6127.

TABLE 1

G.l.c. conditions for analysis of mixtures of *pp*-′disubstituted benzophenones and derived alcohols *

Substituent	t_r (min.) Alcohol	t_r (min.) Ketone	L (ft.) and % of QF-1	Temp. (°C)	N_2 pressure (lb. in.$^{-2}$)	*m*	*n*	*R*
None (H)	5·6	8·1	12, 8%	190	15	1·03	300	5·65
Me	1·9	4·2	7, 6	200	20	1·16	237	7·67
F	3·4	16·7	12, 8	180	10	1·21	240	1·99
Cl †	7·9	12·0	12, 8	200	25	0·60	223	6·04
MeO †	7·4	28·4	7, 6	180	25	1·00	230	15·3
These were modified as below for analysis of the reduction of pairs of ketones by aluminium hydride.								
F † and	3·8	6·4	12, 8%	190	20	0·734	166	6·13
Cl †	12·9	19·8				0·828	213	5·80
F † and	21·4	36·0	12, 8	130	30	0·583	1660	21·4
H †	13·8	32·8				0·652	1450	25·6
H and	8·0	11·9	12, 8	180	15	1·07	185	5·1
Me	14·4	29·2				1·33	226	9·4
Me † and	7·2	31·4	12, 8	‡	15	0·910	134	20·0
MeO †	35·0	55·2				0·720	1530	15·0

* The ether solutions must not be left to stand in the light before analysis as the concentration of ketone is reduced, probably by pinacol formation. † As its trimethylsilyl ether. ‡ 170 °C for 30 min., then 170—220 °C at 5 °C per min.

first 30% of the reductions were followed because exchange of the formed diarylmethoxide ions would lead to uncertainty in the nature of the hydride donor. The rate constants given in Table 2 refer to reactions at 0 °C with the hydride in excess (10 equiv.) and were evaluated graphically (Figure 1) from the pseudo-first-order equation (3) where the molar concentration (b)

$$k' = \frac{2{\cdot}303}{t} \log \frac{a}{a - x} \qquad (3)$$

of the hydride was taken as constant under these conditions and where $k' = k.b$, k being the second-order rate constant, other symbols having their usual meaning.

G.l.c. gave the measured ratio alcohol produced: unchanged ketone $= R$ and for a detector response factor m the corrected ratio $mR = x/(a - x)$, therefore $x = amR/(1 + mR)$ and $(a - x = a/(1 + mR)$ so that $a/(a - x) = 1 + mR$ and in g.l.c. parameters the rate equation becomes $k' = (2{\cdot}303/t) \log (1 + mR)$.

In plotting the results we have taken the σ values as twice those for monosubstitution implying that both *para*-substituents are fully effective; this is validated by the consistent Hammett plots so obtained for Meerwein–Ponndorf–Verley reactions of benzophenones[11] and also for their reduction by lithium tetrakis-(*N*-dihydropyridyl)aluminate.[12] We considered the use of σ^- values for the more reactive halogenated ketones but no data were available for a reaction of this type. However, application of the standard statistical correction[13] gave a regression line of slope (ρ) $= 2{\cdot}13$ where the standard deviation ($s = 0{\cdot}24$), the standard error in ρ ($s\rho$) $= 0{\cdot}30$, and the correlation coefficient ($r = 0{\cdot}97$), were within acceptable limits.[14]

The large positive ρ value shows that in the transition state the aromatic groups interact with a centre carrying a significant negative charge. The result therefore

TABLE 2

Hammett constants and rates of reduction of *pp*′-disubstituted benzophenones by lithium tri-t-butoxyaluminium hydride (10 equiv., 2·5 × 10^{-2}M) in tetrahydrofuran at 0 °C

pp′ substnt.	Uncorrected 2σ	Rate constants 10^4k (l. mole^{-1} sec.$^{-1}$)	Corrected 2σ
Cl	0·45	327	0·43
F	0·12	107	0·21
H	0	18·2	0
Me	−0·34	5·65	−0·35
MeO	−0·54	3·13	−0·47

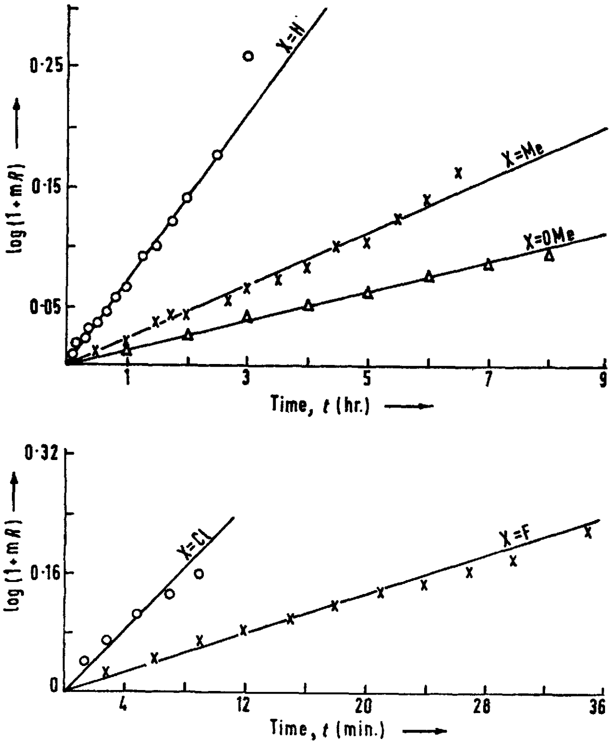

FIGURE 1 Rate plots for the reduction of *pp*′-disubstituted benzophenones $(X{-}Ar)_2C{=}O$ by lithium tri-t-butoxyaluminium hydride up to about 30% reaction

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[11] D. E. Pickart and C. K. Hancock, *J. Amer. Chem. Soc.*, 1955, **77**, 4642.

[12] P. T. Lansbury and R. E. Macleay, *J. Amer. Chem. Soc.*, 1965, **87**, 831.

[13] H. H. Jaffé, *Chem. Rev.*, 1953, **53**, 253.

[14] See J. Shorter, *Chem. in Britain*, 1969, 269.

excludes reduction by a neutral aluminohydride and is consistent with hydride donation by an anion of the type $Al^{-}(OBu^{t})_3H$ (Figure 3).

Reductions with Aluminium Hydride.—Some of the original experiments with simple aliphatic substrates indicated that all the hydrogen atoms of the reducing agent were available; for example, Wiberg and Jahn[15] showed that 3 equiv. of acetaldehyde combined with 1 equiv. of aluminium hydride to form triethoxyaluminium.

We find that the stoicheiometry of reduction of benzophenones is more complex and that the hydrogen atoms of the first-formed alkoxy-derivatives are not available for reduction. This was a reason for again limiting our observations to the first 30% of reaction, but without prejudice to the conclusions about transition states which follow from the Hammett plots.

In establishing conditions for the competitive reductions of pairs of benzophenones, we first introduced equivalent amounts of two ketones into a solution containing one-third of a mole of the hydride (AlH_3); g.l.c. showed that only limited amounts of the alcohols were formed after prolonged contact. We concluded that each Al_2H_6 unit could reduce *ca.* 1 equiv. of a benzophenone. For competitive reduction we therefore used sufficient aluminium hydride to reduce 1 equiv. of an equimolar mixture of two ketones (Table 3), assuming that between 1 in 3 and 1 in 6 hydrogen atoms were available for reduction.

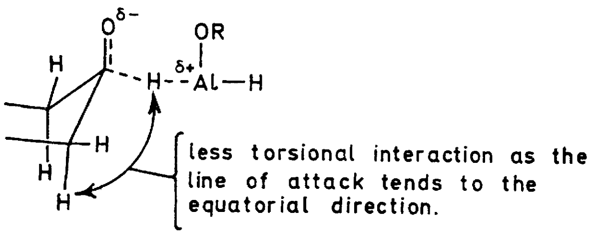
Before discussing the kinetics of aluminium hydride reduction we note two points of general interest which arose from the study of stoicheiometry. The first concerns the feasibility of using the reagent for the selective reduction of aliphatic ketones. This was demonstrated, and the stoicheiometric finding confirmed, through the partial solvolysis of aluminium hydride by the prior addition of 1 equiv. of diphenylmethanol, to afford diphenylmethoxyaluminium dihydride. The modified reagent did not react with benzophenone but it converted 4-t-butylcyclohexanone into a mixture of epimeric alcohols. The second point follows from this, since the composition of the mixture [*trans* (eq) 76%; *cis* (ax) 24%] is significantly different from that [*trans* 84%; *cis* 16%] given by aluminium hydride under the same conditions. The different steric result can be accounted for in the terms of our previous paper.[3] Thus the slower reduction by the alkoxyaluminium dihydride leads to a transition state which is further from the reactants and this has the effect of reducing the torsional interaction between axial α-hydrogen atoms and entering hydride as shown in Figure 2; in consequence the yield of axial alcohol resulting from this mode of attack is increased.

In evaluating the relative rate constants for the competitive reduction of pairs of benzophenones we assumed that the reaction was of the first order in ketone.[16] Given that k_1 and k_2 are the rate constants for the two ketones in molar concentrations a_1 and a_2 respectively, and that b is the initial concentration of the reducing agent, then after time t we have equations

$$-\mathrm{d}x/\mathrm{d}t = k_1(a_1 - x)(b - x - y)^n \qquad (4)$$

$$-\mathrm{d}y/\mathrm{d}t = k_2(a_2 - y)(b - x - y)^n \qquad (5)$$

(4) and (5) where x and y represent the extent of reduction of a_1 and a_2 respectively and n is the order of the reaction in aluminium hydride. Equation (6) follows.



less torsional interaction as the line of attack tends to the equatorial direction.

FIGURE 2

By integration and putting $x = y = 0$ when $t = 0$ we find equation (7), or in g.l.c. parameters, equation (8).

$$\frac{\mathrm{d}x}{(a_1 - x)} = \frac{k_1 \mathrm{d}y}{k_2(a_2 - y)} \qquad (6)$$

$$\frac{k_1}{k_2} = \frac{\log\,[(a_1 - x)/a_1]}{\log\,[(a_2 - y)/a_2]} = \frac{\log\,(\text{unchanged fraction of } a_1)}{\log\,(\text{unchanged fraction of } a_2)} \qquad (7)$$

$$\frac{k_1}{k_2} = \frac{\log\,(1 + m_1R_1)}{\log\,(1 + m_2R_2)} \qquad (8)$$

For accurate analysis of the area under the peaks of the chromatograms it was necessary to have an appreciable conversion of the less reactive ketone into the corresponding alcohol. The ketones were not therefore all compared directly with benzophenone (k_0) but with their nearest neighbour on the reactivity scale. The rates relative to k_0 (Table 3) were then obtained by proportion $k_1/k_0 = (k_1/k_2)(k_2/k_0)$. From the above 2σ values and application of the statistical correction[13] a regression line of slope (ρ) 0·89 ± 0·07(6) was obtained. The standard deviation ($s = 0{\cdot}059$) and the correlation coefficient ($r = 0{\cdot}99$) were satisfactory.

The relative strength of aluminium hydride as a Lewis acid is unknown, but in view of the demonstrated[17] acidity of diborane some Lewis acid catalysis might be expected for aluminium hydride reductions of benzophenones. This is not so however, for the slope of the Hammett plot has the same sign as that obtained for the reduction with lithium tri-t-butoxyaluminium hydride and the ketone must interact similarly in both transition states (Figure 3), but the smaller magnitude

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[15] E. Wiberg and A. Jahn, *Z. Naturforsch.*, 1952, **7b**, 581.

[16] *Cf.* W. N. Moulton, R. E. Van Atta, and R. R. Ruch, *J. Org. Chem.*, 1961, **26**, 290, and ref. 10.

[17] H. C. Brown, 'Hydroboration,' Benjamin, New York, 1962, p. 248; A. Hajos, 'Komplex Hydride,' V.E.B., Berlin, 1966, p. 279.

of ρ for the aluminium hydride reaction shows that less negative charge accumulates on the carbonyl carbon atom. As the formation and breaking of bonds is therefore almost synchronous, a cyclic transition state is preferred to one formed by a termolecular collision. There is evidence[18] of a monomeric aluminium hydride species in freshly prepared solutions but the nature of the transition state need not depend on the distribution of reagents in solution. Loss of activity due to precipitation of polymer during storage[2,19] makes the state of the reagent uncertain.

TABLE 3

Determination of the relative rates of reduction of *pp*′-disubstituted benzophenones by aluminium hydride in tetrahydrofuran at 0 °C

Ketone mixt. x_1/x_2	Molar ratio x_1/x_2	Moles of AlH_3	Uncorrected yields of alcohols (%)		Corrected for detector response		Relative rates	
			x_1	x_2	x_1	x_2		
Cl/F	1 : 1	$\frac{1}{3}$	14·9	6·7	12·7	4·9	2·67	2·66
	1 : 1	1	22·1	9·8	19·0	7·4	2·74	
	1 : 1	2	43·2	22·7	38·6	17·7	2·51	
	2 : 1	1	14·6	5·9	12·2	4·8	2·72	
	2 : 1	4	64·6	40·7	60·2	33·4	2·27	
F/H	1 : 1	1	17·0	14·2	10·7	8·4	1·10	1·12
	1 : 1	2	25·3	20·8	15·4	14·4	1·14	
Cl/H			By calculation from above mean results				3·03	
Me/H	1 : 1	2	11·5	23·2	14·8	24·4	0·570	
MeO/Me	1 : 1	2	23·8	29·7	18·3	27·8	0·623	
MeO/H			By calculation from above results				0·355	

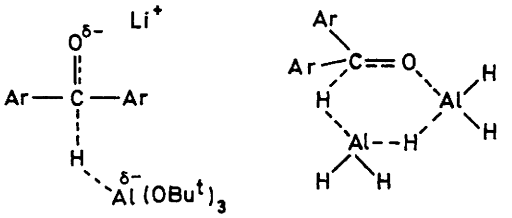

FIGURE 3

Because of the high absolute reaction rates we considered the possibility that the reaction was diffusion-controlled: in this event rates would be expected to vary with the conditions of mixing the reagents. We found (Table 3) that doubling the concentration of dichlorobenzophenone relative to the difluoroketone, and variations of up to sixfold in the concentration of aluminium hydride, gave the same result for their relative rates of reduction. This was also true within similar limits of experimental error when the aluminium hydride concentration was varied in the competitive reduction of benzophenone and its difluoro-derivative; diffusion control is therefore excluded for the more reactive benzophenones and cannot feature in the reduction of the other less reactive analogues that we have studied.

With information to hand on the reductions with lithium tri-t-butoxyaluminium hydride and aluminium hydride it became worth while to examine the more complex system [equation (2)]. A mixture of aluminium hydride and 5 equiv. of tri-t-butoxyaluminium reduced benzophenone and its halogeno-derivatives to a limited extent, but the dimethyl- and dimethoxy-benzophenones did not react. This result is like that obtained in the determination of the stoicheiometry of the aluminium hydride reaction with an excess of mixed benzophenones, where diphenylmethoxyaluminium dihydride was found to be unreactive. The similarity between the two systems was confirmed by the addition of 1 equiv. of 4-t-butylcyclohexanone to the mixed reagent containing unchanged or partially consumed aryl ketones. By analogy with the earlier experiment the cyclic ketone was completely reduced to a mixture of epimeric alcohols (*trans* 73%; *cis* 27%). Evidently exchange occurs to give a t-butoxyaluminium hydride which cannot reduce benzophenones; the limited reduction observed in some experiments is probably effected before exchange is complete by some residual aluminium hydride.

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[18] See N. M. Alpatova, T. N. Dymova, Yu M. Kessler, and O. R. Osipov, *Uspekhi Khim.*, 1968, **37**, 216.

[19] D. C. Ayres and R. Sawdaye, to be published.