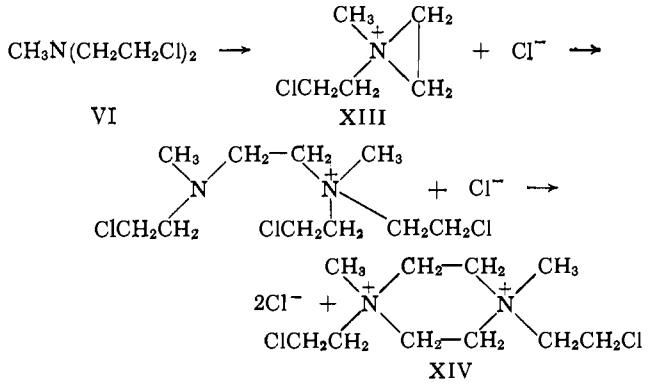
peak height does not necessarily have the same relation to concentration for each species.



VI XIII XIV

Observations were begun 1 min. after neutralization of the hydrochloride salt. The amount of mustard VI was measured from the N–CH_3 singlet height at δ = 2.35 p.p.m.; the aziridinium ion XIII from the N–CH_3 singlet at δ = 3.17 p.p.m.; and the piperazinium ion XIV from the ring methylenes at δ = 4.1 p.p.m. Although Bartlett, *et al.*,[5] attempted to use the thiosulfate titration technique for estimation of the aziridinium ion concentrations in their studies of this compound, the rate of reaction with the ring was too slow to be useful. The n.m.r. technique has the advantage that intermediates which accumulate are easily observed. There is the added advantage that any change in mechanism with changing conditions may also be observed, as well as any side reactions.

In a study of a series of halogenoethyl-N-alkyl-1-naphthylmethylamines, Graham[2] found that the fluoro compounds were inactive as antagonists of adrenaline, noradrenaline, and histamine in contrast to the chloro, bromo, and iodo analogs. However, it is possible that *in vivo* the fluoro compounds are oxidized to precursors of fluoroacetic acid by amine oxidase and their toxicity masks any adrenergic blocking action.[23]

(23) F. L. M. Pattison, "Toxic Aliphatic Fluorine Compounds," Elsevier Publishing Company, New York, N. Y., 1959.

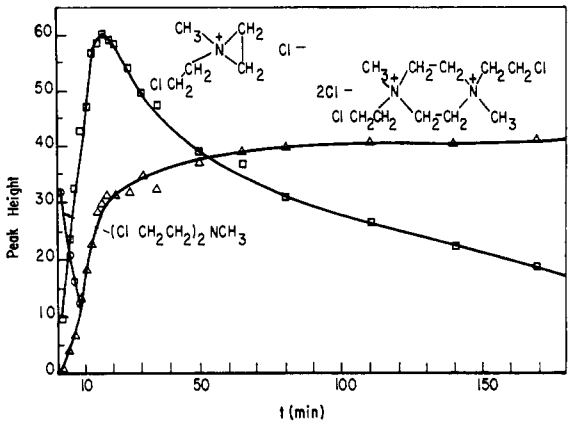


Figure 4. Change in concentration of the species involved in the solvolysis of N-methylbis(2-chloroethyl)amine in D_2O at 37°.

Recently, Russian investigators[24] have reported that some 2-fluoroethylamine derivatives are active as antitumor agents, and Pettit and Smith[12] have found that bis(2-fluoroethyl)amine inhibited the growth of Walker 256 carcinoma at near-toxic levels; similar results were obtained in our laboratory with 2-chloro-2′-fluorodiethylamine.[25] Since it has been shown that many tumors are not inhibited by fluoroacetate, it is possible that the antitumor activity of these compounds is due to their action as biological alkylating agents.

Acknowledgment. We wish to thank the research committee of Arthur D. Little, Inc., for their support of this work, Mr. R. J. Bruni for assistance in preparation of the compounds, and Mrs. Nancy L. King for assistance in obtaining the n.m.r. spectra and kinetic data.

(24) See, for example, L. S. Erukhinov, V. P. Zolotsev, and S. V. Kagramanov, *Urologiia*, 27, 54 (1962); *Cancer Chemotherapy Abstr.*, 3, 487 (1962).

(25) Z. B. Papanastassiou, R. J. Bruni, and P. L. Levins, paper in preparation.

On the Role of Electrophilic Catalysis in Competitive Reductions of Ketones by Lithium Tetrakis(N-dihydropyridyl)aluminate and Metal Borohydrides

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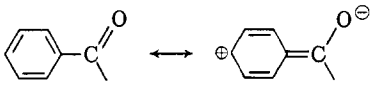
Contribution from the Department of Chemistry, State University of New York at Buffalo, Buffalo 14, New York. *Received September 26, 1964*

Benzophenone is more reactive than phenyl t-butyl ketone toward reduction by lithium tetrakis(N-dihydropyridyl)aluminate (LDPA), but the opposite order was observed when sodium borohydride in isopropyl alcohol was the reducing agent. It is proposed that electrophilic catalysis is minimized in the LDPA reactions, in which case aryl groups conjugate less effectively with the carbonyl function, thus magnifying their normally masked −I effects. Even sodium borohydride itself shows different relative reactivities with ketones in going from alcohol to pyridine solvents. The relative rates of reduction of a series of benzophenones by LDPA correlate with Hammett constants better than σ^+ constants and give $\rho = +1.5$. All four dihydropyridyl groups in LDPA show comparable reactivity as hydride donors and there is no rate difference in reduction of 2,4′-dichlorobenzophenone by 1,2- and 1,4-dihydropyridyl groups in LDPA.

(1) Alfred P. Sloan Foundation Fellow, 1963–1965.
(2) National Institutes of Health Predoctoral Fellow, 1963–1964.

Introduction

The relative reactivities of various types of ketones in nucleophilic additions at the carbonyl group have been extensively studied,[3] particularly the formation of oximes, semicarbazones, cyanohydrins, and hydrazones. Although the retarding effects of steric bulk and electron release at the reaction site have been qualitatively established in these investigations,[3] such reactions have multistep mechanisms and it is not always clear which step is rate-determining in a particular situation. A kinetically simple carbonyl addition reaction is sodium borohydride reduction, and Brown and co-workers have used this reaction in a thorough examination of structural effects on carbonyl reactivity.[4] It was shown that alkyl substitution at C-α lowers the reactivity of ketones toward nucleophilic attack by both steric bulk and +I inductive effects.[4a] In addition, aryl ketones showed reduced reactivity in cases where conjugation, which stabilized the ground state relative to the transition state, was possible, *i.e.*

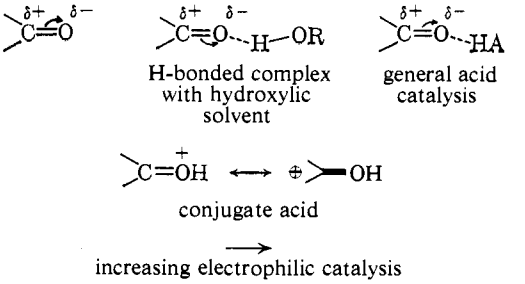


In phenyl *t*-butyl ketone, steric inhibition of resonance resulted in greatly enhanced reactivity due to the more dominant −I effect exerted by the phenyl group.[4a] Thus, replacing an α-methyl group by phenyl *lowers* reactivity in acetone by a factor of 7.4 at 0° but *increases* it in pinacolone by a factor of 31.5 at 0°, as shown in selected data of Brown (Table I).[4a]

Table I. Relative Rates of Reduction of Ketones by Sodium Borohydride in 1-Propanol[4a]

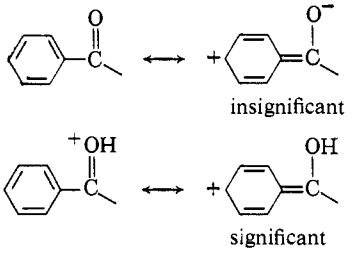
Ketone	Relative rate, 0°	ΔS^*, e.u.
Acetone	1.00	−39.1
Acetophenone	0.136	−32.4
Pinacolone	0.0815	−41.5
Phenyl *t*-butyl ketone	2.47	−40.1

Our interest in carbonyl reactivity toward nucleophiles was aroused in studies utilizing lithium tetrakis(N-dihydropyridyl)aluminate (henceforth designated LDPA) as a reducing agent for a variety of polar unsaturated groups.[5] Specifically it was observed that benzophenone underwent reduction more rapidly than either dialkyl or aryl alkyl ketones and that this unprecedented reactivity could be used in selectively reducing diaryl carbonyl groups of diketones, such as 4-(*p*-benzoylphenyl)-2-butanone.[5] Since the opposite reactivity sequence holds for sodium borohydride reductions in alcohol solvent,[4c] we sought an explanation for the LDPA reactions. It occurred to us that electrophilic catalysis would be at a minimum, if not completely absent, in pyridine solvent, since the latter would coordinate with lithium ion and trivalent aluminum more effectively than carbonyl oxygen. This is generally not the case in other carbonyl addition reactions. Formation of imine bonds by reaction of nitrogen bases (*e.g.*, hydroxylamine, semicarbazide) with aldehydes and ketones is subject to general acid catalysis whereas cyanide or hydroxide attack is not acid catalyzed.[3a] However, even in the latter cases, hydrogen bonding by hydroxylic solvents may increase the polarization of the carbonyl group.[3a]



Furthermore, certain aprotic solvents such as dimethyl sulfoxide form 1:1 complexes with carbonyl groups,[6] resulting in modified reactivity. Pyridine, however, does not specifically solvate carbonyl groups.[6]

Thus LDPA reactions may involve free ketone molecules rather than complexes involving coordination with oxygen[3a] or four-center bonding with dipolar solvents due to dipole–dipole attraction.[6] Since charge-delocalization resonance is more significant than charge separation it seems reasonable to assume that conjugation of aryl groups with the carbonyl group is much less significant in the free ketone than the conjugate acid (as the other extreme), if other factors are considered equal.



The effect of solvent polarity on the importance of charge-separation resonance forms in ground-state resonance hybrids has been studied by Taft, *et al.*,[7] by examining the F^{19} n.m.r. spectra of *para*-substituted fluorobenzenes. It was shown that deshielding of fluorine by −R substituents is most pronounced in good solvating media where dipolar contributing forms, with charge at the periphery of the molecule, are better stabilized. Pyridine was shown to be a poor solvating medium on this basis, thus further deemphasizing dipolar resonance contributions in ketones under LDPA reaction conditions.

On this basis, we may expect aryl ketones such as benzophenone to show enhanced reactivity toward LDPA in pyridine, whereas in reactions in alcohol,[4]

(3) For reviews see (a) W. P. Jencks in "Progress in Physical Organic Chemistry," Vol. 2, S. G. Cohen, A. Streitwieser, Jr., and R. W. Taft, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, Chapter 2; (b) J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter 11.

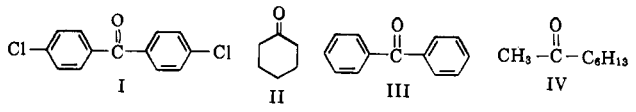
(4) (a) H. C. Brown and K. Ichikawa, *J. Am. Chem. Soc.*, **84**, 373 (1962); (b) H. C. Brown and K. Ichikawa, *Tetrahedron*, **1**, 221 (1957); (c) H. C. Brown, O. H. Wheeler, and K. Ichikawa, *ibid.*, **1**, 214 (1957); (d) H. C. Brown and K. Ichikawa, *J. Am. Chem. Soc.*, **83**, 4372 (1961).

(5) P. T. Lansbury and J. O. Peterson, *ibid.*, **85**, 2236 (1963).

(6) C. D. Ritchie and A. Pratt, *ibid.*, **86**, 1571 (1964).

(7) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, *ibid.*, **85**, 709, 3155 (1963).

Table II. Competitive Reductions of Ketones with Metal Borohydrides at 25°



I II III IV

Run(s)	Ketones	Reducing agent–solvent	$k_{Ar_2C=O}/k_{R_2C=O}$
1, 2	I and II	$NaBH_4$–C_5H_5N	10.3 ± 0.7
3, 4	I and II	$LiBH_4$–pyridine	2.65 ± 0.15
5[a]	I and II	$LiBH_4$–pyridine	2.3 (from kinetic runs)
6, 7	III and IV	$LiBH_4$–pyridine	3.75 ± 0.05
8, 9[b]	I and II	$NaBH_4$–diglyme	1.4 ± 0.1
10	I and II	$NaBH_4$–diglyme	1.4
11, 12	I and II	$LiBH_4$–diglyme	0.37 ± 0.05
13, 14	III and IV	$LiBH_4$–diglyme	0.80 ± 0.02
15[c]	I and II	$LiBH_4$–diglyme (+ LiCl)	0.12
16[c]	III and IV	$LiBH_4$–diglyme (+ LiCl)	0.40
17, 18[d]	I and II	$LiBH_4$–CH_3OH	0.31 ± 0.04
19, 20[d]	III and IV	$LiBH_4$–CH_3OH	0.093 ± 0.006

[a] Rate constants at 25 ± 1° were: I, 30.5 × 10^{-3} l./mole-sec.; for II, 13.6 × 10^{-3} l./mole-sec. [b] Rate constants at 25 ± 1° were: I, 2.94 × 10^{-3} l./mole-sec.; for II, 2.10 × 10^{-3} l./mole-sec. [c] With ketone concentration *ca.* 0.075 *M* and $LiBH_4$ 0.003–0.02 *M*, the added lithium chloride concentration was 0.3 *M*. [d] Composites for all four stages of reduction involving alkoxyborohydrides. One referee has pointed out the possibility that alkoxyborohydrides may not be the actual reducing agent in these reactions.

in which charge delocalization may be involved in the hydrogen-bonded complex,[8] reactivity is reduced relative to alkyl ketones. A dramatic example of the catalytic effect of alcohols on carbonyl additions is in diazomethane additions to ketones, many of which are inert when the reactions are attempted in pure ether but proceed satisfactorily in alcohol–ether solutions, or, for that matter, when lithium chloride is added.[9] In addition, Brown and Ichikawa showed that the reactivity of sodium borohydride toward acetone disappeared in going from hydroxylic solvents to aprotic solvents such as acetonitrile, pyridine, etc.[4d] These workers also found that added lithium ion enhanced the reactivity of borohydride in isopropyl alcohol, one possible explanation being coordination with carbonyl oxygen[4d] although other factors may be operative.

If the above reasoning is qualitatively correct, one should be able to reverse the reactivity of sodium borohydride toward various types of ketones by changing solvent from alcohols to pyridine. In particular, phenyl *t*-butyl ketone should not show unique reactivity due to steric inhibition of resonance.[4a] In a preliminary study,[10] we did in fact show that representative diaryl ketones reacted more rapidly than dialkyl ketones in competitive reductions with both lithium and sodium borohydrides in pyridine, whereas lithium but not sodium borohydride reductions in diglyme gave the usual reactivities (dialkyl ketones > diaryl ketones.) It was concluded that lithium ion was an effective electrophile[11] in diglyme, but less so in pyridine, and served a function similar to alcohols in polarizing the carbonyl group. Some relative rate data from our earlier work[10] are listed in Table II.

The results shown in Table II support the idea that the reduction of *electrophilic catalysis* is a major factor on the selectivity observed with LDPA.[5] The present paper concerns further studies with LDPA, namely, substituent effects on reactivity of the benzophenones and competitive rate studies of benzophenones *vs.* phenyl *t*-alkyl ketones. The latter studies are of particular importance in checking the ideas set forth above. Since enolizable ketones have been shown to undergo some enolization as well as reduction[12] it was not possible to use them in studying structural effects on reactivity. Information has also been gained on the steric requirements of LDPA, as well as the relative bulks of 1,2- and 1,4-dihydropyridyl groups in LDPA itself.

Result and Discussion

I. Structure–Reactivity Relationships in LDPA Reductions. A series of *para*-substituted and *para,para'*-disubstituted benzophenones were reduced competitively in pairs in order to determine whether the relative rates correlated better with σ or σ^+ values. As Jencks points out,[3a] if resonance interactions between *para* substituents and the carbonyl group of aryl ketones are important in the ground state but diminish in the *transition* state for nucleophilic addition (ρ positive), the rates will correlate better with σ^+ constants (or a modified linear free-energy equation, such as that of Yukawa and Tsuno), whereas if ground-state *para* resonance interaction is insignificant, σ constants will give a better Hammett plot. Experimentally, pairs of benzophenones were allowed to react with LDPA in pyridine at 36° and the reactions sampled with time. Ketone concentrations were determined by ultraviolet spectroscopy and/or gas chromatography. The relative rates were obtained from the equation

$$k_a/k_b = (\log [A]/[A]_0)/(\log [B]/[B]_0)$$

by plotting log $[A]/[A]_0$ *vs.* log $[B]/[B]_0$, in which case the slope of the resultant line is the rate ratio k_a/k_b. It was found that a plot of log k/k_0 *vs.* σ (or 2σ for *para,para'*-disubstituted benzophenones) gave a good fit with $\rho = +1.5$.[13] Even the *para,para'*-disubstituted benzophenones fit the regression line well, as would be expected if substituent effects were largely

(8) W. W. Brandt, *ibid.*, **85**, 2628 (1963).
(9) C. D. Gutsche, *Org. Reactions*, **8**, 369 (1954).
(10) P. T. Lansbury, R. E. MacLeay, and J. O. Peterson, *Tetrahedron Letters*, 6, 311 (1964).
(11) For examples of the catalytic effect of lithium ion compared with other alkali metal cations, see (a) W. H. Puterbaugh and W. S. Gauga, *J. Org. Chem.*, **26**, 3513 (1961); (b) C. R. Hauser and W. H. Puterbaugh, *J. Am. Chem. Soc.*, **75**, 4756 (1953); (c) W. H. Puterbaugh and R. L. Readshaw, *ibid.*, **82**, 3655 (1960); (d) W. I. O'Sullivan, F. W. Swamer, W. J. Humphlett, and C. R. Hauser, *J. Org. Chem.*, **26**, 2306 (1961).
(12) Preliminary studies by J. O. Peterson in these laboratories have shown that the disappearance of ketone (followed by n.m.r. or infrared) in reactions of LDPA with 2-octanone, acetophenone, etc., is faster than the rate of formation of the corresponding alcohols, although still smaller than the rate of reduction of benzophenone under identical conditions. A detailed study of the relative rates of enolization and reduction in a representative group of enolizable ketones is currently in progress and the results will be published soon.
(13) By varying concentration ratios of ketone(s) to LDPA and by determining relative rate ratios at various stages of competitive reductions, it was possible to calculate ρ-values corresponding to the (hypothetical) first, second, third, and fourth equivalents of hydride transferred from LDPA, should these transfers occur in stepwise fashion. For all stages, $\rho = +1.47 \pm 0.03$, in excellent agreement with the over-all ρ, suggesting that each dihydropyridyl group had equivalent reactivity as judged by sensitivity to substituent effects in the ketones. The latter hypothesis was further strengthened by the relative constancy of k_2 for benzophenone when the ketone:LDPA ratio was varied (see Table II).

Table III. Relative Rates of Reduction of Benzophenones with LDPA at 36.0°

Substituents in $(C_6H_5)_2CO$	k_x/k_0	Substituents in $(C_6H_5)_2CO$	k_x/k_0
None[a]	1.00	4-Bromo	2.29
3-Fluoro	2.80	4-Methyl	0.538
3-Chloro	3.52	4-Trifluoromethyl	5.14
3-Bromo	3.67	4,4′-Difluoro	1.24
3-Methyl	0.811	4 4′-Dichloro	5.01
4-Fluoro	1.12	4,4′-Dimethyl	0.286
4-Chloro	2.16		

[a] In four kinetic runs[15] at 36.0°, in which the molar ratios of benzophenone to LDPA were varied by a factor of 10, the average rate constant, k_2, was 3.76×10^{-3} l./mole-sec., with an average error of $\pm 0.42 \times 10^{-3}$.

inductive in origin. When the relative rate data were plotted *vs.* σ^+ values, a bad scatter of points was noted (Table III), further verifying the unimportance of ground-state aryl–carbonyl conjugation.[14,15]

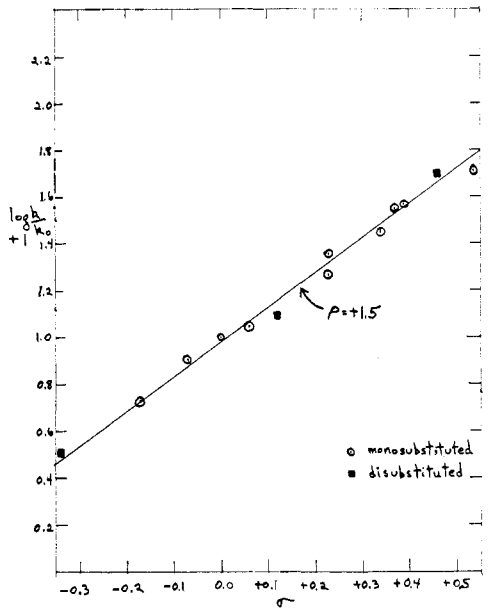


Figure 1. Correlation of rates of reduction of benzophenones by LDPA with Hammett σ-constants.

The magnitude of ρ for LDPA reductions is somewhat less than that for borohydride reductions. For example, $\rho = +2.65$ for sodium borohydride in isopropyl alcohol reductions of two- and three-substituted fluoroenones[16a] and +2.6 for *meta*- and *para*-substituted acetophenones.[16b] Furthermore, we have studied the reduction of twelve *meta*- and *para*-substituted benzophenones by lithium borohydride in anhydrous pyridine (where only one hydride is transferred[17]) and obtained $\rho = +2.81$, using Hammett σ constants. The rate constants were determined by infrared spectroscopy[11] and the data are summarized in Table IV.

Table IV. Rates of Reaction of Benzophenones with Lithium Borohydride in Pyridine at 26 ± 1°

$$R_2C{=}O + LiBH_4 + C_5H_5N \rightarrow R_2CHOLi + C_5H_5N{:}BH_3$$

Substituents on benzophenone	$[Ketone]_0$	$[LiBH_4]_0$	$k \times 10^3$, l./mole-sec.	k/k_0
None	0.0657	0.0795	1.35	1.00
4-Fluoro	0.0666	0.0795	2.16	1.60
3-Fluoro	0.0655	0.0758	11.4	8.45
4,4′-Difluoro	0.0633	0.0795	4.82	3.56
4-Chloro	0.0653	0.0758	5.99	4.44
3-Chloro	0.0666	0.0795	16.0	11.9
4,4′-Dichloro	0.0662	0.0795	30.5	22.6
3-Bromo	0.0662	0.0758	17.7	13.1
4-Methyl	0.0642	0.0795	0.524	0.388
3-Methyl	0.0662	0.0758	0.982	0.728
4,4′-Dimethyl	0.0675	0.0795	0.160	0.074

It is not known why the ρ-values for borohydride and LDPA reductions in pyridine are so different, although there is, of course, no reason for expecting similarity since the reducing agents are quite dissimilar.

II. Competitive Reductions of Benzophenone and Phenyl t-Alkyl Ketones by LDPA. As pointed out in the introduction, aryl-substituted ketones generally react more slowly than dialkyl ketones, when steric factors are constant, except when ground-state resonance stabilization is inhibited (as in phenyl *t*-butyl ketone). Thus, Brown, *et al.*, find $k_{benzophenone}/k_{pivalophenone} = 0.15$ at 35° for sodium borohydride reduction in isopropyl alcohol. With LDPA in pyridine, where ground-state dipolar resonance contributions in *all* ketones are supposedly negligible, this rate ratio may be expected to reverse itself on the basis of predominating inductive effects. These competition reactions have now been run and the expected reversal has indeed resulted. The appropriate data are shown in Table V, together with data for phenyl 1-norbornyl ketone

Table V. Competitive Reductions of Benzophenone and Phenyl *t*-Alkyl Ketones with LDPA and Sodium Borohydride

R in C_6H_5COR	*T*, °C.	Reducing agent and solvent	k_{Ar_2CO}/k_{ArCOR}
t-Butyl	25	$NaBH_4$ in *i*-C_3H_7OH	0.12[a]
t-Butyl	35	$NaBH_4$ in *i*-C_3H_7OH	0.15[a]
t-Butyl	35	$NaBH_4$ in CH_3OH	0.08[b]
t-Butyl	36	LDPA in pyridine	3.9
1-Norbornyl	36	$NaBH_4$ in CH_3OH	0.3[b]
1-Norbornyl	36	LDPA in pyridine	2.5

[a] Data from Brown, *et al.*[4a,c] [b] These relative rates are composites for all four stages of reduction involving alkoxyborohydrides.

(14) Since the data did not correlate well with Taft's σ^0 values, which reflect *only* inductive contributions by the substituents, a minor contribution by *para* resonance interaction to the ground state is indicated. This is, of course, taken into consideration in the original Hammett substituent constants.

(15) Direct rate measurements were made at 23° on most of the benzophenones used in the competitive reductions and at 36° for benzophenone itself. The rate constants were obtained from the equation $dx/dt = k_2(a - 4x)(b - x)$, where a is initial ketone concentration and b is initial LDPA concentration, by plotting $\ln (a - 4x)/(b - x)$ *vs.* t and getting k_2 from the slope. Ultraviolet spectroscopy or v.p.c. analysis of hydrolyzed aliquots taken from the reaction was the method for determining the concentration of ketones at various intervals ($a - 4x$). The rate constants (for benzophenone, $k_2 = 1.5 \times 10^{-3}$ l. mole^{-1} sec.$^{-1}$) were again plotted against σ (or 2σ) and a ρ-value of +1.45 obtained, in close agreement with the ρ from competition experiments. The rate constants obtained directly may not be too reliable, however, because of difficulties in determining the exact concentrations of LDPA (see Experimental).

(16) (a) G. G. Smith and R. P. Bayer, *Tetrahedron*, **18**, 323 (1962); (b) H. Kwart and T. Takeshita, *J. Am. Chem. Soc.*, **84**, 2833 (1962).

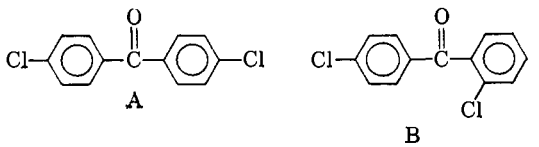
(17) C. D. Ritchie, *Tetrahedron Letters*, 2145 (1963).

which was included as a somewhat less hindered substrate.

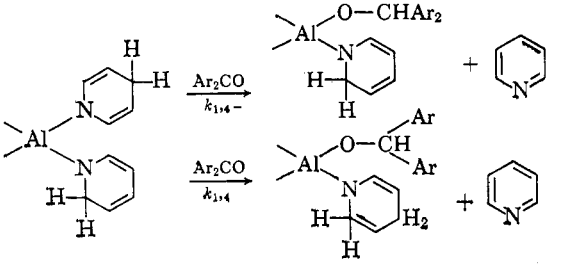
It appears that one may generally expect aryl ketones to show greater reactivity than related alkyl ketones *if* electrophilic catalysis is minimized or not involved.[18] Unfortunately, most nucleophilic additions to ketones require electrophilic catalysis of some sort and hence the reversal of reactivity in a selected series of ketones may not be realized in practice.

Although the selectivity observed in reducing 4-(*p*-benzoylphenyl)-2-butanone by LDPA[5] can be partially attributed to protection of the aliphatic carbonyl group by enolization,[12] there can be little doubt that diaryl ketones are more readily reduced than other types[19] by this reagent.

Another possible explanation of the relative rate ratio for competitive reductions of benzophenone and phenyl *t*-butyl ketone by LDPA is that the steric requirement of LDPA is sufficient to make reaction with the latter ketone difficult. That steric hindrance is not the major factor is shown by examining the stereochemistry of reduction of 3,3,5-trimethylcyclohexanone, where bulky reducing agents lead to a predominance of axial alcohol (*trans*-3,3,5-trimethylcyclohexanol) resulting from equatorial attack (kinetic control).[20] Sodium borohydride in methanol gives 81% axial alcohol at 27° (up to 98% by lowering the temperature to −40°),[21] whereas LDPA gives only 55%, thereby suggesting that LDPA has a smaller steric requirement for reduction than the four stages of reduction by borohydride. On the other hand, phenyl *t*-butyl ketone is *ca.* 12 times more reactive than benzophenone toward sodium borohydride in methanol, so the steric hindrance hypothesis would suggest that LDPA would give even higher values for $k_{\text{pivalophenone}}/k_{\text{benzophenone}}$, which was not observed! Additional evidence for the smaller steric requirement of LDPA is provided by results of competitive reductions involving 4,4′-dichlorobenzophenone (unhindered carbonyl) and 2,4′-dichlorobenzophenone (hindered carbonyl), which



give, for LDPA in pyridine, $k_A/k_B = 1.97$; and for $NaBH_4$ in methanol (four stages), $k_A/k_B = 3.26$. Clearly, the borohydride reduction is more sensitive to steric hindrance in the ketone. Furthermore, by n.m.r., it was possible to follow the relative rates of reduction of 2,4′-dichlorobenzophenone by 1,2- *vs.* 1,4-dihydropyridyl groups in LDPA, with the result that $k_{1,2\text{-}}/k_{1,4\text{-}} =$



0.99 ± 0.15. Thus, both types of dihydropyridyl groups in LDPA are of similar bulk insofar as reacting with carbonyl groups by hydride transfer. Details of the mechanism of reduction still are not known.

In summary, it seems that the reversal of relative rates of reduction of benzophenone and phenyl *t*-alkyl ketones is a consequence of electrophilic catalysis (or lack of it) rather than steric differences in the reagents. The importance of electrophilic catalysis should always be considered in addition to polar, steric, and conjugative effects in the ketone when assessing carbonyl reactivity.[22] Finally, the linear free-energy relationship of solvolysis rates of certain cycloalkyl *p*-toluenesulfonates and the reduction rates of the corresponding cycloalkanones, which was noted by Brown and coworkers,[4b,23] can be more satisfactorily rationalized by noting that hydrogen-bonded complexes (which somewhat resemble α-hydroxycarbonium ions, as discussed above) are probably involved in the latter reductions, rather than uncomplexed ketones.

Experimental[24]

Materials. Most of the benzophenones were commercially available; those unavailable were synthesized by Freidel–Crafts acylation reactions. All were recrystallized from 95% ethanol to constant melting point and checked for purity by v.p.c. The melting points of the benzophenones corresponded closely with the literature values as did those of the benzhydrols derived from them by lithium aluminum hydride reduction. Phenyl *t*-butyl ketone was synthesized from pivaloyl chloride and phenylmagnesium bromide[25] and purified *via* the crystalline oxime.

The complex metal hydrides were obtained from Metal Hydrides, Inc., and used as such.

For LDPA reactions, reagent grade pyridine was stored over barium oxide prior to use. For borohydride reductions in pyridine, the reagent grade solvent was distilled from KOH pellets and stored over Linde 4-A molecular sieves.

Preparation and Analysis of LDPA Solutions. The solutions of LDPA were prepared from lithium aluminum hydride and pyridine as described previously,[5] by adding *ca.* 0.5 g. of the hydride to 50 ml. of anhydrous

(18) Furthermore, any dipolar ground-state resonance can be reduced by using a nonpolar solvent. An example[7] of the latter phenomenon is the fact that in the acylation of a series of anilines in benzene, a σ-value of +1.00 is required for the *p*-nitro group, whereas $\sigma^- = +1.27$ was derived from data on acidity of anilinium ions *in water*, in which case direct resonance interaction played a major role in stabilizing the base.

(19) Naturally this excludes compounds heavily substituted with −I substituents, *e.g.*, 1,1,1-trifluoro-2-decanone and hexachloroacetone. Qualitative observations indicate that these ketones react very rapidly but no competitive rate measurements have been made.

(20) H. Haubenstock and E. Eliel, *J. Am. Chem. Soc.*, **84**, 2363 (1962).

(21) P. T. Lansbury and R. E. MacLeay, *J. Org. Chem.*, **28**, 1940 (1963).

(22) It is not inferred that all of the reactivity effects reported in this paper are a result solely of variable degrees of electrophilic catalysis, since it is difficult to separate the various factors involved. We do, however, wish to draw greater attention to this factor than has previously been accorded it. Also, although we have focused attention on the role of catalysis in the ground state, it is possible that transition state differences might also be responsible for reactivity differences.

(23) H. C. Brown, "The Transition State," Special Publication No. 16, The Chemical Society, 1962, p. 140.

(24) Infrared spectra were taken on a Beckman IR5-A spectrometer and ultraviolet spectra on a Perkin-Elmer Model 202 instrument. Vapor phase chromatography analyses were performed on an F and M Model 300 chromatograph.

(25) J. H. Ford, C. D. Thompson, and C. S. Marvel, *J. Am. Chem. Soc.*, 57, 2619 (1935).

pyridine in a rubber septum-stoppered bottle. A hypodermic needle was originally inserted to vent any gas, then removed after the initial reaction. After aging for at least 40 hr.,[5] the actual concentration of LDPA was checked by allowing an aliquot of the preparation to react overnight with *excess* benzophenone, then determining the amount of ketone remaining. Since benzophenone reacts rapidly with all four dihydropyridyl groups in LDPA,[5] the concentration of the latter was readily calculated from the amount of ketone consumed.

Competitive Reductions of Benzophenones with LDPA. In a typical procedure, *ca.* 2 mmoles of each ketone was weighed into a clean, dry test tube and 5 ml. of pyridine was added. The tube was stoppered tightly with a rubber septum and placed in a constant temperature bath (temperature 36.0°) for 1 hr. A serum bottle containing LDPA was also allowed to reach bath temperature. By means of a hypodermic syringe, 5 ml. (~0.88 mmole) of the LDPA solution was added to the ketone solution and the tube was shaken vigorously, then returned to the bath. At 5–10 min. intervals (more or less depending on the reactivity of the individual ketones), 1.0-ml. aliquots were withdrawn and hydrolyzed with dilute hydrochloric acid. The mixtures were extracted with ether and the ether solutions washed with saturated salt solution and dried over sodium sulfate. The composition of each product mixture was determined by v.p.c., using a 5-ft. 20% Apiezon M–20% 1,4-butanediol succinate on Chromosorb W column and a helium flow rate of 200 cc./min. The column temperature was varied (from 140 to 180°) depending on the ketones being studied. The per cent reduction of each ketone was determined from the peak areas of ketone and alcohol and checking with values obtained from known ketone–alcohol mixtures. The relative reactivity, k_A/k_B, was determined by plotting log % A remaining *vs.* % B remaining for each aliquot. The plots gave good straight lines, with slope = k_A/k_B, and passed through the origin. Almost all of the benzophenones were studied this way. However, 4-fluoro- and 4-methylbenzophenones and their related benzhydrols could not be completely separated from benzophenone and benzhydrol by v.p.c. and in these cases competitive experiments with 4-chloro- and 4-bromobenzophenone were run. Thus, the rate of reduction of 4-fluorobenzophenone relative to benzophenone ($k_{4\text{-F}}/k_0$) was calculated

$$k_{4\text{-F}}/k_0 = (k_{4\text{-F}}/k_{4\text{-Br}})(k_{4\text{-Br}}/k_0)$$

In order to check the effect (if any) of ketone concentrations on the relative rates of reduction, a series of runs were made as above with equimolar quantities of benzophenone and 4-chlorobenzophenone in which the molarity of ketone was changed. The relative rates were essentially unchanged as shown in Table VI.

Competitive Reductions with Borohydrides in Aprotic Solvents. The reductions using sodium and lithium borohydride in pyridine or diglyme were followed by infrared spectroscopy[17] at 26 ± 2°. Standard solutions of borohydride were prepared in serum bottles sealed with rubber septums and the concentrations determined immediately before use by the iodate method.[26]

Table VI

Concn. of each ketone, *M*	$k_{4\text{-Cl}}/k_0$
0.20	2.29
0.10	2.21
0.067	2.34
0.05	2.29

A typical competitive reduction of benzophenone and 2-octanone with lithium borohydride in pyridine was carried out as follows. Using a hypodermic syringe, 5 ml. of a pyridine solution of lithium borohydride was added to a small sealed vial. Again using a syringe, 1 ml. of the ketone solution (0.4 *M* in each) was added and the mixture quickly shaken for a few seconds. A sample was quickly transferred to a 0.2-mm. NaCl infrared cell (the reference cell contained only pyridine) and a series of absorbance readings in the carbonyl region (ν_{max} 1710 cm.$^{-1}$ for 2-octanone, 1660 cm.$^{-1}$ for benzophenone) was made at frequent intervals. The cells were kept in a desiccator between readings. The relative rates were determined by plotting log A_t/A_0 for one ketone *vs.* the other, where A_t and A_0 are the absorbances of the carbonyl peaks at time t and at the beginning of the run. It was independently shown that ketone concentrations and absorbance were linear in the concentration range used. The results of a typical run are indicated in Table VII.

Table VII

Reading	2-Octanone A_t	2-Octanone log A_t/A_0	Benzophenone A_t	Benzophenone log A_t/A_0	$k_{(C_6H_5)_2CO}/k_{2\text{-oct}}$
Start	0.440	0.0	0.485	0.0	...
1	0.425	−0.015	0.430	−0.052	3.47
2	0.380	−0.063	0.280	−0.239	3.80
3	0.347	−0.103	0.205	−0.374	3.63
4	0.330	−0.125	0.166	−0.466	3.72
5	0.310	−0.152	0.124	−0.592	3.61
6	0.303	−0.162	0.125	−0.588	3.56
				Av. $k_{C_6H_5CO}/k_{2\text{-oct}}$ = 3.63 ± 0.09	
				From slope, $k_{(C_6H_5)_2CO}/k_{2\text{-oct}}$ = 3.74	

The relative rates of borohydride reductions in diglyme were obtained in the same manner as the pyridine reactions. Relative rates of competitive reductions by sodium and lithium borohydride in methanol were based on *product analyses* (by v.p.c.) after equimolar amounts of the two ketones underwent incomplete reduction by a deficiency of borohydride. The latter data therefore reflect a composite of all four stages of reduction involving alkoxyborohydrides.

Determination of the Rate Constants for $LiBH_4$–Pyridine Reduction of Benzophenones. The infrared technique was essentially the same as that used in the competitive reductions (above). In a typical run, 5 ml. of a 0.0954 *M* solution of lithium borohydride in pyridine was combined with 1 ml. of a 0.39 *M* benzophenone solution in the same solvent. A portion of this solution was immediately transferred to a 0.2

(26) D. A. Lyttle, E. H. Jensen, and W. A. Struck, *Anal. Chem.*, **24**, 1843 (1952).

mm. sodium chloride cell and the absorbance of the carbonyl peak followed with time. The usual second-order integrated rate expression for reactions with 1:1 stoichiometry was used and the rate constant obtained from the plot of $\ln (b - x)/(a - x)$ *vs.* time.

The data from a typical run for benzophenone at 25° is presented in Table VIII.

A repeat run gave $k_2 = 1.30 \times 10^{-3}$ l./mole-sec. The other benzophenones were studied analogously and the rate constants are recorded in the Discussion.

Competitive Reduction of 2,4′-Dichlorobenzophenone by 1,2- and 1,4-Dihydropyridyl Groups of LDPA. The decrease in concentration of the 1,2- and 1,4-dihydropyridyl groups of LDPA, as a solution of 2,4′-dichlorobenzophenone was added, was followed by

Table VIII[a]

Min.:sec.	Absorbance[b]	X	$a - x$	$b - x$	$\ln (b - x)/(a - x)$[c]
0:00	0.380	...	0.0657	0.0795	0.191
4:20	0.358	0.0039	0.0618	0.0756	0.203
8:55	0.341	0.0067	0.0590	0.0728	0.211
14:45	0.335	0.0079	0.0578	0.0716	0.215
21:40	0.322	0.0100	0.0557	0.0695	0.223
31:20	0.310	0.0121	0.0536	0.0674	0.227
41:30	0.278	0.0177	0.0480	0.0618	0.253
50:40	0.282	0.0170	0.0487	0.0625	0.247
63:30	0.260	0.0207	0.0500	0.0588	0.260
74:40	0.242	0.0239	0.0418	0.0556	0.285
84:25	0.240	0.0242	0.0415	0.0553	0.287
98:30	0.224	0.0270	0.0387	0.0525	0.304
115:00	0.210	0.0274	0.0363	0.0501	0.322
131:30	0.196	0.0319	0.0338	0.0476	0.342
150:20	0.182	0.0342	0.0315	0.0453	0.365
170:00	0.171	0.0361	0.0296	0.0434	0.382
188:00	0.160	0.0380	0.0297	0.0415	0.405
209:00	0.141	0.0413	0.0244	0.0382	0.448
239:00	0.130	0.0432	0.0225	0.0363	0.476
250:00	0.130	0.0432	0.0225	0.0363	0.476

[a] Initial concentrations: *a*, benzophenone, 0.0657 *M*; *b*, lithium borohydride, 0.0795 *M*. [b] The benzophenone band at 1660 cm.$^{-1}$. [c] Slope of plot = 1.115×10^{-3} min.$^{-1}$; $1/(b - a) = 72.5$ l./mole; k_2 = slope $\times$ $1/(b - a) = 1.35 \times 10^{-3}$ l./mole-sec.

n.m.r. spectroscopy. The 1,2-dihydropyridyl group has a signal at 250 c.p.s. (downfield from internal TMS) corresponding to the C-2 methylene protons,[5] and the C-4 methylene protons of 1,4-dihydropyridyl groups have their signal at 200 c.p.s.[5] *t*-Butylbenzene was used as an internal standard, so that the concentration changes of the two dihydropyridyl groups at various stages of reaction could be followed.

An n.m.r. sample tube containing 1 ml. of LDPA solution with *t*-butylbenzene added was scanned on the A-60 spectrometer and the C-2 and C-4 methylene signals as well as the *t*-butyl signal were integrated in both directions. Using a syringe, 0.1 ml. of a 2 *M* solution of 2,4′-dichlorobenzophenone was added to the tube, which was shaken and allowed to stand for 5 min. The above three signals were then integrated from both directions. Two more 0.1-ml. portions of ketones were added as above and the areas of the three peaks determined by integration. Using the integrated values of the 200 c.p.s., 250 c.p.s., and *t*-butyl peaks, the % consumption of 1,2- and 1,4-dihydropyridyl groups was calculated, from which $k_{1,2}$-/$k_{1,4}$- was obtained graphically. The data are summarized in Table IX.

Table IX. Competitive Reduction of 2,4′-Dichlorobenzophenone by 1,2- and 1,4-Dihydropyridyl Groups of LDPA

	Relative integrated n.m.r. peak areas					
Ml. of ketone added	*t*-Butyl	C-2 methylene	C-4 methylene	log % 1,2-remaining	log % 1,4-remaining	$k_{1,2}$-/$k_{1,4}$-
...	6.95	14.9	13.6	...	...	...
...	6.8	14.7	13.2	...	...	...
0.1	10.0	14.8	14.1	−0.162	−0.140	1.16
...	9.7	13.6	12.9	−0.186	−0.168	1.11
0.2	19.0	17.4	14.3	−0.371	−0.413	0.90
...	16.2	15.8	12.5	−0.343	−0.402	0.86
...	16.2	15.3	11.7	−0.357	−0.430	0.83
...	16.8	16.8	12.2	−0.334	−0.428	0.78
0.3	14.8	8.4	8.8	−0.578	−0.516	1.12
...	16.4	8.8	9.6	−0.602	−0.518	1.16
					Av. $k_{1,2}$-/$k_{1,4}$ =	0.99
						0.15 ±

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